

PUBLIC WORKSHOP
CURRENT STATE AND FURTHER DEVELOPMENT OF
ANIMAL MODELS OF SERIOUS INFECTIONS
CAUSED BY ACINETOBACTER BAUMANNII AND
PSEUDOMONAS AERUGINOSA

March 1, 2017

DoubleTree by Hilton Hotel
Washington, D.C.-Silver Spring
Pinnacle Grand Ballroom, 2nd Floor
8727 Colesville Road
Silver Spring, MD 20910

Reported by: Michael Farkas
Capital Reporting Company

P A R T I C I P A N T S

Speakers and Panelists

Thushi Amini, Ph.D.

Associate Director for Research

Office of Antimicrobial Products (OAP)

CDER, FDA

David Andes, M.D.

Professor, Departments of Medicine, Medical

Microbiology and Immunology

Head, Division of Infectious Diseases

University of Wisconsin

Robert Bonomo, M.D.

Professor of Medicine, Pharmacology, Molecular Biology

and Microbiology

Chief, Medical Service, Louis Stokes Cleveland

Department of Veteran Affairs Medical Center

Case Western Reserve University

P A R T I C I P A N T S

(Continued)

David Boucher, Ph.D.

Health Scientist Division of CBRN Countermeasures

Biomedical Advanced Research and Development

Authority (BARDA)

Helen Boucher, M.D.

Director, Infectious Diseases Fellowship Program

Associate Professor of Medicine

Tufts University School of Medicine

Ed Cox, M.D., M.P.H.

Director, Office of Antimicrobial Products (OAP)

CDER, FDA

Binh Diep, Ph.D.

Associate Professor

Division of HIV, Infectious Diseases, and Global

Medicine

University of California, San Francisco

P A R T I C I P A N T S

(Continued)

John Farley, M.D., M.P.H.

Deputy Director, Office of Antimicrobial Products (OAP)

CDER, FDA

Joanna Goldberg, Ph.D.

Professor, Department of Pediatrics, Division of

Pulmonary, Allergy, Cystic Fibrosis and Sleep

Emory University

Tina Guina, Ph.D.

Program Officer

NIH/National Institute of Allergy and Infectious

Diseases (NIAID)

Judith Hewitt, Ph.D.

Chief, Biodefense Research Resources Section

NIH/NIAID

P A R T I C I P A N T S

(Continued)

Julie Hutt, DVM, Ph.D., DACVP

Veterinary Pathologist

Lovelace Respiratory Research Institute

Robin Isaacs, M.D.

Chief Medical Officer

Entasis Therapeutics

Jane Knisely, Ph.D.

Program officer

NIH/NIAID

Matthew Lawrenz, Ph.D.

Associate Professor, Center for Predictive Medicine

Department of Microbiology and Immunology

University of Louisville School of Medicine

P A R T I C I P A N T S

(Continued)

Gianluigi Li Bassi, M.D., Ph.D.

Researcher, Department of Pulmonary and Critical
Care Medicine

University of Barcelona, Spain

Gabriel Meister, Ph.D.

Research Leader

Battelle Biomedical Research Center

Samuel Miller, M.D.

Professor of Medicine, Microbiology and Genome
Sciences

University of Washington

Sumathi Nambiar, M.D., M.P.H.

Director, Division of Anti-infective Products
FDA

P A R T I C I P A N T S

(Continued)

John Rex, M.D.

Chief Medical Officer and Director at F2G, Ltd.

Chief Strategy Officer at CARB-X - F2G, Ltd.

Andreas Wallnofer, Ph.D.

Interim Head of Development

Polyphor

Daniel Zurawski, Ph.D.

Senior Scientist, Principal Investigator, Division of

Bacterial Diseases, Department of Wound Infections

Walter Reed Army Institute of Research (WRAIR)

Public Participants

Joseph Campbell, NIAID

Tom Dreier, BARDA

Carl Gelhaus, MRI Global

Jennifer Hoover, GlaxoSmithKlein

P A R T I C I P A N T S

(Continued)

Tomas Maira-Litran, Brigham and Women's Hospital in
Harvard Medical School

Lynn Meisel, Eurofins Pharma Discovery Services

Craig Rayner, D3 Medicine

William Weiss, University of North Texas Health
Sciences Center

C O N T E N T S

PAGE

Clinical and Scientific Challenges 15

Introductory Remarks and Panel Introduction

Sumathi Nambiar, M.D., M.P.H., FDA 15

A Clinician's Perspective

Helen Boucher, M.D., Tufts Medical Center 28

Challenges with Clinical Trial Design

for a Drug Targeting a Single Species

of Bacteria

John Rex, M.D., CARB-X, F2G, Ltd.

Andreas Wallnofer, Ph.D., Polyphor

Robin Isaacs, M.D., Entasis Therapeutics 43

Lessons Learned and Considerations for Animal

Model Development 79

C O N T E N T S

(Continued)

PAGE

Lessons Learned from the Development of
Animal Models of Inhalational Anthrax,
Pneumonic Plague, and Tularemia

Judith Hewitt, Ph.D., NIAID

Gabriel Meister, Ph.D., Battelle

Biomedical Research Center

80

Approaches and Important Considerations
in Animal Model Development for Bacterial
Infections

Julie Hutt, DVM, Ph.D., Lovelace

Respiratory Research Institute

Ed Cox, M.D., M.P.H., FDA

111

Break

140

C O N T E N T S

(Continued)

PAGE

Pathogenesis

Session Co-Chairs: Samuel Miller, M.D.,
and Robert Bonomo, M.D.

140

Pathogenesis of Pseudomonas

Joanna Goldberg, Ph.D., Emory University

141

Pathogenesis of Acinetobacter

Robert Bonomo, M.D., Case Western Reserve
University

151

Public Presentations

168

Moderated Panel Discussion (with
Audience Q&A)

185

Lunch

204

C O N T E N T S

(Continued)

PAGE

Approaches to Animal Model Development,

Future Direction/Next Steps

Session Co-Chairs: Sumathi Nambiar, M.D.,

and Jane Knisely, Ph.D.

204

PK/PD Considerations for Animal Model

Development

David Andes, M.D., University of Wisconsin

205

Mouse Model of Pseudomonas Infection

Matthew Lawrenz, Ph.D., University of

Louisville

222

Mouse and Pig Models of Acinetobacter

Infection

Daniel Zurawski, Ph.D., Walter Reed Army

Institute of Research

234

C O N T E N T S

(Continued)

PAGE

Rabbit Model of Pseudomonas Pneumonia

Binh Diep, Ph.D., University of California,

San Francisco

264

Ventilated Pig Models of Pseudomonas

Pneumonia

Gianluigi Li Bassi, M.D., Ph.D.,

University of Barcelona

280

Break

295

Research Support and Resources

David Boucher, Ph.D., BARDA

Tina Guina, Ph.D., NIH/NIAID

Thushi Amini, Ph.D., FDA

295

C O N T E N T S

(Continued)

PAGE

Moderated Panel Discussion (with
Audience Q&A)

311

Closing Remarks

355

1 P R O C E E D I N G S

2 Clinical and Scientific Challenges

3 Introductory Remarks and Panel Introduction

4 DR. NAMBIAR: So good morning, and welcome
5 again to today's workshop. We are here to discuss the
6 current state and further development of animal models
7 of serious infections caused by Acinetobacter baumannii
8 and Pseudomonas aeruginosa.

9 I'm Sumathi Nambiar, and I'm from the Division
10 of Anti-Infective Products in the Center for Drug
11 Evaluation Research at the FDA.

12 So in the last couple of years we've seen
13 products come through that target a single bacterial
14 species, and these bacteria are typically not very
15 frequently identified at any one body site of
16 infection. So the reason we are having this discussion
17 today is that we recognize that there is potential
18 clinical utility for such products, but we also
19 recognize that there are many challenges and
20 difficulties in developing such drugs.

21 As I already mentioned, it's not that
22 infections due to Pseudomonas aeruginosa or

1 Acinetobacter baumannii are rare or infrequent; the
2 issue here is that they occur infrequently in any one
3 infection type, making it very difficult to enroll in a
4 clinical trial. And in contrast to many other rare
5 human diseases, acute bacterial infections pose
6 additional unique challenges. These patients are sick,
7 there's an urgent need to start effective therapy --
8 sorry. Why is it not showing up on the -- sorry, I
9 didn't realize it wasn't coming up on the slides.
10 Sorry. Okay, so here we go.

11 For people on the phone, would you mind muting
12 your phones? We're hearing a lot of background noise.
13 So people calling into the meeting, would you please
14 mind muting your phones? We do hear a lot of
15 background noise.

16 So we've been discussing this topic
17 internally, and again for the last couple of years, and
18 last summer we had a 2-day workshop. On the first year
19 of the workshop, we discussed how one can facilitate
20 antibacterial drug development for patients who have an
21 unmet need. And the second day was really focused on
22 developing an antibacterial drug that targets a single

1 species, and we're hoping that today's workshop would
2 be a continuation of the discussion that we started
3 last year.

4 So on day one, it was clear that there are
5 significant challenges in conducting a trial to show
6 superiority in patients that have infections due to
7 multidrug-resistant organism. We heard about the
8 difficulties that Achaogen experienced in conducting
9 their superiority trial with plazomicin.

10 There's a clear message that it is very
11 important to understand how the drug behaves, the
12 pharmacokinetics of the drug, in the target population
13 in which the product is being studied.

14 On the second day, where we discussed drugs
15 that act only against a single species that is
16 identified infrequently, we had a lot of discussion
17 about the practical difficulties in conducting such a
18 trial. There was discussion about potential trial
19 designs based on a hypothetical example. And all the
20 options discussed had challenges and limitations, and
21 you will hear more about this hypothetical case in the
22 presentation from Dr. Rex this morning. And there was

1 also discussion at the workshop on potential roles for
2 animal models of infection in studying such drugs.

3 So just to recap, what are some of the options
4 for clinical development for such products that we have
5 discussed? So one option certainly is to conduct a
6 non-inferiority trial at any one body site of
7 infection.

8 An example would be hospital-acquired
9 bacterial pneumonia, ventilator-associated bacterial
10 pneumonia. Such a trial is potentially feasible if
11 you're willing to accept greater uncertainty, which
12 translates to a wider non-inferiority margin than we
13 would use in standard development programs. Such a
14 trial will not need to limit enrollment to patients who
15 have infections only due to specific resistance
16 phenotypes, it could be an all-comer population.

17 Availability of a rapid diagnostic test would
18 certainly help identify these patients but will not
19 change the frequency with which these infections occur.
20 In a non-inferiority trial, it will be very important
21 to consider the potential for confounding by
22 concomitant therapies which are used either to treat

1 other pathogens which are identified in polymicrobial
2 infections, are often used empirically in these very
3 sick patients.

4 Additionally, especially for a drug that
5 treats Acinetobacter, the treatment effect for
6 colistin-based comparator regimens may be difficult to
7 assess.

8 Superiority trials are easy to interpret and
9 assess efficacy compared to best available therapy, and
10 such a trial will need to enroll patients with
11 Pseudomonas or Acinetobacter, which are resistant to
12 available therapies so then one can demonstrate
13 superiority, but it is difficult to identify or enroll
14 enough patients who have infection only due to the
15 multidrug-resistant phenotype.

16 Such a trial could enroll patients with one or
17 more body sites of infection, but it's important to
18 keep in mind that demonstrating superiority over
19 existing therapy can be difficult, and this opportunity
20 is often time-limited and dependent on available
21 therapy being suboptimal because once new therapies
22 become available, their ability to demonstrate to

1 superiority becomes more difficult.

2 In the context of a drug that just targets
3 Pseudomonas aeruginosa, one other option we had
4 discussed was conducting a study in patients who have a
5 great, higher, likelihood of having infections due to
6 Pseudomonas, such as patients with cystic fibrosis, but
7 it does raise the question of, how does one extrapolate
8 from the CF population to non-CF population? whether
9 that raises additional concerns.

10 The last option that was considered is the
11 potential for approval under the Animal Rule where
12 efficacy data is obtained from animal models of
13 infection, and this might be a potential option if an
14 informative efficacy trial in humans is not feasible.
15 The animal efficacy data that will be obtained, should
16 this approach be pursued, will certainly be
17 supplemented with clinical data from patients who have
18 a variety of infections caused by these organisms.

19 So I'll just give you a little bit of
20 background on developing a product under the Animal
21 Rule. It's in our Code of Federal Regulations, 314.600
22 to 650, and for Biologics, it's 601.90 to 95.

1 Approval under the Animal Rule applies to
2 certain new products that have been studied for their
3 safety and efficacy in ameliorating or preventing
4 serious or life-threatening conditions which are caused
5 by exposure to lethal or permanently disabling toxic,
6 biologic, chemical, radiologic, or nuclear substance
7 when definitive human efficacy studies cannot be
8 conducted because it would be unethical to deliberately
9 expose healthy volunteers to lethal or permanently
10 disabling toxic substance, and field trials have not
11 been feasible.

12 When we rely on evidence of effectiveness from
13 animal studies, there are four criteria that need to be
14 met: that the pathophysiologic mechanism is reasonably
15 well understood; the effect is demonstrated in more
16 than one animal species expected to react with a
17 response predictive for humans, unless the effect is
18 demonstrated in a single animal species that represents
19 a sufficiently well-characterized animal model; the
20 endpoints used in the animal studies is clearly related
21 to the desired benefit in humans and is generally the
22 enhancement of survival or prevention of major

1 morbidity; and, lastly, the data or information on the
2 kinetics and pharmacodynamics of the product in animals
3 and humans allows us to select an effective dose in
4 humans.

5 There are some additional requirements for
6 products approved under the Animal Rule. There is a
7 need to do postmarket studies to provide evaluation of
8 the safety and benefit if and when situations arise
9 where the study is feasible and ethical. If needed, we
10 could impose restrictions to ensure safe use of the
11 product. And, lastly, labeling should include
12 information to patients that, for ethical or
13 feasibility reasons, the product was approved based on
14 studies, efficacy studies, in animals alone.

15 So here are some examples of Animal Rule drug
16 approvals in the infectious disease arena.
17 Levofloxacin, ciprofloxacin, and moxifloxacin were
18 approved for plague under the Animal Rule. And for
19 inhalational anthrax, in addition to levofloxacin, we
20 have two monoclonal antibodies that are approved. And
21 then I've also listed some examples in the non-
22 infectious diseases space.

1 So just to give you an idea of what kind of
2 animal studies was done for levofloxacin -- and you
3 will hear a lot more about the animal models for plague
4 in Dr. Hewitt's presentation -- this was a placebo-
5 controlled study in African green monkeys. Important
6 to note, that levofloxacin was already approved for
7 other indications based on clinical trial data,
8 including respiratory infections such as community-
9 acquired and nosocomial pneumonia.

10 So demonstration of efficacy in one species
11 was considered adequate. The AGMs were exposed to
12 *Yersinia pestis*, it was a specific strain, and they
13 either received intravenous levofloxacin or placebo
14 post-trigger, and the mortality in the levofloxacin arm
15 was significantly less compared to that in the placebo
16 arm.

17 So what do we hope to accomplish in today's
18 workshop. We hope that discussions at today's meeting
19 will help provide a better understanding of the
20 relevant animal models of infection, the advantages and
21 shortcomings of the currently available approaches,
22 help us identify key areas for further work or

1 development, and the role that animal models might play
2 in the development of such drugs so that we can get
3 these products to patients.

4 And before I conclude, I just wanted to
5 present a slide on the "Limited Population Pathway for
6 Antibacterial and Antifungal Drugs" because that might
7 come up during our discussion today and it's very
8 relevant to products that would be developed using
9 extremely small clinical trial datasets.

10 So as many of you are aware, the 21st Century
11 Cures Act was signed into law on December 13th of last
12 year, and Section 3042 of the Act covers the limited
13 population pathway for antibacterial and antifungal
14 drugs. And this pathway is for drugs that are intended
15 to treat a serious or life-threatening infection in a
16 limited population of patients who have unmet need.

17 Labeling for products approved under this
18 pathway will include "Limited Population" in a
19 prominent manner and also a statement that the drug is
20 indicated for use in a limited and specific population
21 of patients. And products approved under this pathway,
22 there is a requirement for pre-submission of

1 promotional materials.

2 So we do have a fairly busy agenda for today.

3 In the morning, we will talk about the clinical and
4 scientific challenges in developing some products. We
5 will hear examples both one from Polyphor for an anti-
6 pseudomonal drug, and we'll hear from Entasis
7 Therapeutics on an example of a drug that targets
8 Acinetobacter. We have a session on "Lessons Learned
9 and Considerations for Animal Model Development"
10 followed by a session on "Pathogenesis" of
11 Acinetobacter baumannii and Pseudomonas aeruginosa
12 infections.

13 Following lunch, we'll talk about the
14 "Approaches to Animal Model Development, Future
15 Direction, and Next Steps." And we'll conclude with a
16 panel discussion. There is opportunity for the
17 audience to participate during the session, so we do
18 encourage you to participate. Your comments and
19 questions are certainly very, very valuable to us and
20 help us formulate our thoughts moving forward.

21 So with that, I'll take the opportunity to
22 thank all the panel members for participating and also

1 for introductions.

2 Dr. Guina, maybe we'll start with you.

3 DR. GUINA: Sure. Can you hear me? My name
4 is Tina Guina. I'm a program officer in Drug
5 Development Section in Office of Biodefense Research
6 Resources and Translational Research in Division of
7 Microbiology and Infectious Diseases at NIAID.

8 DR. BOUCHER: Hi. I'm David Boucher. I'm a
9 project officer with BARDA's Division of CBRN
10 Countermeasures.

11 DR. DIEP: Hi. Binh Diep, from the University
12 of California, San Francisco.

13 DR. LAWRENZ: I'm Matt Lawrenz, from the
14 University of Louisville.

15 DR. ANDES: David Andes, from the University
16 of Wisconsin.

17 DR. GOLDBERG: Joanna Goldberg, Emory
18 University.

19 DR. BONOMO: Robert Bonomo, Case Western
20 Reserve and Cleveland VA Medical Center.

21 DR. MILLER: Samuel Miller, University of
22 Washington.

1 DR. KNISELY: Jane Knisely, NIH/NIAID.

2 DR. COX: Good morning. Ed Cox, Director of
3 the Office of Antimicrobial Products, CDER, FDA.

4 DR. FARLEY: Hi. John Farley, Deputy
5 Director, Office of Antimicrobial Products, CDER, FDA.

6 DR. REX: John Rex, Chief Medical Officer at
7 F2G and Chief Strategy Officer at CARB-X, a public-
8 private partnership supporting antibacterial R&D.

9 DR. WALLNOFER: Andreas Wallnofer, Acting Head
10 of Polyphor.

11 DR. ISAACS: Good morning. I'm Robin Isaacs,
12 Chief Medical Officer of Entasis Therapeutics.

13 DR. HEWITT: Judy Hewitt, NIAID.

14 DR. MEISTER: Gabe Meister, Battelle
15 Biomedical Research Center.

16 DR. HUTT: Julie Hutt, Lovelace Respiratory
17 Research Institute.

18 DR. NAMBIAR: Two of our panel members
19 unfortunately couldn't be here, so they'll be joining
20 us by phone.

21 Dr. Li Bassi, would you like to introduce
22 yourself? Hello, Dr. Li Bassi, are you on the line?

1 (No response.)

2 DR. NAMBIAR: All right. Dr. Boucher, are you
3 on the phone?

4 DR. BOUCHER: Good morning. It's Helen
5 Boucher, from Tufts Medical Center and Tufts University
6 School of Medicine.

7 DR. NAMBIAR: All right. So Dr. Boucher is
8 our first speaker for today, and will have to join us
9 by phone, as she couldn't be here in person.

10 Dr. Boucher is the Director of Infectious
11 Disease Fellowship Program at the Tufts Medical Center
12 and Professor of Medicine at Tufts University School of
13 Medicine. Dr. Boucher's clinical interests include
14 infections in immunocompromised patients and Staph
15 aureus infections. Her recent interests focus on Staph
16 aureus and the development of new anti-infective
17 agents.

18 Dr. Boucher, I'll pull up your slides in a
19 minute.

20 A Clinician's Perspective

21 DR. BOUCHER: Thank you very much, Sumathi.
22 And thank you for the kind invitation to be there

1 today. I'm really sorry not to be with you all in
2 person. We actually have another regulatory body, the
3 ACGME, here on campus for a visit, so I had to stay
4 here for these days. But I'm certainly with you in
5 spirit. I'm looking forward to learning a lot during
6 the course of the day.

7 I've been asked to talk about a clinician's
8 perspective on the topics of developing studies to
9 study infections due to Acinetobacter and Pseudomonas.
10 On the second slide are my disclosures.

11 And on slide three, I thought we could just
12 sort of start our discussion of the day -- actually, if
13 you can go back to slide 3, please -- just with sort of
14 stating what's really well known to all of us who are
15 here, but this notion that we have perhaps returned to
16 the pre-antibiotic era. And I think observations like
17 the findings of mcr-1 and -2, with transmissible
18 colistin resistance and the sort of onslaught of truly
19 multidrug-resistant Gram-negative organisms in the
20 environment and our food chain and now unfortunately in
21 our patients, it's frankly scary to all of us and
22 something that we're contending with across the country

1 and around the world.

2 As a clinician, we have long been sort of
3 forced to use the drugs that we have often with less
4 than ideal data. So, for example, we've had to learn
5 how to use inhaled and parenteral colistin, a lot of
6 creative ways to use drugs like fosfomycin for ESBL and
7 related Gram-negative infections, and tigecycline for
8 multidrug-resistant infections despite known safety
9 limitations. I think that's not even to mention the
10 various combinations that we find ourselves using quite
11 creatively in the clinic.

12 Another sort of comment to make at the
13 beginning of the day is that this discussion we're
14 having about using and developing new drugs is part of
15 a bigger strategy to combat antimicrobial resistance.
16 And certainly our efforts in infection prevention
17 stewardship and surveillance are very, very important,
18 and efforts like the CARB initiative are helping us at
19 least to make some strides forward in this regard.

20 On slide 4 is a list that's familiar to many
21 of us. And if you could just advance one more time,
22 please. This is a CDC list of pathogen threats from

1 2013, and, appropriately, the organisms that we're
2 discussing today, Acinetobacter and Pseudomonas, are
3 listed here as serious threats, along with a lot of
4 other organisms of concern, including CRE, which were
5 listed as urgent threats.

6 If you turn to slide 5, just this week, the
7 WHO list of priority pathogens for which new
8 antibiotics are urgently needed was released, and very
9 importantly and timely for our discussions today,
10 Acinetobacter and Pseudomonas have risen to critical
11 priority, and clearly that's very much in line with
12 what we see in the clinic and what's being observed
13 around the world.

14 Other pathogens that we've spent a lot of
15 efforts on -- (phone line skips) -- CRE are still quite
16 important, as are other things more globally, such as
17 Campylobacter and Salmonella and GC.

18 If we turn to the next slide, looking at where
19 we've come in terms of (phone line skips) development
20 progress, our IDSA 10 by '20 Initiative has made some
21 progress with six antibiotics approved so far in this
22 decade, including two that are active against Gram-

1 negatives, but clearly gaps remain and certainly
2 there's more to be done, which brings us to our
3 discussion today.

4 On slide 7, I thought it might be helpful to
5 talk about a couple of actual patient cases that might
6 demonstrate the importance of what we're undertaking.

7 So the first case I'll share is a 71-year-old
8 lady who had laryngeal cancer, underwent surgery,
9 chemotherapy, and radiation, and that was several years
10 ago. She was cured of the cancer, but home on oxygen
11 for her breathing chronic issues and had had some
12 admissions to the hospital for tracheobronchitis, and
13 had to go to rehabilitation, and came back to us from
14 rehab with fever, flank pain, and breathing issues.

15 Next slide. She basically wasn't that sick,
16 she had a cough, she had nasty sputum, but didn't have
17 fever or other constitutional symptoms. Her evaluation
18 did not show a virus or any other cause of infection.
19 And ultimately her blood and sputum grew a Gram-
20 negative that was identified as a multidrug-resistant
21 Klebsiella with metallo-carbapenemase.

22 She did quite well that time, cleared her

1 blood cultures, and did not need to be intubated or put
2 back on the breathing machine. We treated her with an
3 interesting combination of tigecycline and colistin
4 both inhaled and IV, and she tolerated a transition
5 ultimately to minocycline.

6 On the next slide, her case progressed, and
7 she came back to us again with pneumonia later in the
8 winter, and then again in the spring, and ultimately
9 she presented with respiratory failure and
10 tracheobronchitis and urinary tract infection, again
11 coming from rehab. She did well, got a 5-day course of
12 levofloxacin, but cultures of sputum and urine came
13 back with a CRE, a *Klebsiella pneumoniae* producing
14 carbapenemase.

15 Now her respiratory status got worse, she's
16 back in the emergency room, still sick, now febrile,
17 needing more oxygen, and her urine grows greater than
18 100,000 *Klebsiella*, and we got the call that it was a
19 multidrug-resistant organism. And so really what does
20 that mean?

21 On the next slide, you can see the profile
22 that came back from the laboratory showing resistance

1 to all of the antibiotics listed here. And,
2 importantly, on the lower right-hand side, this
3 organism was resistant to our two new agents,
4 ceftolozane-tazobactam and ceftazidime-avibactam, in
5 addition to our other kind of standard therapies,
6 (inaudible) aminoglycosides.

7 So in the next slide, we discussed this with
8 her family and the patient and the fact that there was
9 going to be predictable renal, neurologic, and other
10 toxicity if we attempted further therapy, and she
11 elected to transition to hospice care and passed away.
12 So this was a lady who was cured of cancer but ended up
13 dying of a resistant infection.

14 If we turn to another type of case, this is a
15 gentleman, a 46-year-old gentleman, who had heart
16 failure along with the usual comorbidities of diabetes
17 and obesity, and he came to us in cardiogenic shock and
18 required placement of a heart pump, a left ventricular
19 assist device. But before this, he was a healthy, or
20 apparently healthy, young guy working full-time and was
21 married with two young sons.

22 In the next slide, you see that a few months

1 later after placement of his ventricular assist device,
2 he comes back to us with what started as some local
3 irritation at the site, but got a little worse, as you
4 can see in the photograph. That erythema and kind of
5 purulent stuff was a local infection with a skin bug,
6 *Corynebacterium*. Initially did okay with that, but
7 came back a month later with worsening drainage, and
8 now grew a Gram-negative organism, *Enterobacter*.
9 Again, we managed this with local care and some oral
10 antibiotics initially.

11 In the next slide, you can see a photo of his
12 device. He had the HeartMate II device, on the left.
13 And it's implanted into the heart and then into a
14 pocket in his abdomen, just to give you a sense of the
15 anatomy. He sort of progressed and made it for 2 more
16 years actually.

17 In the next slide, he came back to us with a
18 device complication where the device itself stopped
19 working, so he had to have the pump exchanged, and so
20 he went to the device on the right side of the slide we
21 just saw, and had a bit of a rocky post-operative
22 course, as patients do after that kind of a procedure.

1 But he went home and did well for a few months, but
2 came back again with drainage at the driveline site
3 like we saw in that earlier photo, this time with Staph
4 aureus, another skin organism. It was MSSA, and he was
5 treated quite kind of by the book with empirical
6 vancomycin and then his therapy was narrowed down to
7 cefazolin and then cephalexin.

8 In the next slide, we can see that he
9 struggled and had a few (phone line skips) admissions
10 with infection. And his last admission, he came in
11 with pain and increased drainage, and now when we
12 looked at a CAT scan, there was actually infection
13 going deeper into the tissue of his abdomen. So he was
14 put on intravenous antibiotics, and this time the
15 cultures came back with Pseudomonas, and, indeed, his
16 Pseudomonas was resistant to ciprofloxacin,
17 aminoglycosides and -- oh, sorry, ciprofloxacin and
18 meropenem, but susceptible to aminoglycosides.

19 He didn't do well despite antibiotics. And he
20 was not a candidate for aminoglycosides because of the
21 ventricular assist device. You're not longer a
22 candidate if you have renal failure. And he wasn't a

1 candidate for another pump exchange. And he wasn't a
2 candidate for a transplant because they couldn't
3 control his infection. So this 46-year-old man
4 ultimately had to go to hospice, and he passed away as
5 well.

6 So if you turn to the next slide, these cases
7 I think -- and many others that my colleagues in the
8 room I'm sure have seen -- show us that infections from
9 resistant pathogens are serious and could happen to us
10 and our families. Certainly having drugs that can
11 target these pathogens would be useful to our patients.
12 And the data that we have is often less than what we
13 would hope. And Dr. Nambiar highlighted a lot of these
14 issues in her earlier talk.

15 Certainly, we do often use data from
16 infections at standard body sites, like urinary tract
17 infections, for example, as the foundation from which
18 we build. And we have to extrapolate, as clinicians,
19 to treat our patients because of the various ways in
20 which they present. And this allows -- we often rely
21 on a variety of sources of information to do this.

22 On slide 18, we know that clinical trials in

1 these areas are very challenging, and Dr. Nambiar
2 highlighted a lot of these issues. But I think there
3 are really only a few areas where testing narrow-
4 spectrum drugs in a clinic is really tractable, and
5 that would be things like Staph aureus and skin
6 infections, gonorrhea, and things like C. diff, and
7 Pseudomonas in cystic fibrosis, as was highlighted
8 earlier.

9 Certainly, we know that we need a path forward
10 for infections like Pseudomonas and Acinetobacter, and
11 we're going to hear about some candidates that are
12 emerging, which is great.

13 Dr. Nambiar highlighted the issue of
14 difficulty in enrolling in clinical trials because
15 these types of patients, especially with one
16 particulate site of infection, are rare, and, frankly,
17 that's good from a clinical perspective, we don't want
18 it to be otherwise. Dr. Nambiar also highlighted some
19 of the complexities and really inadequacies in both
20 non-inferiority and superiority approaches in this
21 regard.

22 Diagnostic tests, and rapid diagnostic tests

1 in particular, probably won't fix this problem because
2 they won't create the patients. They might help us
3 identify them faster, which is good. And Dr. Rex will
4 talk next about some of the other challenges and
5 options that we discussed in the July workshop.

6 On slide 19, several ideas have emerged about
7 ways we can address this challenge. Certainly, PK/PD-
8 based dose selection and validation are very important.

9 Animal models, in particular, validated animal
10 models, after the fashion of the Animal Rule, are going
11 to be discussed.

12 Validated external controls perhaps with open-
13 label data even with test agents might be useful.

14 And very small clinical datasets, as Dr.
15 Nambiar mentioned, perhaps also with pooling of data
16 from multiple body sites, may be options in terms of
17 ways we can use clinical data.

18 As we think about overall development plans, I
19 think a couple of themes deserve some attention. One
20 is using a fully validated Animal Rule in the settings
21 when we have no clinical efficacy data in the so-called
22 Tier D development that Dr. Rex will discuss. And then

1 there is the option perhaps of using good animal
2 models, maybe multiple different animal models, some of
3 which will be discussed later today, along with limited
4 clinical efficacy data as a path forward.

5 In slide 20, from a clinical perspective, I
6 think as we look at developing drugs when we can't have
7 fully powered clinical trials and when we're thinking
8 about using animal studies in a bigger way, clinically,
9 we hope that those infections will have some reasonable
10 human correlates and that PK/PD can be optimized to
11 understand and predict efficacy at a variety of body
12 sites, such as the lungs, the bloodstream, and intra-
13 abdominal infection, the worst clinical cases.

14 So in slide 21, pulling this all back together
15 and kind of summarizing where we are from the clinical
16 perspective on these narrow-spectrum indications, I
17 think in 2017, we are forced to use drugs with limited
18 data in the clinic in order to address the patients
19 that we see. And looking ahead, I think the work in
20 July, as highlighted earlier by Dr. Nambiar, really
21 showed us that additional clinical development plans,
22 non-inferiority or superiority studies just may not be

1 feasible.

2 When we look at small clinical studies, having
3 high-quality data is very important. Having adequate
4 safety data is very important. That's not necessarily
5 the focus of today's discussion, but I wanted to make
6 sure we highlighted that as part of a clinical
7 (inaudible). And we really think that using clinical
8 trial networks is a way to help to enhance the quality
9 of the data that we do obtain. And we hope to see the
10 inclusion of multiple body sites and infection types in
11 order to help clinicians have useful data.

12 Next slide, please. In terms of animal
13 studies, perhaps using the Animal Rule in addition to
14 PK/PD studies we believe can provide a foundation for
15 clinical development either in the scenario of the
16 Animal Rule with no clinical data or in the scenario of
17 using some animal models, good animal models, with some
18 clinical data.

19 The LPAD mechanism, as Dr. Nambiar mentioned,
20 does ensure that the use of these agents will be in a
21 limited population with needed safeguards. We believe
22 that ID physician-led stewardship will help ensure that

1 these patients are managed in the best way possible.

2 And, very importantly, just a couple of days
3 ago, the WHO raised Acinetobacter and Pseudomonas,
4 along with CRE, to the critical priority pathogens, and
5 so they've moved from serious to critical in the past 3
6 years. So I think that further emphasizes the
7 importance of our figuring out a way forward for
8 studying these infections.

9 And, finally, just to bring us right back to
10 the most important thing, our patients. The time to
11 figure this out is now, and we're very gratified to be
12 here today, and hopeful that we'll come up with some
13 really good options forward.

14 And with that, I'll thank you very much for
15 your attention.

16 DR. NAMBIAR: Thank you, Dr. Boucher. Thank
17 you for agreeing to participate via phone. I know you
18 have a busy day with other regulators onsite.

19 So with that, we'll move on to the next
20 session, which is to talk about the "Challenges with
21 Clinical Trial Design for a Drug Targeting a Single
22 Species of Bacteria." So we have three speakers in

1 this session: John Rex, from CARB-X; Andreas
2 Wallnofer, from Polyphor; and Robin Isaacs, from
3 Entasis Therapeutics.

4 So I'll introduce Dr. Rex first, who is well
5 known to many in the field as an ID physician and drug
6 developer with 30 years of development and policy
7 experience focused on antimicrobial drugs. Dr. Rex's
8 experience includes moving compounds from early pre-
9 clinical development through all the development phases
10 in the context of various academic and non-academic
11 positions.

12 Dr. Rex, thank you.

13 Challenges with Clinical Trial Design for a
14 Drug Targeting a Single Species of Bacteria

15 DR. REX: Thank you, Dr. Nambiar.

16 And let me remind everybody who is on the
17 phone, please be on mute. We're hearing all of your
18 papers rattle beautifully, which is a little difficult
19 on our end. Thanks.

20 So thanks, Dr. Nambiar, for the opportunity to
21 be here. My disclosures and affiliations are shown on
22 this slide.

1 And our focus for today is narrow-spectrum
2 drugs. Let me just make the observation that we're not
3 here talking about narrow spectrum. Narrow spectrum
4 has some values, there are some important potential
5 microbiological advantages to being narrow, but really
6 what we're saying is we need drugs for Pseudomonas and
7 Acinetobacter. These are really hard bugs to find
8 drugs for. And if you narrow your focus to a single
9 genus, you sometimes have more luck finding a new
10 agent.

11 And so I'm aware now of several candidates
12 that they really are focused on Pseudomonas or
13 Acinetobacter, and the molecule looks interesting, it
14 just doesn't have other activities. So it would be
15 delightful if it had those other activities, it would
16 make it easier to develop, quite honestly, but I don't
17 want to walk away from drugs that look like they might
18 actually work here because I think we need a collection
19 of things.

20 Pseudomonas and Acinetobacter are sort of the
21 "Darth Vader" of bacteria, and we really need a bunch
22 of tools. And so some of them are narrow, and we need

1 to find a way to develop them. So that's really kind
2 of the setup for today.

3 With Andreas and Robin, we're going to do a
4 little three-part act. We're going to give you three
5 somewhat worked out examples of how you might develop a
6 drug. And the theme that you're going to hear
7 repeatedly is Helen has already told you about the
8 unmet need, what you're going to hear from the three of
9 us is that clinical trials can only get you so far with
10 these drugs, but there are some things you can do to
11 help yourself move forward. And there are three key
12 ideas that I would like you to listen for as you go
13 through the presentations today.

14 The first is the PK/PD theme that you've heard
15 many times, is that MICs and drug exposures are pretty
16 strong in this area; they're a little stronger than
17 they are in other therapy areas. PK/PD gives you an
18 independent proof of causality that reduces your need
19 for empirical validation by clinical trials. Having
20 said that, though, there have been exceptions. PK/PD
21 is imperfect. And there will again be exceptions, I am
22 sure.

1 And so my message is that we should always
2 seek as much clinical data as possible, but we should
3 be willing to lean more on PK/PD if required.

4 The second thing, idea, I want to be sure
5 you're aware of is a bit of mental shorthand that is
6 helpful in having these conversations. This is an idea
7 that we introduced several years ago just as a way to
8 help break down the conversation into useful blocks.
9 And the idea goes under the rubric of the tiered mental
10 model, which is to say that there are four broad
11 categories of anti-infective development programs.

12 At Tier A, you're in the situation where you
13 can do multiple Phase 3 trials. You can generate a lot
14 of standard quality clinical data.

15 Tier D, the other end, is the Animal Rule
16 situation where you can't generate any clinical data,
17 you can demonstrate some safety data, but you just
18 can't demonstrate, at least you hope you can't
19 demonstrate, clinical data.

20 In between, we have Tier B, which is where
21 it's possible to do a Phase 3 study, maybe once, it's
22 hard, but it's possible.

1 And then Tier C is the situation where you
2 can't even quite do the Phase 3 trial, I should say the
3 standard dimension Phase 3 trial, a fully powered, full
4 size, what you would expect, Phase 3 trial. And pretty
5 clearly, we're here where we are today is talking about
6 Tier C and Tier D. It's a helpful way to put yourself
7 in the right mental box.

8 And Tier C, I think of it as animal models,
9 plural, with clinical data. It's the animal model data
10 are helping you validate the PK/PD relationship. You
11 can generate some clinical data. You're looking for it
12 to be consistent, but it will not be at the usual
13 statistical strength. And these are taken together.

14 Tier D, as has been said, no clinical efficacy
15 data possible. You can get the safety data. The
16 animal data are actually -- they are the controlled
17 trial until such time as you do a field trial. And
18 here you really want the models to be even more close
19 to being a mimic of the human disease if you can.

20 So it's a continuum. You do the best you can.
21 Drug labeling should be suitably cautious as you go
22 from A -- more and more cautious as you go from A to B

1 to C to D. And the LPAD language, and also there is
2 some parallel language with EMA, that talks about how
3 you might describe the limited datasets, should you
4 have them in that fashion.

5 The third idea to be aware of is that
6 superiority is not an escape hatch for us. I'm often
7 asked, "Why don't we just show that the new drug is
8 superior to the old drugs? Because wouldn't that be
9 easier? The clinical trials would be smaller. It
10 would be cleaner." And you're right, it would be
11 cleaner, it would be smaller, but paradoxically,
12 superiority is painful, indeed, I would say it's an
13 ugly path for antibiotics.

14 We're not treating migraines. Inadequate
15 therapy of serious infections leads to death. We must
16 never knowingly randomize to ineffective therapy.
17 Hence, if you want to routinely use superiority as the
18 way you get to new drugs, you're going to have to let
19 some things happen. One is you're going to have to let
20 AMR progress such that highly resistant strains are
21 sufficiently common that you can get them in a trial,
22 and then the best available standard of care needs to

1 not really be very good. And then you would see
2 superiority, but that superiority would be based on
3 something kind of unpleasant, and this is not a
4 hypothetical. Let me show you a real life example.

5 So Achaogen showed some data just before
6 Christmas this past year about their new product,
7 plazomicin, where they were studying it for culture-
8 proven carbapenem-resistant Enterobacteriaceae
9 infections. And in this study, they randomized to the
10 best available care these days, which is a colistin-
11 based standard of care. That is the best available
12 therapy at the time they were doing the study.

13 And what you see in the graph is they've got
14 these two groups, and the plazomicin group had 11 or 12
15 percent mortality, and the colistin group had a 40
16 percent mortality, and that's really quite different.
17 And notice that the denominator is small. This is a
18 small trial, but it actually suggests superiority of
19 the plazomicin-based therapy.

20 Now, I point out, why did they see that? If
21 you do the math, it means that about six people on the
22 standard of care arm died due to the standard of care.

1 So I'm glad to have the clarity of the data on
2 colistin's relative lack of efficacy and the value of
3 the plazomicin control arm, but this is a steep price
4 to pay on a routine basis. As colistin is displaced as
5 standard of care, I hope that the next drug goes up
6 against plazomicin, and it just becomes harder and
7 harder to ever show something like this again.

8 So with that as my context, let me talk about
9 Drug X-1, which is the first of the three drug examples
10 where we're going to talk about how you might develop
11 such a drug. X-1 was a drug that was invented as a
12 hypothetical for a workshop last summer where we had
13 about 100 people, and we spent a day talking about,
14 "How would you develop this drug?"

15 And we made up the case to really simplify the
16 storyline. It was an activity limited just to
17 Pseudomonas. We made up very clean pharmacology, a
18 very clean Phase 1 program. The imaginary sponsor even
19 did an imaginary study in Phase 2 in non-CF
20 bronchiectasis and showed that their proposed dose
21 knocked down organism burden in the lung. So the drug
22 got into the lung and it had an effect on the bacteria.

1 It was not a study you can always do, but we made up
2 the simplest possible case and said, all right, X-1
3 looks really useful. How in the world would you bring
4 this to registration?

5 So we thought about it and we said, well, we
6 could devise a study arm if you put X-1 with ertapenem,
7 which is a carbapenem that lacks activity against
8 Pseudomonas, but it hits all the Enterobacteriaceae,
9 it's stable to ESBLs, it's indicated for complicated
10 intra-ab, it's indicated for skin, it's indicated in
11 the lung. So it's got all the body sites covered in
12 terms of getting in there.

13 And the PK actually has been modeled, was
14 modeled briefly last year, and then Paul Ambrose's
15 group has modeled it in more detail, and we have to say
16 that ertapenem looks like it should be just fine for
17 ventilator-associated pneumonia. There will be an
18 abstract on this at ASM Microbe this summer.

19 So if you put ertapenem with X-1, you've
20 basically got a regimen, you can put it against the
21 standard carbapenem, and anytime you treated a
22 Pseudomonas, the X-1 would be the component that was

1 treating the Pseudomonas, and so you would have a clear
2 demonstration of that.

3 There is a bit of an unreserved complexity
4 around the need for the frequent wish for initial dual
5 coverage that we need to resolve, get another debate in
6 this area, but the point is it looks like you can
7 develop a study arm.

8 The real issue is a mathematical one, which is
9 the rate of cases of Pseudomonas is low. You typically
10 have to enroll before the culture result becomes
11 available. Typical rates of Pseudomonas and nosocomial
12 pneumonia, intra-ab, and UTI are shown. And a
13 diagnostic test, importantly, won't fix this problem.
14 Diagnostics don't create the patients with the
15 infection, they only help you find them. You still
16 have to screen the number of patients required to find
17 the patients with these infections.

18 And this leads to a trial problem, which is
19 that if you just say, "I want a standard dimension
20 Phase 3 study, endpoint 20 percent failure, non-
21 inferiority margin 10 percent, power 90 percent," you
22 need 672 evaluable cases, 336 per arm, and if you back

1 that up to evaluable equals culture-proven, you need
2 either 3,000, 6,000, or 22,000 patients in your Phase 3
3 trial, which is clearly large enough for safety, but
4 not feasible for actual development.

5 And I will observe that we have two examples
6 recently that show that nosocomial pneumonia trials
7 sort of enroll between 250 to 300 patients a year. So
8 that 3,000-patient study is about a decade's worth of
9 work.

10 So in designing options for X-1, we put some
11 constraints on it. We said it's got to be common
12 sense. We can't have a BFMI -- Brute Force, Massive
13 Ignorance -- solution. We can't presume perfect
14 diagnostics, instant susceptibility, instant knowledge,
15 that only Pseudomonas is present. We're not going to
16 have a superiority study because we're not going to
17 have a perfectly timed MDR Pseudomonas aeruginosa
18 outbreak. We've only got enough money for about 1,000
19 people.

20 And the money question is an interesting one.
21 You might say, well, maybe we -- because a community
22 could study 20,000, but if you commit 20,000 to

1 studying one drug, you can't study anything else. So
2 it's not just money. The idea of studying an enormous
3 program, it interferes with being able to do anything
4 else.

5 Add-on therapy is unlikely to play out.
6 Standard of care plus X-1 was unlikely to be better
7 than standard of care because standard of care could
8 only be done in settings of susceptible Pseudomonas.
9 In short, we wanted to keep the miracle count less than
10 1. We would accept luck, but we wouldn't expect it.

11 The imaginary sponsor invented an imaginary
12 screening device based on having found a monoclonal
13 antibody in the Sigma Catalog to pyocyanin. And we
14 thought maybe you could create a little lateral flow
15 device that would get you up slightly in terms of your
16 culture-positive rate. We have (inaudible) you can get
17 up to 25 percent and 16.5 percent. It wasn't a clear
18 test, but we thought, well, maybe you could do
19 something like that to increase the rate of
20 Pseudomonas.

21 So putting it together, and listening to
22 Helen, Helen said, "I would like to see data in a

1 variety of body sites." You know, sort of we thought
2 we would spread it out a little bit. So what we came
3 up with was this design on this slide as sort of our
4 base case: two trials that would generate data in
5 three indications, and the hope was that if all three
6 indications sort of demonstrated the same direction in
7 terms of response, you would be convinced by putting it
8 together.

9 So there was an RCT with separate sub-arms for
10 nosocomial pneumonia and complicated intra-ab. And we
11 tortured the data to create two subsets that were two
12 tiny non-inferiority studies with absolutely the widest
13 margins we could possibly justify based on any data we
14 could find in the literature, 30 percent for nosocomial
15 pneumonia and 25 percent for complicated intra-ab, and,
16 yes, those are enormous margins. And we randomized
17 2:1, and there's the size there, 915 subjects. It just
18 barely fits. But remember, if all of it lined up, you
19 would have multiple bits of data pointing in the same
20 direction.

21 We also said we would do an open-label study
22 in patients with limited treatment options where we

1 just play "Go Fish," bring us your most difficult case
2 and collect some data.

3 Is it feasible? Well, maybe. Hitting these
4 numbers would be hard. It's just at the bounds of
5 feasibility.

6 Is it credible? Maybe. You know, this really
7 does -- we really have pushed the design limits very
8 hard.

9 The discussion at the workshop was helpful
10 because we had 100 people in the room and people were
11 very engaged, and as we debated it, what we concluded
12 was we hadn't overlooked some trick. There wasn't some
13 clever thing that we could do instead of this. We were
14 stuck. And they are going to be limited.

15 We also talked a little bit about what
16 happened when we couldn't even squeak out these very,
17 very difficult NI designs. And, again, no clever ideas
18 came up at that time.

19 So, in short, our basic conclusion was there
20 wasn't a trick, we weren't overlooking things.
21 Sometimes clinical data would be very limited, and the
22 tradeoffs were going to be required. And, by the way,

1 this has been written up, and there's a paper that I
2 think is just about to be able to say it's in press at
3 JID that describes these ideas.

4 So this is my last slide, which is to say that
5 narrow-spectrum drugs, it isn't just that it's narrow,
6 it's just that for *Pseudomonas* and *Acinetobacter*, these
7 are often going to be narrow, and if you want these
8 drugs, we have to facilitate these pathways.

9 I've given you an example that we cooked up
10 last summer as a possible way. You're about to hear
11 two more examples. And I'll just say again that all
12 three of the examples you're going to hear have clear
13 limitations, but if you want to see any progress here,
14 we're going to have to accept these tradeoffs. And my
15 last comment is that lack of action would be action
16 that has consequences.

17 So thank you very much.

18 DR. NAMBIAR: Thank you, Dr. Rex.

19 So our next speaker in this session is Dr.
20 Wallnofer, and he will discuss with us their experience
21 in developing POL7080. Dr. Wallnofer is a clinical
22 pharmacologist with additional expertise in

1 pharmaceutical medicine and business management.

2 Dr. Wallnofer spent more than 20 years at
3 Hoffman-La Roche, where he was a member of the R&D
4 Leadership Team and Head of Clinical Research and
5 Exploratory Development. And in his current role, he
6 is at Polyphor as Interim Head of Development since
7 2016.

8 Thank you, Dr. Wallnofer.

9 DR. WALLNOFER: Thank you for the
10 introduction. And let me first thank the organizers
11 for the kind invitation to this workshop.

12 So my talk is on behalf of Polyphor. Polyphor
13 is a Swiss biotech company that has developed a novel
14 class antibiotic against *Pseudomonas aeruginosa*. And
15 nosocomial pneumonia is the leading cause of death of
16 nosocomial infections in the U.S., and *Pseudomonas* is,
17 as we just discussed, one of the most frequent
18 pathogens in infections with *Pseudomonas*, have adverse
19 outcome, and particularly patients that are infected
20 with MDR strains, they have increased risk of
21 mortality. So we really think it's important to
22 develop such new medicines for patients' needs and to

1 the community in times of increased resistance
2 development.

3 So I'm acting as the Head of Clinical
4 Development at Polyphor, and I'm consulting with the
5 company on this program and on others.

6 The molecule that we are talking about is
7 murepavadin, which is a first (inaudible) of novel
8 class antibiotics that target specifically proteins at
9 the outer membrane of Gram-negative pathogens. This
10 specific mechanism of action allows to target specific
11 pathogens and makes the mechanism of action specific to
12 targeted therapies.

13 The molecule is highly effective against
14 Pseudomonas, including resistant strains. It's a
15 cyclopeptide, as you can see in the right corner there.
16 It has very favorable pharmacokinetics, distributes
17 well to the lung. Distribution is similar to the free
18 plasma fraction. And it has a half-life elimination
19 kinetics of 6 to 8 hours at an acceptable safety
20 profile.

21 Now, the drug has been, of course, extensively
22 studied preclinically. As you can see here, this slide

1 reflects the pathogen's specificity of the compound
2 with high potency against the different Pseudomonas
3 specimen.

4 Strains from all geographies of the world have
5 been assessed. And as is shown here, murepavadin is
6 active against Pseudomonas for non-resistant and
7 resistant strains. It's a similar comparison. And
8 that's also shown here. And the drug was investigated
9 in a neutropenic mouse model, that you see that the
10 drug was efficacious even in models where polymyxin was
11 hardly active. There are further data that show that
12 murepavadin can overcome colistin resistance that
13 indicates the importance of this novel antibiotic.

14 The drug is eliminated, cleared, renally, and,
15 hence, we adjust the dosing according to renal
16 function. There is a very substantial PK/PD effort
17 done for the development of this program, and all this
18 modeling, integrating the clinical and preclinical
19 data, we have indicate that at the proposed dosing
20 regimen, we would cover 400 percent at the MIC of 0.25
21 and up to 80 to 90 percent at 0.5.

22 So this is just a quick screen of the profile

1 of the molecule, and should actually illustrate that
2 you really have here a very potent anti-pseudomonal
3 agent that is active also against resistant strains.
4 Murepavadin has the potential to become a precision
5 medicine. It is suited for guided therapy and
6 stewardship as a tailored medicine for patients at risk
7 of MDR infection.

8 And we also feel for the data that we have
9 that the drug has a limited risk of resistance
10 development of cross-resistance with other commonly
11 used antibiotics. And obviously given the mechanism of
12 action, it doesn't put pressure on the microbiome, and
13 therefore has a lower risk of secondary infections.

14 The drug has been already studied in clinical
15 studies. Eight studies have been conducted. There was
16 one study in the target population that was a small
17 study focused on PK and safety. Nevertheless, some
18 early exploratory efficacy data were collected there.
19 There was a low mortality, and that case was actually
20 reinfection after discontinuation of the therapy.
21 There were several cases of MDRs in that trial. And
22 all of these cases resolved. Obviously, you cannot say

1 too much from such a small trial, and many of the
2 reports are rather anecdotal. And the true question
3 is, of course, how can we study this systematically to
4 really prove the efficacy and the benefit-risk of this
5 medication?

6 Here are some comments about the challenges
7 now from a company perspective. I mean, it's in a way
8 reiterating what has been said before by Professor
9 Boucher and John Rex and Sumathi in the introduction.
10 It is difficult to apply traditional drug development
11 or clinical trial as scheduled to such a drug.
12 Superiority trials are almost impossible.

13 And the conduct of the trials is limited, of
14 course, by the availability of the patients, by the
15 logistics to include these patients within a short time
16 window and get informed consent from the relatives, as
17 well as by co-medication that may affect the scientific
18 evaluation and conclusiveness of these trials. So many
19 factors have to be managed in order to get to a valid
20 scientific experiment.

21 We have done some initial feasibility
22 evaluations of the protocol under consideration, and

1 they go into the direction that they probably would
2 need 10 centers to recruit one patient per month. So
3 it is challenging.

4 The other challenge that we have faced is that
5 the different regulatory agencies in the U.S. and
6 Europe, they put emphasis on different aspects. So the
7 guidance from the European partners was more about
8 demonstrating efficacy in the resistant strains,
9 whereas the FDA gave us a very clear message that
10 actually what really would help the evaluation of the
11 drug is to demonstrate efficacy against Pseudomonas as
12 monotherapy. Obviously, both points are valid, and
13 they would form together a comprehensive picture of the
14 value and effectiveness of the drug.

15 Now, on the very good side is that we have
16 really -- and I must really also thank the FDA
17 colleagues for the very constructive discussions that
18 we have because everybody tries to get their head
19 around, how can we do this in a correct, scientifically
20 correct, medically correct, way? And we reached
21 conclusions with European and FDA regulators about how
22 we could do this.

1 So basically the conclusion from several
2 discussions we had with the agency was that we really
3 would actually go down the avenue of this X-1 trial
4 that John was alluding to. So basically murepavadin
5 would be combined with ertapenem in the study arm, and
6 compared to meropenem as an active. It would be a non-
7 inferiority trial in the mITT populations and only in
8 the patients that really have confirmed Pseudomonas.
9 There needs to be a diagnostic test in the trial to
10 identify these patients up front.

11 And the issue that John raised about the need
12 for empiric dual coverage would be managed by allowing
13 amikacin in both arms up to 72 hours with the caveat
14 that the decision needs to be made before
15 randomization.

16 So taking all of this together, I think it is
17 challenging, but we concluded with this joint effort of
18 the different parties -- clinicians, regulators, and us
19 -- that it is challenging, but it can be done.

20 One open question was about the utility of
21 ertapenem to be the joint partner for murepavadin.
22 Obviously, ertapenem is not active against Pseudomonas.

1 That's why it makes it the right setup in this study
2 design. It doesn't work against Acinetobacter. It
3 happens, of course, fortunately, only in very few
4 patients. The issue was, do we have enough coverage
5 against Enterobacteriaceae?

6 And in collaboration with Paul Ambrose's
7 groups, we modeled planned dosing regimen and came to
8 the conclusion that it would be okay and suitable and
9 medical justifiable to combine our drug with ertapenem.
10 So that design would lead to conceptually to compare
11 the efficacy of our medicine, murepavadin, as a
12 monotherapy against Pseudomonas protected by ertapenem
13 against other possible pathogens.

14 The study would run primarily at what we call
15 a usual drug resistance center. These are centers
16 which do not have high incidence of MDR for the simple
17 reasons because actually if you end up with too many
18 patients in double coverage, the interpretation would
19 be difficult. So we would go primarily to those sites.

20 And obviously from that perspective, we will
21 have only very few patients that are truly MDR or XDR.
22 They must be studied in another way, which we are

1 discussing with the European colleagues. And we think
2 that we are close to cracking the problem. We don't
3 underestimate, we really don't underestimate, the
4 logistic challenges to run such a study, but we feel
5 that this is one of the most encouraging parts of the
6 story, that the joint efforts of industry, clinicians,
7 and regulators, that we can address this problem and
8 develop this novel antibiotic that may be important for
9 patients and physicians.

10 So thanks for your attention. And I think
11 we'll discuss later about it. And sorry for my voice.

12 DR. NAMBIAR: Great. Thank you, Dr.
13 Wallnofer, for sharing your experience with trying to
14 develop this compound.

15 So our third speaker in this session is Dr.
16 Robin Isaacs, from Entasis Therapeutics. Dr. Isaacs
17 will be discussing their experience with developing a
18 drug that targets Acinetobacter, Sulbactam ETX2514.

19 Dr. Isaacs has extensive experience as a
20 pharmaceutical executive in the development and launch
21 of vaccine and infectious disease products. During the
22 18 years he spent at Merck, Dr. Isaacs was involved

1 with the worldwide development, regulatory submissions,
2 and approval of many anti-infective products, including
3 vaccine products.

4 Thank you, Dr. Isaacs.

5 DR. ISAACS: Thank you. And thank you very
6 much to the organizers of the meeting for inviting us
7 to present. Entasis is a relatively new biotech
8 company that was formed in 2015, and our lead product
9 is Sulbactam ETX2514 for the treatment of
10 Acinetobacter.

11 Before I proceed any further, I just wanted to
12 put in one disclaimer, that the thoughts that are
13 presented in the following slides represent the
14 thoughts of Entasis, and represent the evolution of our
15 thoughts and how we may develop Sulbactam ETX2514 for
16 the treatment of Acinetobacter.

17 As Dr. Boucher has already pointed out,
18 Acinetobacter baumannii is a significant unmet medical
19 need, and that's reflected in the new WHO update to the
20 list of pathogens. It's one of the six ESCAPE
21 pathogens. There are approximately 60- to 100,000
22 infections in the U.S., and approximately 130,000

1 infections in the EU5 per year based on Decision
2 Resources data. And commonly, Acinetobacter infects
3 the bloodstream, lung, urinary tract, and skin.

4 There is a significant difference between
5 Acinetobacter and Pseudomonas on two parts. One is the
6 extraordinarily high level of mortality associated with
7 Acinetobacter in critically ill patients. In treated
8 patients, currently the mortality rate is approximately
9 40 percent, and in untreated patients, it's
10 approximately 80 percent.

11 The second is that approximately 60 percent of
12 the Acinetobacter isolates in the U.S. -- and in some
13 countries in the world, greater than 90 percent of the
14 isolates -- are multidrug-resistant. So the issue with
15 Acinetobacter is it's a relatively limited pathogen in
16 terms of number of cases, but the majority of the cases
17 represent multidrug-resistant cases.

18 And the data that I'm showing here on the
19 bottom is just to give you some notion on a worldwide
20 basis of imipenem as an example of a broad-spectrum
21 highly effective beta-lactam and resistance amongst
22 Acinetobacter where you can see that on a worldwide

1 basis, approximately 64 percent of strains are
2 resistant.

3 Sulbactam ETX2514 is in clinical development
4 as a pathogen-specific drug to treat *Acinetobacter*
5 *baumannii*. As Dr. Rex pointed out, it's difficult to
6 get broad-spectrum agents which cover everything you
7 want them to cover, and *Acinetobacter* and *Pseudomonas*
8 are agents of infection which have proved particularly
9 difficult to cover with broad-spectrum drugs.

10 Sulbactam will be familiar to many in the
11 audience. It's a beta-lactam that's widely used as a
12 beta-lactamase inhibitor in the combination product
13 Unasyn. But as a beta-lactam, it also has intrinsic
14 activity, and one of its most remarkable features of
15 its intrinsic activity is activity against
16 *Acinetobacter baumannii*.

17 ETX2514 is a novel non-beta-lactam, beta-
18 lactamase inhibitor, and its unique feature relative to
19 other available beta-lactamase inhibitors is its broad
20 coverage of Class D beta-lactamases in conjunction with
21 very broad coverage against Class A and C. And data
22 from looking at panels of contemporary *Acinetobacter*

1 strains indicate that if you're going to resurrect a
2 beta-lactam against Acinetobacter, by covering beta-
3 lactamases, you need to be able to cover Class D as
4 well as Class A and C.

5 So, for example, in a large panel that we
6 published last year, almost all of the Acinetobacter
7 had Class D expression, but only 12 percent of those
8 expressed only Class D beta-lactamases. The other 88
9 percent expressed Class D along with either A and/or C,
10 and in most cases, more than one example of each of the
11 beta-lactamases in each class at the same time.

12 ETX2514 is very potent in vitro and in vivo
13 and restores the activity of Sulbactam against
14 contemporary multidrug-resistant Acinetobacter.
15 Sulbactam alone in our panels had an MIC90 of 64. When
16 you add ETX2514 at 4 mcg/ml in the wells, the MIC90
17 came to 4 mg/L, and that is the breakpoint for
18 Acinetobacter in the Unasyn combination. And greater
19 than 99 percent of over 1,000 isolates from 2014 had an
20 MIC less than or equal to 4 mg/L.

21 So the preclinical profile is very strongly
22 suggestive of efficacy. The question is, how are we

1 going to get it to market and prove that in a way that
2 satisfies the requirements of the regulatory
3 environment?

4 So what are the challenges? The challenges
5 are that you have to be able to identify patients with
6 *Acinetobacter baumannii* infection. They represent
7 approximately 2 percent of hospitalized Gram-negative
8 infections on a worldwide basis in the U.S. and the
9 European countries. The patients are sick. They're
10 usually hospitalized. They generally have compromised
11 health. They're often in intensive care units. They
12 generally receive broad-spectrum coverage. And
13 patients may have renal impairment, leading to the need
14 to be able to have renal dosage estimate early in
15 clinical development.

16 About half the patients will have pulmonary
17 infections either with or without bloodstream
18 infection. And when we look at this, what you're
19 basically looking at is a very sick group of patients
20 in intensive care settings where, as has been pointed
21 out this morning, it's difficult to run clinical
22 studies.

1 So how do we translate this into a development
2 program? Clearly, identification of patients with
3 Acinetobacter baumannii infections is important. How
4 do we enrich for that? Well, in the case of
5 Acinetobacter baumannii, I'll remind you what I pointed
6 out earlier, multidrug resistance is actually the norm
7 rather than the rarity.

8 The target of a new therapy is to meet the
9 unmet medical need, in this case, multidrug-resistant
10 pathogens. And although Acinetobacter baumannii
11 infections are relatively uncommon, multidrug
12 resistance is very common. And so if we can use
13 routine microbiology to identify Acinetobacter
14 baumannii within 48 hours, we can enrich for multidrug
15 resistance by allowing up to 48 hours of prior therapy
16 to enroll patients in the studies.

17 Enrollment can be done prior to knowledge of
18 the resistance pattern of the Acinetobacter because
19 approximately 60 percent on average of what you enroll
20 will be multidrug resistant.

21 To reinforce points that may have been made
22 previously also, rapid bedside diagnostic would help

1 enrichment, but it's not going to help increase the
2 incidence of disease actually in the community. So
3 it's really a way to try and enrich for populations
4 while minimizing prior antimicrobial therapy. It would
5 be helpful, but isn't essential. There are a number of
6 companies, as you all know, that are working in the
7 rapid diagnostic space, and we continue to monitor this
8 as a potential way to assist in the clinical
9 development program.

10 The other element of identification, a key
11 element of identification, is where to find the
12 patients. And there are some hot spots for
13 Acinetobacter in the world. In the U.S. and the EU,
14 it's in intensive care units, where they account for
15 somewhere between 5 to 10 percent of ventilator- and
16 hospital-acquired pneumonias.

17 But on a much more broader geography basis,
18 and as this slide shows, which is taken from a review
19 by Chung et al., you can see that in countries such as
20 Thailand and Taiwan and other countries in Asia, that
21 actually Acinetobacter is either the number one or the
22 number two pathogen in hospital-acquired and

1 ventilator-acquired pneumonias.

2 So geographic siting of the clinical studies
3 becomes a very important factor in identifying patients
4 with Acinetobacter.

5 The last point I wanted to make before I sort
6 of get to the general plan that we think is achievable
7 and workable is to discuss the fact and to reinforce
8 the fact that we're enrolling patients who are sick
9 with significant co-morbidities. It's important to
10 understand pulmonary penetration, because pneumonia is
11 such a common feature, and renal dosage estimate early
12 in the development strategy so that when you start
13 Phase 3, you can enroll all of these sick patients
14 without having to restrict enrollment because you don't
15 have a renal dosage estimate, for example.

16 There needs to be substantial and substantive
17 preclinical efficacy data prior to the clinical studies
18 to establish PK targets likely predictive of efficacy
19 and to establish clinical dose using robust modeling of
20 Phase 1 pharmacokinetic and preclinical pharmacodynamic
21 targets. This is to reinforce points that have already
22 been made by each of the speakers this morning.

1 While establishing Phase 3 readiness, it's
2 important, I believe, to generate a limited amount of
3 safety data in relatively healthy patients so that you
4 have a baseline to review safety data in the much
5 sicker population that you will see in the Phase 3
6 program.

7 So then how do we establish efficacy? And I'm
8 just going to walk through this slide because it really
9 is a sequenced discussion of what the Phase 3 program
10 would look like. In taking advantage of preexisting
11 guidance and the unmet medical need, an event-driven
12 study based on multidrug-resistant pathogens, enrolling
13 patients with proven *Acinetobacter baumannii*
14 infections, and focusing on common infections, that is,
15 lung and/or bloodstream, and a non-inferiority
16 comparison against a standard of care regimen, and
17 utilizing a hard endpoint such as 28-day mortality,
18 would require, if you make reasonable assumptions as to
19 how many patients you can enroll and are prepared to
20 take a certain level of statistical risk, about 200
21 patients in a 1:1 randomization, so 100 patients in
22 each arm, to provide approximately 118 to 120 patients

1 with multidrug-resistant infections.

2 This study would be set up as an event-driven
3 study. And what do I mean by that? You would enroll
4 all-comers with Acinetobacter, but the primary efficacy
5 endpoint would be analyzed based on multidrug-resistant
6 isolates, so essentially you would be counting the
7 number of patients with multidrug-resistant isolates,
8 and you would trigger the final endpoint analysis when
9 sufficient had been enrolled.

10 The study would have 80 percent power. It
11 would assume a mild degree of superiority of 40 percent
12 mortality in the comparator group, similar to what
13 Achaogen showed, and that data was shown earlier by Dr.
14 Rex, and a small advantage of 35 percent mortality in
15 the experimental group.

16 The other key thing that I feel is -- and this
17 goes to a point that Dr. Boucher made -- you need to
18 get data which really helps physicians understand how
19 the drug works, and although the primary efficacy
20 endpoint would focus on lung and/or bloodstream
21 infections, patients who aren't eligible for that
22 comparative arm, so patients with other infection

1 sites, could be enrolled into an open-label arm where
2 they all get therapy with Sulbactam ETX2514, and that
3 data would then become supportive and would provide
4 efficacy and safety data in a population beyond the
5 primary efficacy population.

6 So then what might an NDA package look like
7 built around that single Phase 3 study of approximately
8 200 patients in a comparative arm? And what other
9 supportive data could be generated from the subjects
10 who aren't enrollable in that comparative arm?
11 Clearly, a strong microbiology package; strong evidence
12 of in vivo efficacy in relevant animal models; and
13 robust demonstration of PK/PD parameters based on in
14 vitro hollow fiber and in vivo animal models.

15 We don't have the ability really to dose range
16 in a conventional manner with this kind of study
17 population, so the dose for Phase 2 and Phase 3 would
18 need to be based on high probability of target
19 attainment using robust modeling of preclinical and
20 clinical data, similar to the approach that was
21 mentioned a few minutes ago.

22 The safety database, assuming that the drug is

1 generally well tolerated, of approximately 300 to 400
2 patients consistent with published FDA guidance
3 documents and demonstration of efficacy compared to
4 standard of care in a Phase 3 non-inferiority study
5 with a step-down to superiority once non-inferiority
6 has been proven.

7 Finally, you clearly need to be able to
8 justify the non-inferiority margin based on
9 comprehensive review of the available data. And as has
10 been pointed out by Dr. Rex and others, that's
11 challenging, but there is actually quite a lot of data
12 out there that one can work through to establish a non-
13 inferiority margin.

14 The last point that I want to leave you with
15 is that this is not easy, it's complicated, but we do
16 believe that as you focus down and drill down to the
17 kind of 200-patient study size, this is something which
18 is achievable over an 18- to 24-month time period.
19 It's important to focus on a relatively short time
20 period because if the study needs to run too long, then
21 you start to end up in the situation of changing
22 resistance patterns, changing background therapy, and

1 an increased reluctance to enroll subjects in the
2 study. So it's important to get a study size which is
3 enrollable in a feasible amount of time, and we believe
4 that that's possible with the kind of approach that we
5 have suggested here.

6 Thank you so much for your time.

7 DR. NAMBIAR: Thank you, Dr. Isaacs.

8 What we would do is take 5 minutes to see if
9 there are any clarifying questions that people have to
10 ask of the presenters before we move to the next
11 session. I think we're running just on time, so if
12 there aren't any major concerns or questions that need
13 to be addressed right away, we can do that in the
14 afternoon session.

15 (No response.)

16 Lessons Learned and Considerations for Animal
17 Model Development

18 DR. NAMBIAR: All right. So seeing none, we
19 can go into our next topic, which is on "Lessons
20 Learned and Considerations for Animal Model
21 Development." We have four speakers in this session.

22 Our first speaker is Dr. Judith Hewitt, who is

1 the Chief of the Research Resources Section in the
2 Office of Biodefense Research Resources and Translation
3 Research in the Division of Microbiology and Infectious
4 Diseases at NIAID.

5 Dr. Hewitt's group is responsible for several
6 division-wide resources that provide research agents,
7 animal models, and screening services to facilitate the
8 development of vaccines and therapeutics or diagnostics
9 for infectious disease other than AIDS.

10 Dr. Hewitt.

11 Lessons Learned from the Development of Animal
12 Models of Inhalational Anthrax, Pneumonic Plague, and
13 Tularemia

14 DR. HEWITT: Thank you. I am going to tell
15 you today about an animal model of pneumonic plague. I
16 want to tell you first of all that this is one of the
17 lowest hanging fruits in terms of things that have been
18 accomplished under the Animal Rule and hopefully will
19 convince you that even though it was low hanging fruit,
20 it was still not simple or fast.

21 Here is my disclaimer. Very boring Federal
22 employee.

1 So I'm going to give you the bottom line up
2 front about what we were able to accomplish this. I
3 will later get into some individual animal data. Then
4 I'll do some study-to-study comparisons to convince you
5 of reproducibility of the model and how we compared
6 this animal model to human disease, and with some
7 recommendations, lessons learned.

8 This African green monkey model of pneumonic
9 plague is rapidly fatal. So I have two
10 fluoroquinolones plotted here on this same graph. And
11 so the control groups die quickly, in a matter of 3 to
12 5 days, where the treated animals -- and the treatment
13 is indicated by the bar across the top -- is very
14 effective. There was one animal in each of these
15 studies that died, one due to a catheter failure, so it
16 was not adequately dosed, the other one was sacrificed
17 because it had non-plague-related complications.

18 This timeline slide gives you a sense of both
19 the time that it took to conduct the studies as well as
20 get through the regulatory process with the Animal
21 Rule.

22 So early on -- and I want to draw your

1 attention to the scale of this timeline starting in
2 2002 and ending in 2016. So right after the anthrax
3 letters, an NIH/FDA working group got together, decided
4 on a number of already approved antibiotics that could
5 be tested in a model. The blue boxes are about the
6 funding stream. NIAID then opened up pre-IND file with
7 FDA in 2003 and began the work.

8 So the first thing we did was all the yellow
9 boxes along the bottom of this timeline show the actual
10 animal study work. The first thing we did was a
11 natural history study where we looked at the disease in
12 these African green monkeys. We did a number of PK
13 studies for the various drugs that we tested. And the
14 ciprofloxacin efficacy study was conducted around 2005.

15 We then did a number of additional natural
16 history studies in the 2007 to '08 timeframe because we
17 wanted to be able to test additional drugs at different
18 sites. The levofloxacin efficacy study was conducted
19 in 2009.

20 Our initial guidance from FDA was that it was
21 easiest to work with a drug sponsor. We had been
22 working with Johnson & Johnson on levofloxacin all

1 along. That drug was still under patent at that time,
2 and so we went with them to their pre-sNDA meeting
3 where FDA communicated their desires for what should be
4 included in the sNDA package. One of those things was
5 an additional PK study. I'm going to come back to
6 emphasis on PK later. So that's the last of the
7 levofloxacin PK studies there. Really, it was a
8 bridging study that addressed some concerns lacking in
9 the earlier studies.

10 So during these discussions then FDA came up
11 with a pathway for NIAID to submit generic drugs. So
12 we quickly put together the ciprofloxacin package in a
13 pre-IND, and both of these packages were submitted to
14 FDA around the same time, went to advisory committee
15 thereafter, and the levofloxacin sNDA was approved
16 within a month then. The cipro sNDA was approved
17 somewhat later due to the actual NDA holder, which was
18 not NIAID, putting together their package and updating
19 their label.

20 The other thing I want to point out here is I
21 also indicated moxifloxacin here as well. That
22 efficacy study was done in 2013, and that approval came

1 in 2015. So clearly, with all of the discussions that
2 we had on this animal model, we laid the pathway for
3 subsequent drugs to have a quicker route to approval.

4 So what did the sNDA submission look like?
5 400 megabytes and 250 files may not be very large in
6 typical drug development, but this is an Animal Rule
7 submission, and there is really no clinical trial data
8 in here. As Sumathi mentioned earlier, these are
9 approved drugs with a lot of clinical use. We didn't
10 have to do any new safety data. So 79 percent of the
11 submission went into Module 4. We have 18 reports that
12 are listed here along with references, datasets, case
13 report forms.

14 Then the important thing that we also
15 submitted was a white paper into the clinical module,
16 and this is where we described clinical disease and
17 compared clinical disease to animal disease, and I'll
18 come back to that.

19 So this is a summary of the four natural
20 history studies that we did in the African green monkey
21 model. The other thing that I need to point out is
22 that we struck gold with this very first model. We

1 didn't need to pursue a number of different animal
2 models. So what you can see here are the challenge
3 doses that we gave all of these animals and the mean
4 time to death and mortality across these studies. In
5 this slide, I want to point that in the very first
6 study we had two animals that survived the challenge,
7 but as you can see in the last column, those two
8 animals were neither bacteremic nor febrile. So what
9 we were able to establish here is a very good
10 correlation between bacteremia and fever as signs of
11 disease and correlating very well with mortality.

12 So here are some individual animal data from
13 that first natural history study. We monitored
14 bacteremia daily. We were limited in terms of the
15 number of blood draws that we can take from these
16 animals. So all of the animals that got sick were
17 bacteremic by 72 hours, and you can see the two
18 surviving animals that survived got lower challenge
19 doses and were never bacteremic during the course of
20 this study.

21 These animals also had telemetry implants, so
22 we were able to monitor a number of physiological

1 parameters in real time. So in this slide, I'm showing
2 you body temperature for two animals. The red upper
3 line is one of the animals that succumbed to disease,
4 and the blue lower line was one of the survivors that
5 got the lower challenge dose. And we also have
6 baseline data in addition to the data I'm showing you
7 here, which is just post-challenge.

8 And you can see a nice diurnal pattern in
9 temperature early after challenge, and that's disrupted
10 around 72 hours, which is the typical time that we see
11 fever in animals that get sick. There is some noise in
12 temperature here with a survivor, but that animal
13 returns to a typical diurnal pattern and survives.

14 This next slide shows you heart rate in those
15 same two animals. And what you can see here is there
16 is not quite the distinction between the survivor and
17 the non-survivor as there was in the temperature data.

18 We also measured respiratory rate in this
19 study visually. And what you can see here is that the
20 two animals that survived had a normal respiratory rate
21 throughout the study. But beginning sometime after 72
22 hours, really more in the 96-hour timeframe, the

1 animals that died of pneumonic plague had rapid and
2 dramatic increases in respiratory rate. Each of the
3 animals was anesthetized when they were showing signs
4 of clinical disease, around 80 or 83 hours. And so we
5 were able to take a chest radiograph at that time.

6 So this is the series from one of the animals.
7 So zero hour was at the time of challenge. An
8 independent blinded radiologist reviewed these
9 radiographs later, rated this one as normal. Then at
10 the 83-hour time point, the rating here was mild
11 disease. And then the last radiograph was taken just
12 prior to euthanasia of this particular animal, and the
13 independent radiologist rated this one as severe
14 disease.

15 So this slide puts together all of the
16 endpoints that we measured along with except for the
17 chest radiographs, this is the same animal. And so you
18 can get a sort of comprehensive picture of what's going
19 on. Around 72 hours or 76 hours, animals develop a
20 fever, and they're also bacteremic at this time point.
21 It takes more than 24 hours, typically 48 hours, to
22 culture the bacteria on a plate, so we really use the

1 telemetry indication of fever to give us a trigger to
2 treat in subsequent drug studies.

3 So now I'm going to show you comparisons
4 across the four natural history studies. So here is
5 the Kaplan-Meier survival across those studies showing
6 consistent time of death, typically in this 3- to 5-day
7 time range, where the highest challenge dose studies
8 resulted in death somewhat earlier than the later
9 challenge dose studies. And you can see the two
10 survivors here.

11 When we look at bacteremia across all of the
12 studies, we start to see some bacteremia on day 2. The
13 study -- the light blue bar at the far right there is
14 the highest challenge dose study, and in that case, all
15 of the animals were bacteremic on day 2, but the vast
16 majority of animals are bacteremic on day 3.

17 This graphic shows you the impact of challenge
18 dose on time to death. So you see something of a
19 relationship in that higher challenge doses lead to a
20 shorter time to death in this model. And that's
21 depicted again here in this slide, where we're showing
22 mean times by studies, so the left edge of each of

1 these bars is the mean time to fever in a study. The
2 right-hand edge of the bar is the mean time to death.
3 And so what we're showing here is the therapeutic
4 window in this model, which ranges from 30 to 40 hours.

5 We also had a pathologist review all of the
6 slides from all of these natural history studies. I'm
7 just showing you the lung pathology here. What you can
8 see is that in the 34 animals that were diseased, the
9 vast majority of them showed bacteria, edema,
10 hemorrhage, and inflammatory infiltrates in the lung.

11 So, again, all of this data taken together
12 summarized the clinical course of disease in the animal
13 models. I summarized this while a clinical colleague
14 went to the literature to find descriptions of human
15 disease because there really aren't that many cases of
16 pneumonic plague in these times.

17 But there was some information on outbreaks in
18 the modern era. There were significant outbreaks in
19 China in the 1800s, and a lot of those outbreaks were
20 transmitted through shipping routes, and we had some
21 outbreaks here in this country in the early '20s, and
22 there were excellent clinical descriptions at that

1 time. And I'm showing you here one of the references
2 that we used in our clinical description. This
3 publication from 1926 had very good descriptions of
4 human pneumonic disease. I need to point out that most
5 cases of infection with plague result in bubonic
6 disease, which is a less severe form.

7 So my clinical colleague used these
8 descriptions to summarize human disease. We treated
9 our drafts and were both astounded at what we were
10 reading and how it basically mirrored what we had just
11 written for the other species.

12 So here is a disease comparison of human
13 disease and African green monkeys. The time course is
14 the same, temperature is elevated in all cases.
15 *Yersinia pestis* is present. In the human cases, it was
16 mostly examined microscopically from sputum, whereas in
17 our animal studies, we were culturing from blood or
18 lung and nasal fluid. Heart and respiratory rate were
19 elevated in all of the cases. Pulmonary infiltrates
20 are seen in both models. And the lung pathology is
21 very similar.

22 So now to get into bridging from animals to

1 human in order to test these drugs. What's imperative
2 is that you can use human PK information to determine a
3 dose to give animals that gives you a similar PK
4 profile so then when you test animal efficacy, you can
5 be assured that you are not exceeding the drug profile
6 that you would expect to see in humans. And then, of
7 course, you are trying to convince the FDA that this
8 translates into human efficacy, the question marks here
9 reflecting that we may never really know how effective
10 these drugs are in humans.

11 So what did we learn throughout this decade-
12 long program? We need to talk to FDA early about the
13 selection of an animal model and the correlation to
14 human disease. We were in constant communication with
15 FDA about this. The correlation to human disease in
16 this particular case we wrote up closer to the end of
17 the program. FDA would like to see that earlier.

18 You need to standardize methods and reagents
19 as early as possible. We did this to a large extent.
20 Quality in how the animal studies are conducted is
21 extremely important. And the pharmacokinetics are also
22 extremely important. If there was any weaknesses in

1 any of our studies, it really came in this
2 pharmacokinetic bridge. And there are some suggestions
3 here for how you should pay attention to that.

4 And my last point here is that pivotal Animal
5 Rule studies replace Phase 3 clinical trials. And so
6 it's really important to understand that the
7 expectation around these animal studies on FDA's part
8 are really the same as how they would treat Phase 3
9 clinical trials. Blinded, randomized, case report
10 forms on individual subjects, validated assays: all of
11 that is really important as you're thinking about these
12 Animal Rule studies.

13 So this slide really recapitulates many of the
14 same points, but it's a little more forward looking.
15 If you were beginning a program, how would you go about
16 this?

17 So first you have to understand the human
18 disease that you're trying to model, including the
19 route of infection. As you develop that animal model,
20 it's important, as a community, to identify the
21 relevant strain that you want to use, characterize that
22 strain well, and use master and working banks of those

1 strains.

2 You need to select one or more species that
3 are going to be most relevant to humans. In our case,
4 we were very fortunate that we hit that with the very
5 first species we worked on.

6 You need to collect data to identify relevant
7 endpoints. I showed you some of our data on fever and
8 bacteremia.

9 You need to establish the reproducibility of
10 your model. A model isn't a model if it only works in
11 one laboratory.

12 Ideally, you would have proof of concept for
13 intervention and be able to establish a trigger for
14 treatment.

15 I can't emphasize the selection of an
16 effective dose. Again, this is where PK becomes
17 extremely important, and the quality systems to support
18 efficacy testing of these drugs under GLP is also
19 extremely important.

20 My colleagues wanted to emphasize some of the
21 timelines around conducting these kinds of studies, so
22 we came up with a generic timeline for GLP challenge

1 efficacy study. There are ranges here for different
2 models. And you can see that it takes anywhere from 6
3 to 24 months to conduct one of these studies.

4 Clearly, the complexity increases as you are
5 going up in species. You can have savings of time if
6 you can overlap some of these different phases of the
7 studies, or obviously if a study is more complicated,
8 that's going to lead to increased times to get your
9 final study report.

10 And with that, I will stop and thank you for
11 your attention.

12 DR. NAMBIAR: Thank you, Dr. Hewitt.

13 Our next presenter is Dr. Meister, from the
14 Battelle Biomedical Research Center. Dr. Meister has
15 more than 15 years of research experience in viral and
16 bacterial pathogenesis and in supporting medical
17 countermeasure development. Dr. Meister currently
18 serves as a principal investigator on multiple U.S.
19 Government-funded programs that are focused on
20 developing in vivo models of infectious diseases and in
21 assessing efficacy of candidate treatments against
22 biodefense pathogens.

1 Dr. Meister.

2 DR. MEISTER: Thank you very much. Thanks to
3 the organizers for allowing me to be here today. It is
4 an honor to talk about some of the work that I was
5 fortunate enough to participate in over the past decade
6 or so.

7 I'll start with my disclosure statement. I do
8 work for Battelle. We are a nonprofit organization,
9 and we do provide contract research services to
10 numerous government and commercial entities. I don't
11 have any personal financial conflicts of interest. I
12 have no financial relationships with any of the
13 companies we do work for or investments in any of
14 products that we test.

15 And that kind of leads me into kind of another
16 caveat. I'm going to be talking about Bacillus
17 anthracis in inhalational anthrax. And a disease, from
18 a bioterrorism perspective, was pretty well studied,
19 leading up to the development efforts of a therapeutic
20 animal model. And so I will say we -- and when I say
21 "we," the folks, to include U.S. Government, sponsors,
22 the regulatory agency, the CROs, like Battelle,

1 performing the work in the BSL-3 laboratories, and the
2 product sponsors developing the products -- had a
3 pretty good foundation of information regarding the
4 pathology of the disease, some of the animal models
5 that were available. And so really I'm going to talk
6 today about how we kind of refined and tried to
7 optimize what we had at the time to suit the needs of
8 the product sponsors, the regulatory community, and
9 U.S. Government in building stockpile needs.

10 That being said, we're all well aware of what
11 happened in 2001, and this initiated obviously an
12 onslaught and a lot of research interest in
13 understanding what we had available to combat Bacillus
14 anthraxis and inhalational anthrax considering, despite
15 the best medical care, about 50 percent mortality rate
16 following Amerithrax attacks.

17 There was obviously an unmet medical need.
18 There were some programs evaluating vaccines, so some
19 antimicrobials. And at the time, antibody passive
20 protection of monoclonal antibodies or immune globulin
21 therapies -- and I make a distinction here when I talk
22 about treatment indication.

1 I believe in 2002, 2003, 2004 timeframe, there
2 was I think an emphasis put upon vaccination in the
3 sense that if we were to immunize, we could probably
4 protect the general population with an effective
5 vaccine, but I think that also became very clear that
6 that was going to be very costly, very time-consuming,
7 and there was a lot of pressure I think to prepare us
8 for the, quote, next attack if there were to be one.

9 And so there was a renewed emphasis put on
10 optimized treatments, therapeutic treatments
11 specifically. And so when moving into that area, we
12 were fortunate in understanding kind of the mechanisms
13 of pathology, for those of you not familiar with
14 Bacillus anthraxis and what the toxin does. And I will
15 caveat my talk today, I am going to be focusing on the
16 work that was done for the monoclonal antibody that was
17 developed, the monoclonal antibodies that were
18 developed, for the treatment of inhalational anthrax.
19 It was predominantly based on the toxin.

20 And so we heard earlier about the Animal Rule
21 and having to understand the pathogenicity of the
22 disease, having to understand clearly how your product

1 ameliorates that disease process. You've got to be
2 able to demonstrate the effectiveness of your product
3 in multiple animal models that would reliably predict
4 an outcome in humans. You have to have a very well-
5 defined endpoint. And then you have to link kind of
6 your PK -- you have to have a firm understanding of
7 what your pharmacokinetic profile is so that you can
8 bridge what you're observing in animals from an
9 efficacy perspective to what you're seeing in humans
10 from a PK perspective.

11 And so we knew that inhalational anthrax was a
12 toxin-mediated disease to some degree, and there was
13 some initial work suggesting that utilizing an
14 antitoxin shortly after infection or exposure to
15 *Bacillus anthracis* via the inhalational route of
16 exposure could be efficacious, it could actually
17 improve survival rates quite substantially.

18 I think some of that early work was questioned
19 because it was early intervention. We saw a case in
20 2001 where I think the data strongly suggested the
21 longer you wait, the less effective the current
22 standard of care was. And so I think there was an

1 emphasis put on developing an animal model in which we
2 could begin to understand treatment after diagnosis,
3 what the effect of these products would be. And so
4 this mechanism of pathology and knowing this helped us
5 when working with the monoclonal antibodies.

6 But as we began to think about modeling
7 therapeutic treatment, there were I'll call a few
8 requirements that were asked of us. We have to define
9 the disease at this point in time, early 2000s. I
10 think there were a few publications out in the animal
11 models clearly articulating the pathology, the terminal
12 pathology, observed, and I think there were very strong
13 links between the bacteria, the toxin, and those
14 pathological observations, and many of those were very
15 consistent with the limited clinical cases that we had.

16 But there was a gap. There was I think a lack
17 of understanding of what occurs at the time of exposure
18 to the time of, quote, presentation, if you will. And
19 so some of the work that I'll talk about today is what
20 we did to define the disease progression, at least in
21 New Zealand white rabbit.

22 And in addition to that, at the time of this

1 model development initiation, there were two ways in
2 which we thought about potentially diagnosing the
3 disease, a chest x-ray in a rabbit and/or a positive
4 blood culture. In a truncated disease such as 3 to 4
5 days until animals succumb to disease, waiting 16 to 24
6 hours for a positive blood culture could severely
7 hamper the perceived effectiveness of a product. And
8 so there was a lot of work put into developing a rapid
9 diagnostic that could be used somewhat as a surrogate
10 for a blood culture, and I'll talk a little bit about
11 that later on.

12 And then I think one of the things that we
13 heard clearly from a CRO perspective from both the
14 product sponsors, the government sponsors, as well as
15 the regulatory world, was we want to mimic a clinical
16 scenario.

17 I think the Animal Rule strongly suggested
18 that you need a model that mimicked what was observed
19 in human cases, and that included clinical
20 presentation. Were you able to diagnose these subjects
21 as well as appropriate timing of medical countermeasure
22 intervention? Was that going to mimic what was likely

1 to occur upon presentation? And I will caveat all of
2 this by saying that the understanding of the clinical
3 scenario was really based on a very limited clinical
4 database.

5 So I'll move to some of the work that we did.
6 The details of this particular graph and the lines I
7 don't think are critically important. What I want to
8 impress upon you is that we collected as much data from
9 the New Zealand white rabbits as we possibly could.
10 The top left graph represents body temperatures that
11 were collected on an hourly basis.

12 We looked at CBCs, to include total white
13 blood cell counts and the neutrophil-lymphocyte ratio
14 in the top middle and top right graphs.

15 CRP as a nonspecific indicator of inflammation
16 was assessed, bottom left panel.

17 We did cage-side observations every hour
18 beginning roughly 12 hours post-exposure.

19 And then bottom right, we collaborated at the
20 time very initial stages of the animal model
21 development program with the CDC to evaluate
22 circulating LF levels.

1 And we looked at this data and we said, wow,
2 that's very intriguing, we see these changes, we see
3 this increase in body temperature, we see this
4 phenomenon which we observed was a decrease in total
5 white blood cell count, increase in CRP and NL ratio,
6 fairly consistent albeit individualized onset of
7 clinical observations. And this hallmark increased
8 plateau, and then secondary increase in circulating LF
9 levels.

10 And in looking at each parameter
11 independently, it was kind of a neat finding to
12 observe, but when we pulled all of them together, we
13 defined the disease progression.

14 And so to orient you with this particular
15 figure, I've taken all of those parameters and I've
16 added to that a positive bacteremia culture on the top
17 axis to illustrate in black the body temperature
18 profile.

19 So the body temperatures increase at roughly
20 24 hours post-exposure. They seem to correlate very,
21 very well with a positive bacteremia culture, which I
22 will admit is actually confirmed retrospectively

1 because we do have to wait roughly 24 hours for a
2 positive blood culture.

3 And both of those correspond with an increase
4 in LF, which is illustrated here in pink. And many of
5 those fall in line with changes that are -- other
6 clinical changes to include CBC serum chemistry changes
7 that were also alluded to in 2001, or at least observed
8 in 2001, alluded to as maybe predictors or at least
9 correlates of inhalational anthrax infection.

10 And so what we did is we took the data from
11 the exposed animals and we compared them to
12 unchallenged New Zealand white rabbits, and there was a
13 distinct clinical profile. And now we wanted to be
14 able to use that clinical profile, diagnose subjects on
15 an individual basis, and then intervene with a medical
16 countermeasure.

17 And so those were our next steps, demonstrate
18 that that anthrax antitoxin treatment following
19 confirmation of disease was effective, and then
20 evaluate the PK of an antitoxin in the context of the
21 disease because to that date, the PK of the product was
22 observed in healthy human individuals as well as naive

1 New Zealand white rabbits.

2 And then some of the constraints, traditional
3 diagnosis of inhalational anthrax was impractical, and
4 so we did spend a lot of time with NIAID and some of
5 the product sponsors developing a surrogate diagnostic
6 assay that actually detected circulating PA that
7 correlated extremely well with positive blood cultures.

8 And then I will say that in any animal model,
9 there are limitations in data collection, and so we had
10 to work very closely, depending upon the objective of
11 the studies, to prioritize the data and the data type
12 as necessary.

13 And so this is just a Kaplan-Meier curve
14 representing the results that we observed when we
15 tested raxibacumab in New Zealand white rabbits as part
16 of the pivotal monotherapy study. The green line and
17 the red line represent survival in the two dose groups,
18 active treatment arms. The black line represents
19 survival observed in the placebo-treated controls.

20 And so we did not do this data, but I put this
21 up here to try to illustrate how the product sponsor
22 looked at the pharmacokinetic profile of the monoclonal

1 antibody to orient you with this. The red lines
2 represent the pharmacokinetics observed. And then the
3 orange and the green line represent the actual terminal
4 levels of PA or toxin in circulation that were observed
5 in the studies that were conducted leading up to the
6 efficacy study, trying to demonstrate that there was
7 coverage of the monoclonal antibody over the toxin
8 throughout the course of the disease.

9 This data was taken to the FDA during an
10 Anti-Infective Advisory Committee meeting. And when
11 discussed and kind of looked at in detail, there were
12 actually two additional observations made, the first of
13 which was when you looked at inflammation or the
14 inflammatory response in the meninges, in treated
15 animals that succumb to disease, we actually saw an
16 increased observation of inflammation compared to the
17 placebo-treated animals that succumb to disease,
18 potentially suggestive that there is something going on
19 that needed to be further investigated.

20 And in addition to that, many of I think the
21 Advisory Committee panelists wanted to see more
22 information regarding the clinical scenario, and the

1 clinical scenario being that a monoclonal antibody was
2 not likely to ever be administered by itself, but
3 actually in combination with antibiotics.

4 Studies had been run to evaluate that, but
5 those intervention times were actually optimized at the
6 time of diagnosis, and you can see from the bottom
7 right graph that levofloxacin alone compared to
8 survival with raxibacumab plus levofloxacin were
9 actually the same.

10 And so there was no really data available at
11 the time to suggest or support the fact that a
12 monoclonal antibody when given in combination with
13 antibiotics would be potentially additive or superior
14 or provide an improvement over antibiotics alone. And
15 so that started a whole new quest for information and
16 refinements to the model as they were currently used.
17 And the goal was to demonstrate that the antitoxin
18 added benefit to antimicrobial treatment alone.

19 There were some constraints or some requests.
20 A marginal outcome following treatment with antibiotic
21 alone was a request based on the 2001 experience. We
22 were asked to use a humanized dosing of antibiotic.

1 And then the third pillar of that stool being
2 statistical significance observed or a statistically
3 significant improvement in survival observed in the
4 combination treatment versus antibiotic treatment
5 alone. And I will say that moving into this or going
6 into this, we felt strongly these were going to be high
7 hurdles to overcome.

8 And so when we thought about the designs of
9 the study, we took into account three things:
10 antibiotic dose, antibiotic duration, and treatment
11 intervention time.

12 And so looking at this scale, if we're looking
13 at the New Zealand white rabbits, the top line
14 represents when we might administer antibiotics. The
15 second layer is the dose that you're going to provide.
16 And then the third layer is how long you're going to
17 provide it. And I think in the first few studies that
18 were conducted looking at this potential added benefit
19 of antitoxins, PEP, or post-exposure prophylactic,
20 dosing was administered. So antibiotics were given
21 actually early, 7 to 12 to 18 hours post-exposure; an
22 optimal dose, and when I say "optimal dose," it was a

1 dose that was I think close to a pharmacokinetic
2 profile that you would see in humans; and then a short
3 course of antibiotics to mimic kind of patient
4 compliance.

5 When we did this, we realized that we weren't
6 given the antibiotics in a therapeutic setting. The
7 dose was close to humanized. Outcome, survival
8 outcome, observed after cessation suggested that
9 animals that succumb to disease were likely succumbing
10 to disease because of a lack of antibiotic coverage in
11 a later portion of the disease progression. But we did
12 observe added benefit. Unfortunately, this did not
13 meet the three requests of the model.

14 And so we looked at therapeutic dosing, and
15 that would be dosing upon diagnosis. We kept the dose
16 and the duration. The dose was close to humanized.
17 Antibiotic efficacy was near 100 percent, and,
18 therefore there was no margin of error or margin of
19 difference that we could observe, therefore, no added
20 benefit could be concluded.

21 And there was, I guess, a potential for
22 assessing antagonism, which I think was a discussion

1 held at some level.

2 And then, lastly, we tested delayed treatment.

3 And so we gave a dose that was close to humanized. We

4 looked at the efficacy of the antibiotic, and if we

5 delayed dosing long enough, we could get near 50

6 percent survival in the antibiotic treatment alone.

7 And then we actually did observe an increase

8 or an improvement in survival empirically. I will note

9 the P factor, or you will note the P value, is not near

10 0.5, as we had hoped to achieve, but we did observe an

11 increase in survival in combination treatment versus

12 antimicrobial treatment alone.

13 So with that, just to summarize, we were --

14 and when I say "we," all of us in the MCM community

15 that were working on this particular problem -- did

16 have historical data that was the foundation of

17 optimizing the models that we eventually used to assess

18 efficacy.

19 The indication of the product dictated the

20 development pathway. We knew how the products were

21 going to -- or we thought we knew how the products were

22 going to be utilized, and we tried to develop animal

1 models that would mimic that. Many iterations were
2 required before we got to the final model.

3 I can't overemphasize enough that a quality
4 management system was critical to the successful
5 regulatory review of these studies. We put a lot of
6 time and effort in documentation practices,
7 verification, accuracy, data integrity, and I can tell
8 you sitting across the room from FDA inspectors, having
9 to run GLP efficacy studies, not just safety tox
10 studies, is a very stressful situation, but in the end
11 I think the data stood for itself.

12 And then, lastly, this was a collaborative
13 effort. This wasn't anything that was done by a single
14 entity or organization. It was done by many, many
15 people, not only at Battelle, but across the MCMI. So
16 to that end, I just want to acknowledge the Battelle
17 team, the U.S. Government agencies, all of which that
18 participated, and obviously the product sponsors.

19 Thank you.

20 DR. NAMBIAR: Thank you, Dr. Meister.

21 So our next speaker is Dr. Julie Hutt, who is
22 a veterinary pathologist with over 15 years of

1 experience developing small and large animal models for
2 infectious diseases. Dr. Hutt is currently at the
3 Lovelace Respiratory Research Institute, and she has
4 been there since 2002.

5 Approaches and Important Considerations in
6 Animal Model Development for Bacterial Infections

7 DR. HUTT: Thank you. And, again, thank you
8 to the organizers for inviting me. Today I'm going
9 talk about the development of a non-human primate model
10 of inhalational tularemia. We developed this animal
11 model, non-human primate model, of inhalational
12 tularemia. The work was performed over approximately a
13 4- to 5-year period, and it was funded by NIAID.

14 I have a quick disclosure statement. Like
15 Gabe, I work at an entity that performs regulated
16 research for commercial and government sponsors, but I
17 have no financial conflicts of interest myself.

18 So an overview of tularemia in humans at
19 least. It's caused by the species *Francisella*
20 *tularensis*, subspecies *tularensis*, the type A strains.
21 The clinical presentation in humans generally takes one
22 of six forms, with the glandular and ulceroglandular

1 form being the most common, and the pneumonic form
2 being generally the most deadly.

3 I should also mention here that there are
4 currently no new drugs or vaccines under regulatory
5 review, so my focus today will be on the animal model
6 development process and qualification process. I
7 wanted to mention that once the model has been
8 qualified, it will be available for use by the general
9 scientific community for developing and submitting new
10 vaccines and therapeutics under the Animal Rule.

11 So for our studies, similar to anthrax, we
12 were fortunate to have a pretty substantial historical
13 database from work that was done in the '40s through
14 the '60s as part of the bioweapons program. We
15 selected our strain as the highly virulent SCHU S4
16 strain. And we selected the cynomolgus macaque as our
17 primate species.

18 As I said, there was abundant historical data
19 on primarily using rhesus and cynos back from the '50s
20 and '60s. At the time that we started these, the cynos
21 were much more readily available for the studies than
22 rhesus macaques were. And they're also a very robust

1 species to use in the laboratory.

2 We sourced our animals from mainland Southeast
3 Asia. We specifically aborted the animal source from
4 the island of Mauritius because these animals have been
5 geographically isolated for many years, and they have
6 developed some unique and distinct immunologic
7 characteristics that aren't necessarily representative
8 of the species. All monkeys were prescreened for pre-
9 existing humoral and cell-mediated immunity prior to
10 initiation of the studies.

11 Our approach, as I said, based upon the
12 abundant historical literature, was first to establish
13 an LD50 in cynos after head-only inhalation exposure to
14 aerosolized SCHU S4 and then to follow that up with a
15 natural history study in which we had one arm of the
16 study in which the animals had surgical telemeters
17 surgically implanted to measure heart rate, respiratory
18 rate, and core body temperature. And then we had a
19 second series of studies that we did where we
20 euthanized animals at predetermined time points for
21 blood collections for hematology, clinical chemistry,
22 and quantitative microbiology.

1 So for our LD50 study, we used 28 male and
2 female cynos. They were approximately 2 years of age,
3 2 to 3 years of age. Our presented doses ranged from 1
4 6
5 to up to 10 CFUs with particle size of 1 to 3 microns.
6
7 Death occurred on these studies between day 3 and day
8 46 post-challenge. And our calculated LD50 was less
9 than 10 colony-forming units.

10 What we discovered from the LD50 studies was
11 that the clinical presentation, the disease course,
12 time to fever and death were highly dependent upon the
13 challenge dose, not surprisingly. Animals that were

14 5 6
15 challenged with the very highest dose ranges, 10, 10
16 CFUs, generally died within 3 days. Their clinical
17 signs were dominated by the clinical signs related to
18 the respiratory tract, and they had a severe
19 bronchopneumonia at death.

20 The animals exposed to the lowest clinical
21 doses, on the other hand, less than 100 CFUs generally,
22 they animals could survive up to 6 weeks. Death was
primarily attributed to the disseminated disease in the
liver and spleen. And the clinical signs were
primarily related to anorexia, weight loss, and just a

1 generalized malaise.

2 All animals had pleuritis. All animals had
3 pyogranulomatous to necrotizing lesions in the lungs
4 and other organs after dissemination. The lesions
5 varied in chronicity depending upon how quickly the
6 animal died after exposure. Overall, the lesions were
7 similar to what has been reported in the literature for
8 the human disease.

9 So this example shows some of the great lung
10 lesions that we got, and shows some of the extremes of
11 the disease. On the left, the animal shown here has a
12 very multifocal pneumonia. This animal was exposed to
13 30 colony-forming units and survived for 10 days. As I
14 said, the lesions were fairly well distributed. Most
15 of the lung is relatively normal here, and the lesions
16 were very chronic. This animal had very extensive
17 lesions in the liver and spleen.

18 The animal on the right was exposed to over
19 300,000 colony-forming units and survived for less than
20 3 days. This animal had very few lesions in the liver
21 and spleen, but as you can see here, a very extensive,
22 very acute bronchopneumonia at death.

1 However, both animals died from tularemia.

2 So from the LD50 studies, we selected a target
3 challenge dose of 1,000 CFUs. Part of the rationale
4 for this was to be able to -- 1,000 CFUs was a
5 reproducible dosing regimen. It produced a
6 reproducible disease and reproducible time to death.
7 It allowed the animals to survive long enough for us to
8 actually be able to intervene and evaluate and compare
9 the efficacy of vaccines or therapeutics.

10 And the other reason we chose this again goes
11 back to the historical database. There were studies
12 done in the '50s in both humans and in macaques where
13 they were testing the efficacy of the live vaccine
14 strain, and they used a challenge dose of 1,000 CFUs in
15 both the humans and the monkeys.

16 So for the first part of the study, we had the
17 animals implanted with telemeters to measure core body
18 temperature, respiratory rate, and heart rate. What we
19 saw again was a fairly consistent fever onset between 2
20 to 3 days post-exposure, with that loss of diurnal
21 variation in core body temperature. This correlated
22 with an increase in heart rate and respiratory rate.

1 As the disease progressed and the animals got
2 sicker and sicker, their core body temperature
3 eventually started to decrease as they approached
4 death. This later became useful as a euthanasia
5 criteria for subsequent studies.

6 And, again, one of the things that we
7 identified, as was done for the plague studies, was
8 that the onset of fever became a very useful and
9 consistent feature for later antibiotic efficacy
10 studies as a trigger to treat.

11 So this shows some of the data from the
12 telemetry studies. On the top is a summary of the
13 results for the 12 animals. As you see, the average
14 time to fever onset was 47 hours plus and minus 4, and
15 the average time to death after that was 113 hours
16 after the onset of fever. And this was pretty
17 consistent and resulted in the death of the monkeys
18 generally between 6 and 7 days.

19 On the bottom left, you see the variation in
20 core body temperature. The time of exposure to
21 tularensis is marked at the bottom as the challenge
22 time. You can see the normal diurnal pattern that we

1 monitored for 6 days prior to challenge, and then at
2 about 48 hours, the loss of that normal diurnal
3 variation with the onset of the febrile response. And
4 then out at about 160 hours, the core body temperature
5 began to decrease as the animal was essentially cooling
6 down to room temperature.

7 The two slides to the right of that show the
8 corresponding for the same individual animal, changes
9 in C-reactive protein. It's a measure of the acute
10 phase response. And increase in white blood cells,
11 particularly neutrophils, that increased again in that
12 same 2- to 3-day timeframe.

13 So the next part of the natural history
14 studies were done as, as I said, essentially a serial
15 pathology study. We had 16 monkeys, and we euthanized
16 four each on days 2, 4, 5, and 6 post-challenge. We
17 did quantitative blood and organ culture. We did gross
18 and microscopic pathology on all of the organs.

19 What this showed us, again, it was very useful
20 in that it showed that there were multiple portals of
21 entry after head-only exposure, not just the lungs,
22 which isn't surprising in retrospect.

1 Many of these animals had secondary bacterial
2 infections in the nasal cavity associated with
3 presumably commensal staphylococci. We saw local
4 inflammation initially at the initial site of
5 deposition. This was followed in time by progressive
6 inflammation of the draining lymphatic vessels, and
7 followed in time again by progressive inflammation of
8 the draining lymph nodes, and ultimately resulting in
9 hematogenous dissemination to macrophage-rich tissues,
10 such as the liver, spleen, bone marrow, and other lymph
11 nodes in the body.

12 And, again, in this study, it correlated with
13 increased white blood cell counts, activation of the
14 acute phase response between 48 and 72 hours. And
15 terminally, fairly consistently an increase in liver
16 enzymes, as these animals had fairly substantial
17 necrotizing inflammation in the liver.

18 So the challenges and lessons learned, don't
19 laugh, some of them seem very obvious now, but they
20 weren't necessarily at the beginning of these studies.

21 Having a well-characterized starting material,
22 in vitro growth conditions, and aerosol generation

1 conditions is really, really critical for
2 reproducibility of your disease model.

3 Related to the aerosol challenge, again, the
4 presented dose is a calculated dose. It's based on
5 plethysmography. The amount deposited and the location
6 of deposition vary significantly with breathing rate
7 and depth, which, in turn, varies with the depth of
8 anesthesia of the monkey.

9 The particle size dramatically influences the
10 site of deposition and ultimately the LD50. The
11 particle sizes we used in our studies were -- we were
12 targeting between 1 and 3 microns. If you get up to
13 larger size particles, 5, 10 microns, and above, you're
14 going to be depositing higher in the respiratory tract
15 as opposed to the deep lung, which means your
16 mucociliary clearance is going to be greater and your
17 LD50 is going to go up.

18 And then, as I said, it's obvious to us now,
19 but head-only challenge allows the organism a portal of
20 entry, not just from the tracheobronchial tree in the
21 deep lung, but also from all other mucosal surfaces
22 that were exposed to the agent.

1 From the standpoint of telemetry, some of the
2 things we learned were with respect to where the chips
3 or where the probes were implanted. Initially we
4 planted the probes on the diaphragm. Well, if you get
5 an animal with extensive pleuritis, as the disease
6 progresses, they're going to start to breath much more
7 shallowly, which means that the diaphragmatic
8 excursions are going to be less, and you're going to
9 lose your signal.

10 We did some studies where we compared
11 subcutaneous temperature chips to telemetry to detect
12 the onset of fever, and, again, it's obvious now that
13 when you're implanting a temperature chip in the
14 subcutaneous region, at the onset of fever, you're
15 increasing the core body temperature, so the sub-Q
16 chips really aren't going to work very well because
17 it's shunting that blood away from the skin.

18 And then also realize that human activity in
19 the room is going to impact some of the physiologic
20 parameters that you're measuring. So in our case,
21 heart and respiratory rate pretty consistently went up
22 when we had people in the room cleaning cages.

1 Prioritize your sampling. In these monkeys,
2 we took blood samples over a few days up to daily for
3 the first week. We calculated that we could collect 2
4 mls of blood from each animal based upon their body
5 weight, using a publication that describes what I refer
6 to as the Diehl guidelines.

7 The Diehl guidelines for blood collection are
8 written for healthy animals. Animals with a subacute
9 to chronic inflammatory disease don't regenerate the
10 way that a healthy animal would. So you just need to
11 monitor your hematocrits in real time and prioritize
12 the sampling because you don't want to continue to be
13 drawing blood from an animal with a hematocrit of 15
14 percent, or you're going to be impacting the course of
15 the disease.

16 I can't stress enough then also the
17 establishment of endpoints for these types of studies.
18 I cringe when I see the term "moribund euthanasia"
19 because "moribund" has very dramatic differences in
20 meaning to different people. Use a clinical
21 veterinarian for the first studies to really get a good
22 handle on what is a good indicator of when it is time

1 to euthanize. And then once you establish those
2 euthanasia criteria, be very consistent in following
3 them.

4 And, finally, this is from the perspective of
5 the pathologist, collect tissues widely for
6 histopathology. If you aren't looking at tissues,
7 you're not going to see lesions in them. Keep in mind
8 that the studies will eventually be used to detect --
9 to examine the safety of your test article, of your
10 antibiotic, as well as the efficacy. So you're going
11 to want to have a very broad list of tissues that
12 you're examining.

13 In our case, it helped us to identify that
14 there were multiple portals of entry, it helped us to
15 explain some of the differences that we saw in clinical
16 presentation in the disease course with differences in
17 initial dosing. And it also helped us to identify some
18 potential background infections.

19 Monkeys, in particular, are not pristine
20 inbred animals. Background lesions and infections can
21 impact the disease outcomes. There's a very good
22 example in the literature describing a nosocomial

1 infection of an indwelling catheter with Serratia for
2 anthrax studies in an African green anthrax study, in
3 which case animals that were not being treated and
4 should have died did not die, and it was primarily
5 because of nonspecific immune stimulation from the
6 indwelling catheter contamination.

7 We had a similar experience, at least we think
8 we had the similar experience, with the "tuli" studies
9 in that we had one set of studies where the housing
10 facility where we purchased the animals had had an
11 outbreak of Chagas disease, and the animals, in fact,
12 when we went back and looked at some of the tissues
13 around the heart, the animals did show evidence that
14 they had previously been infected with Chagas.

15 And, finally, as Gabe mentioned, these are
16 very large studies, and it's really a team effort. And
17 thank you.

18 DR. NAMBIAR: Thank you, Dr. Hutt.

19 So our last speaker for this session needs no
20 introduction. Dr. Edward Cox is the Director of the
21 Office of Antimicrobial Products at CDER, FDA.

22 DR. COX: Thanks, Sumathi. And I'm just going

1 to make a few comments here from the table. And for
2 folks that are watching on the webcast, I don't have
3 slides. I'm just going to speak a little bit here.

4 And I want to just first start out by thanking
5 Judy, Gabe, and Julie for really the excellent work and
6 the description of all that was done in the animal
7 model development work that you've done, and to thank
8 all the folks that have come here to join us today.

9 And when we started out on this, folks may
10 notice we've got colleagues from NIAID and BARDA at the
11 table, and we brought this idea to them, and the good
12 news it was is that it was enthusiastically embraced,
13 in fact, the response we got from the NIAID and BARDA
14 folks is, "Yeah, we're already thinking about this,
15 we're glad you called."

16 So it's good to have everybody trying to work
17 through this, and also the industry folks that have
18 been pushing along and trying to help us in thinking
19 about potential solutions for species-specific drugs
20 for *Pseudomonas aeruginosa* and *Acinetobacter baumannii*
21 to try and solve these problems.

22 I'll ramble a little bit, but I think I'll try

1 and make some points that I hope are of interest to
2 folks. And I thought we would first talk about some of
3 what we just heard in the presentations. And as you
4 can see, there was really a lot of work that went into
5 developing the animal models described.

6 And one thing that is I think noteworthy in
7 these particular animal models is that the particular
8 pathogen that folks are working with is intrinsically
9 virulent in the animal models, and that helps a lot.
10 It helps a lot when you're trying to get to a lethal
11 animal model that in fact you have an organism that is
12 highly pathogenic in the animals.

13 And if you look at the animal models for
14 anthrax, they were able to develop animal models that
15 if you line up the sequence of events, the tissue
16 pathology, and what's going on, many features of the
17 disease, there's a lot that seems really quite similar
18 to what we see in humans. And we've been able to use
19 these models really to evaluate the efficacy of both
20 antibacterial drugs and antitoxins, so they've been
21 particularly useful.

22 And another thing that comes into play or

1 another factor to think about is that at least for
2 antibacterial drugs, oftentimes we know about their
3 utility in the treatment of other human infections.
4 It's also another very important piece of information
5 to be thinking about the antibacterial drugs that are
6 approved for post-exposure prophylaxis of anthrax or
7 plague, they're approved for a number of other human
8 infections that occur every day, and that occur in many
9 of the same body sites.

10 Similar to what we learned about the anthrax
11 animal model, the plague animal models, again shows
12 many similarities to human disease, and that again
13 helps. And we've similarly been able to use that model
14 for the approval of some drugs in the evaluation of
15 their efficacy.

16 So these are some of the cases that are
17 probably most amenable to the development of animal
18 models of infection because of the intrinsic virulence
19 of the organisms that we're dealing with here. In
20 essence, you don't need to fight mother nature in order
21 to develop an animal model of infection.

22 And one last comment before we leave plague

1 and anthrax and things of that nature, we often think
2 about these organisms in the setting of bioterrorism,
3 but if you think about at least plague, there are, in
4 fact, opportunities and folks who have done some
5 clinical trials out there in the real world. Clinical
6 trials are usually small, difficult to do, take a long
7 time, but there are some studies out there, including a
8 prospective trial, mostly cases of bubonic plague, so
9 it's not inhalational route of exposure.

10 So it's really not that no clinical assessment
11 can be done, it's really more that doing a powered
12 study, even if you accept a fair degree of uncertainty,
13 is not really practically feasible for these
14 conditions. So you can see that there are some
15 diseases that have some degree or some component of
16 disease that occurs naturally, but it's really still
17 not practically feasible to conduct a clinical trial
18 where the Animal Rule has been applied.

19 And even in situations where the animal model
20 is similar in many ways to the disease in humans, there
21 still really is a considerable degree of uncertainty as
22 you're extrapolating to humans. And to some extent,

1 that can be minimized to a significant degree if you
2 have a drug that is approved for a variety of other
3 indications in humans, based upon evidence from human
4 clinical trials.

5 Now, I want to transition just a little bit
6 and talk about an area that may be less familiar to
7 folks that have been particularly involved in the area
8 of antibacterial drug development, and that's some of
9 the issues that have been encountered as we've tried to
10 evaluate the work that's gone on out there to develop
11 animal models for viral diseases.

12 And for the purposes of illustration, it's
13 probably most helpful to jump to one of the most
14 challenging circumstances, and that is the development
15 of animal models for smallpox, you know, a unique
16 pathogen that's been eradicated and has really a
17 tremendous specifies specificity for humans.

18 We had a workshop and an advisory committee
19 meeting to talk about smallpox drug development,
20 smallpox animal models, that would be utilized to
21 evaluate drugs. And just in general, the process
22 served us well because we had a particularly

1 challenging issue to try and solve, so starting with a
2 workshop, discussing some of the science, moving
3 towards an advisory committee.

4 It would provide an opportunity for
5 transparency, for learning, and sharing with the world
6 what some of the challenges are and what some of the
7 solutions are and what some of the options are for
8 solutions and why in this circumstance it's a
9 reasonable way to proceed.

10 And you can see here, the pathogens we're
11 dealing with today are not smallpox, but you can see
12 we're trying to use a similar process to solve some of
13 these problems.

14 So we've mentioned really the strong species
15 specificity of smallpox for humans, and if you want to
16 take variola virus, smallpox virus, and to cause
17 pathogenesis, a lethal model, in non-human primates,
18 you essentially have to give a huge dose of smallpox

8

19 virus. You have to give like 10 plaque-forming units
20 in order to get lethality, somewhere in that
21 neighborhood.

22 And really folks started to look at that and

1 think, what's -- I mean, that's a fairly extreme
2 situation to have to get to. It also involves working
3 with smallpox virus, which raises a bunch of other
4 considerations.

5 So the discussion in the advisory committee
6 also talked about the role of other -- using other pox
7 viruses such as monkeypox in monkeys, mousepox in mice,
8 rabbitpox in rabbits. And the idea here was, I mean,
9 you can see we're sort of using a surrogate virus in a
10 surrogate animal in order to predict efficacy. The
11 idea here was to be able to get to a model that was
12 able to be utilized in order to evaluate the efficacy
13 of these products for this really exceptional
14 circumstance of trying to evaluate a therapy for
15 treatment of smallpox.

16 So that's sort of at the other end of the
17 spectrum. I just wanted to throw that out there so
18 that folks are aware. Obviously, we're hoping not to
19 be at that other end of the spectrum, but there are a
20 range of different development pathways that have been
21 considered under the Animal Rule with the degree of
22 exceptionalness, if you will, dependent somewhat on the

1 pathogen and how it behaves in the particular animal
2 species, the animal models that are being utilized.

3 And if you think about just animal models in
4 general, animal models are generally designed and
5 developed in order to be able to show an effect. And
6 you choose the inoculum size. The species that you
7 choose, their degree of intrinsic resistance or
8 susceptibility of the particular pathogen has obviously
9 a huge impact upon the model, and at what point in time
10 of disease you intervene. I mean, all of these things
11 are chosen in a way in order to be able to show an
12 effect.

13 And the other thing that we run into
14 sometimes, too, that also adds to the challenges is
15 that oftentimes animals may clear the drug differently.
16 So if you're trying to match the human exposure, you
17 may have to give a mini dose somewhere in the interval
18 between when you're going to try and hit sort of a next
19 peak level. So there are a lot of things here that do
20 add to the challenges.

21 And from the Ebola experience, we gained some
22 insights into animal models of infection, and without

1 going into too much detail, I can tell you it's very
2 humbling to have a finding in an animal model of
3 infection that you think correlates with what should be
4 human effectiveness only to see when a compound goes
5 out, even in a trial that's fairly messy, but it looks
6 like the drug didn't have the effect that we had
7 thought we had seen in the -- or that we did see in the
8 animal models. So understanding what effect you need
9 to see in animals, because sometimes you can see an
10 effect, and what correlates with human efficacy can
11 also be quite challenging.

12 So I think as we think about *Acinetobacter* and
13 *Pseudomonas aeruginosa*, we do have some things that can
14 help us. We'll get to hear more about the quality and
15 characteristics of animal models as the day goes on.

16 But another thing that we have here that could
17 be helpful is that we do have some drugs that have
18 performed sort of marginally, if you will, and have
19 that. So we've got drugs that we may be able to
20 utilize in the animal models of infection in order to
21 be able to help us understand, can the model
22 discriminate between a drug that seems to have marginal

1 efficacy and one that's doing better than that?

2 And we all would love to see an informative
3 clinical trial, even if that trial is associated with
4 considerable uncertainty. And really consistent with
5 the desire to think about solutions first, to be able
6 to have a clinical trial conducted was the July 18 to
7 19 workshop that we had last year where we talked about
8 trying to do everything possible to try and make a
9 clinical trial feasible.

10 But really what we're here talking about today
11 is sort of two components, if you will: the supportive
12 information that we can gather from animal models, and
13 then also trying to think about the circumstance of if
14 in fact a clinical trial is not feasible and what role
15 animal models might play in the overall assessment of
16 efficacy for a drug targeting a species such as
17 *Pseudomonas aeruginosa* or *Acinetobacter baumannii*. And
18 if we in fact find that these clinical trials can't be
19 done, we will need to be able to rely to a greater
20 degree on the animal models of infection.

21 If we end up there, using an approach that
22 relies on a greater degree of understanding of efficacy

1 from animal models of infection will lead to a greater
2 degree of uncertainty that everybody grapples with:
3 developers, regulators, health care providers,
4 patients, payers, everybody. But that could
5 potentially be the reality here that we face.

6 And I think where we are today -- and in
7 Helen's slides, she showed the WHO priority pathogen
8 list. Where we are today with multidrug-resistant
9 *Pseudomonas aeruginosa* and *Acinetobacter baumannii*, I
10 mean, in this really limited circumstance, it is
11 reasonable to take on a greater degree of uncertainty
12 so that the development of new options can move forward
13 and provide safe and effective options for patients
14 with serious infections who lack alternatives.

15 And we thought about this a fair bit, and as
16 you start to think about, well, what does the data
17 package look like for such a product? And it's
18 interesting, almost sort of regardless of what route
19 you end up taking or how things come out, the package
20 really is probably fairly similar.

21 And you've seen this on some of the slides
22 projected already today. I mean, you really do the

1 best preclinical work that you can do, you'll do the
2 best PK/PD that you can do, you do the best animal
3 models of infection that you can do, you know, looking
4 for response in the animals, you do the best human PK
5 that you can do, and also try and get some PK from sick
6 patients, and then you'll try and do everything you can
7 to do the best feasible, practical clinical trial, you
8 know, within reason, to be able to look at human
9 response.

10 And you can see that folks who have thought
11 about this a lot are trying to do everything they can
12 to attend to the details of trying to make the trial to
13 be -- increase the likelihood that the trial is likely
14 to be an informative clinical trial. And I think
15 that's really what this is all about.

16 It may still be that there is so much
17 concomitant therapy or prestudy therapy that the trial
18 is difficult to interpret, but I think every step is
19 being taken in order to be able to try and make the
20 trial interpretable.

21 And you've heard from the folks at Polyphor
22 and Entasis and the steps that they've taken to try and

1 design their trials and take steps to increase the
2 likelihood that the clinical trial will be both
3 feasible and provide interpretable data, even with a
4 greater degree of uncertainty. So I think that's a
5 really important part of the effort here.

6 And I think everybody recognizes it's really
7 in everyone's interest to demonstrate efficacy from a
8 clinical trial, but also recognizing that if in fact
9 that's not achievable because of the small numbers of
10 patients in the trial, prestudy therapy, the time it
11 takes to make a diagnosis, concomitant therapy, or
12 patients who have mixed infections who require
13 concomitant therapy, that the reason that we're here
14 today is to talk a little bit more about what the role
15 of clinical trial data -- or how clinical trial data
16 can be complemented by data from animal models of
17 infection.

18 And one thing to keep in mind, too, that if
19 the drug fails in a clinical trial as opposed to the
20 trial not being feasible or not being interpretable, I
21 mean, if the drug truly fails in the clinical trial, it
22 wouldn't be appropriate to try and rescue the program

1 with an animal model of infection or data from animal
2 models of infection.

3 And I think what we're trying to get to, and I
4 think we're really quite close and perhaps even there
5 in some ways, is a route to be able to move forward
6 now. You know, the clinical trials, the design
7 considerations and getting to a clinical trial that is
8 feasible and possible, I think you've heard some really
9 excellent ideas about how to make that achievable,
10 recognizing that there will be a greater degree of
11 uncertainty.

12 We'll hear about the science of animal models
13 of infection here. Folks may have noticed, and you'll
14 hear more about this in a later presentation, we have a
15 Request for Information out there about animal models
16 of infection and additional research that could be
17 done.

18 And I think we're looking at this sort of with
19 a two-pronged approach. One is, what are some of the
20 short-term refinements that may be able to be done
21 relatively quickly that can help improve the animal
22 models of infection that can help folks that are

1 developing drugs now? And then also thinking towards
2 the longer term of things that may go into the future
3 with regards to development of animal models of
4 infection for *A. baumannii* and *Pseudomonas aeruginosa*.

5 So there are paths forward here, and we're
6 working to minimize the degree of uncertainty and
7 increase the likelihood of a successful program and
8 evaluating drugs that are species-specific for
9 *Pseudomonas aeruginosa*.

10 And then if we think down the road, I mean,
11 for drugs that do show safety and efficacy, it will be
12 very important to have full transparency on the
13 limitations of the data that were generated in order to
14 evaluate a particular compound.

15 And I think that the tools that LPAD provides
16 will be very important here, provide tools to mitigate
17 the risk and uncertainties for drugs that have shown
18 safety and efficacy using a more limited and
19 streamlined pathway. And it will also be an important
20 signal to the health care community because the health
21 care community obviously will play a very important
22 role in the prescribing choices that they make to use

1 such products.

2 So just to sort of briefly summarize, I think
3 there are pathways. There are still challenges in
4 development and uncertainties that will be encountered,
5 but as you can see from some of the proposals with
6 regards to clinical trials for species-specific drugs,
7 we're getting to some reasonable options here given the
8 circumstances. And we're also considering if the
9 clinical trials turn out to be infeasible or
10 uninterpretable, how animal models of infection might
11 be able to be utilized and with a greater reliance upon
12 the findings there.

13 So I want to thank you for your attention.
14 And I'll hand it back to Sumathi.

15 DR. NAMBIAR: Thanks, Ed. I think we're
16 running a few minutes late, so if it's okay, we'll take
17 a break right now and if possible, reconvene at 11:15,
18 if that's possible. Thank you.

19 (Break.)

20 Pathogenesis

21 DR. MILLER: Okay. We're going to have two
22 talks on the pathogenesis of these opportunistic

1 infection organisms. And the first is Joanna Goldberg,
2 from Emory University on the "Pathogenesis of
3 Pseudomonas Aeruginosa."

4 Pathogenesis of Pseudomonas

5 DR. GOLDBERG: Thank you very much. And thank
6 you for the organizers for organizing this what seems
7 to be a very interesting and timely meeting. I am
8 going to be telling you about the general background of
9 the outline of pathogenesis of Pseudomonas. And I have
10 nothing to disclose.

11 So the genus Pseudomonas is a predominant
12 microbe in the environment. It has numerous niches and
13 can interact with a variety of hosts. As shown here in
14 this cartoon, Pseudomonas aeruginosa, which is the
15 focus for today's discussion, can live on dead plants
16 and insects. It can also promote plant growth and, in
17 some cases, cause diseases in plants. It's also
18 involved in bioremediation and can produce several
19 novel secondary compounds. Most importantly for today
20 is that this bacterium is the cause of human disease.

21 It is ubiquitous in the environment. It has
22 minimal growth requirements. It can actually even grow

1 in water. It can grow at temperatures between 4
2 degrees and 42 degrees. It's a facultative anaerobe
3 and can grow anaerobically in the presence of arginine
4 or nitrate as a terminal electron acceptor.

5 Most importantly, it is highly antibiotic
6 resistant and it's quite resistant to antimicrobial
7 agents. This resistance is due to its intrinsic outer
8 membrane of the outer membrane impermeability, and it
9 also has numerous efflux pumps as well as its acquired
10 resistance.

11 As previously mentioned, carbapenem-resistant
12 *P. aeruginosa* has just been listed as a Priority 1
13 Critical Pathogen on the WHO priority pathogens list
14 for research and development for new antibiotics.

15 So when we talk about *Pseudomonas aeruginosa*,
16 as we're doing today, there's a large amount of
17 infrastructure available. The first sequenced strain
18 of *Pseudomonas aeruginosa* was PAO1, and that was
19 sequenced in 2000. It has a large genome, large
20 circular chromosome, of about 6.6 megabases, and it
21 also has a large number of open reading frames of over
22 5,580. It also has a high G+C content.

1 This strain PAO1 was a spontaneous
2 chloramphenicol-resistant mutant of the original PAO
3 strain, which was isolated in 1954 from a woman in
4 Melbourne, Australia.

5 Since that time, there has been a large
6 international effort put forth to sequence thousands of
7 *Pseudomonas aeruginosa* genomes. The International
8 *Pseudomonas* Consortium is a repository of isolates from
9 various infections and environmental sources, including
10 from plants and from animals. The strength is that
11 this resource actually has a large amount of metadata
12 associated with it, including its source as well as --
13 its source, the bacterial phenotypes and genotypes, as
14 well as the clinical characteristics of these strains,
15 including their antibiotic-resistant profile.

16 As of this last week, there were 1,588
17 isolates in this consortium, and 979 genomes that were
18 available.

19 In addition, this is not the only -- could you
20 give me a hand with this?

21 (Technical interruption.)

22 DR. GOLDBERG: Okay. Thank you.

1 Okay. So not only is there a large amount of
2 genomic data available, but there is actually a
3 fantastic bioinformatic resource that's available to
4 the Pseudomonas community. Pseudomonas.com is a
5 website that was developed by researchers in the field
6 that provide annotation, transcriptome, and pathway
7 data analysis. The site is manually curated and
8 continuously updated and is basically the gold standard
9 in terms of genomic analysis for any microbe. And it
10 currently includes 184 complete genomes.

11 In addition to the various genomes that are
12 available, there are two different ordered transposon
13 mutant libraries that have been developed. One is
14 based on PA01 and another one is based on strain PA14.
15 PA14, another genomic sequence strain, was isolated
16 from a burn patient, but is also shown to be virulent
17 in a number of different animal, mammalian and non-
18 mammalian models, including infections in the plant
19 Arabidopsis, zebrafish, and wax moth larvae.

20 The Pseudomonas field also has state-of-the-
21 art genetic tools, including a myriad of vectors for
22 the construction of mutants and for the transcriptional

1 and translational fusions. There are both luminescent
2 and fluorescent constructs available for monitoring the
3 expression or looking at bacteria as single cells or
4 for looking at the bacteria in animal models of
5 infection.

6 In addition, there are transposons available
7 for transposon sequencing experiments, and with these
8 available genomes, there are a large amount of RNAseq
9 projects that have been undertaken.

10 Now let's talk about the pathogenesis of P.
11 aeruginosa. Most importantly, as it's been said, it's
12 an opportunistic pathogen. So unlike the situation
13 that we heard about plague, anthrax, and tularemia,
14 this means that this bacteria generally doesn't cause
15 disease in healthy individuals. Infection occurs
16 pretty much only when there is a compromise to the
17 innate immune system. This can be immunocompromised
18 such as individuals undergoing chemotherapy or a breach
19 of the skin or basically any mucosal surface.

20 With respect to animal models, like humans,
21 most animals are generally resistant to infection. For
22 example, intranasal infection of a wild type P.

1 aeruginosa strain in a typical healthy inbred mouse is

5 7

2 lethal at about 10^5 to 10^7 colony-forming units, but if

3 this mouse is made neutropenic, the lethal dose is

100

4 about 10^2 .

5 P. aeruginosa can cause infection at many

6 sites. It is the most common cause of bacterial

7 keratitis after injury either by trauma or in some

8 cases by damage by contact lens.

9 It can cause swimmer's ear and infection of

10 the outer ear canal that develops when water remains in

11 the ear after swimming.

12 It can cause intra-abdominal infections and

13 nosocomial urinary tract infections as well as

14 bloodstream infections and other catheter-related

15 infections.

16 It can cause skin and soft tissue infections

17 varying from the non-lethal hot tub folliculitis to,

18 most importantly, life-threatening infections following

19 wounds and burns.

20 P. aeruginosa is one of the most common causes

21 of hospital-acquired acute pneumonia, especially in

22 mechanically ventilated patients, and these infections

1 can disseminate and be associated with a particularly
2 high mortality rate.

3 It is also the cause of chronic respiratory
4 infections in patients with cystic fibrosis or with
5 COPD. In CF patients, these infections are the most
6 common cause of morbidity and mortality.

7 Interestingly, eye infections and chronic lung
8 infections in CF patients almost always stay localized
9 to the site of infection, while infections in these
10 other sites can often disseminate.

11 Numerous virulence factors have been
12 recognized in *P. aeruginosa*. This slide shows some of
13 the select ones that have been associated with acute
14 infections. For the most part, these have been defined
15 and characterized by the construction of mutants
16 lacking individual factors and then tested in, in vitro
17 or in vivo models of infection.

18 This cartoon shows a sampling of some of the
19 secreted factors, like proteases and the secreted toxin
20 molecule, like pyocyanin. It shows one of the
21 siderophores, pyoverdinin. It also shows some molecules
22 that act as adhesions, including the flagella, the

1 pili, and the LPS.

2 It also shows the secretion systems. Of
3 particular interest is the Type III secretion system
4 that injects exoenzymes directly into the host cell.
5 However, the situation with *P. aeruginosa* is even more
6 complicated than is shown in this slide, as certain
7 strains from certain types of infections express
8 particular virulence factors, for example, strains from
9 corneal infections generally express ExoU and do not
10 express ExoS.

11 Also not shown in this slide are the
12 extracellular polysaccharides, including alginate, Psl,
13 and Pel, all of which have been shown to have a role in
14 biofilm formation.

15 The situation is even more complex when you
16 compare strains from acute infections or from the
17 environment to those that emerge during chronic
18 infection in cystic fibrosis. Those from early
19 infections are generally similar to those found in the
20 environment, and the environment is probably the source
21 of the initial infections in CF patients. However,
22 during chronic lung infection, the *P. aeruginosa* evolve

1 and adapt to the lung.

2 This cartoon represents some of the changes
3 that have been noted during longitudinal studies of
4 isolates from cystic fibrosis patients. Most
5 predominantly, as you can see on the left, the strains
6 make a low level of the exopolysaccharide alginate, and
7 on the right, this green bar represents the
8 polysaccharide being overproduced, giving the bacteria
9 a mucoid phenotype.

10 The bacteria tend to become nonmotile and lose
11 their flagella and pili. Strains tend to mutate, the
12 LasR gene involved in quorum-sensing, and therefore
13 their quorum-sensing is differentially regulated. The
14 chronic isolates secrete less proteases and less
15 toxins. They change from making a lipopolysaccharide
16 that's complete to making one that's LPS "rough" and
17 rendering these strains serum-sensitive, and they also
18 change their lipid A to make it less inflammatory.

19 Interestingly, loss of these factors make
20 these strains less virulent when tested in acute models
21 of infection, but it's obvious that their loss has an
22 important role in the pathogenesis of chronic infection

1 in cystic fibrosis.

2 So there are a number of issues I think we
3 need to think about as we discuss the development of
4 animal models of *P. aeruginosa*. We need to remember
5 that healthy people are generally resistant to
6 infections, that some acute infections can disseminate
7 from the initial site of infection and cause sepsis,
8 while other infections can stay localized; that *P.*
9 *aeruginosa* adapts during chronic respiratory infection
10 in CF patients, and that this situation is actually
11 even more further complicated by the fact that cystic
12 fibrosis itself is a disease that can be caused by one
13 of over 1,700 different recognized mutations in the
14 CFTR gene in the human population, so not all mutations
15 in CF are actually equivalent with respect to their
16 severity.

17 And, finally, strains from particular
18 infections may express different virulence factors that
19 may be important in different types or sites of
20 infection or at different times during infection. And
21 I think these are the most important things to consider
22 as we develop a standardized animal model.

1 DR. MILLER: Okay. We'll move on to our next
2 speaker, Dr. Robert Bonomo, from Case Western Reserve,
3 who will talk about the pathogenesis of Acinetobacter.

4 Pathogenesis of Acinetobacter

5 DR. BONOMO: Thank you very much. Unlike to
6 contrast to Pseudomonas aeruginosa, in Acinetobacter,
7 having dealt with this pathogen for close to 20, 25
8 years in the clinic, I have a little different view
9 about Acineto. This is an organism where resistance
10 and virulence are converging in what we consider now a
11 critically important pathogen.

12 These are my disclosures. I would like to
13 thank the FDA, Mark Adams, Brad Spellberg, and Phil
14 Rather, whom I've worked with, with Acinetobacter over
15 the years. The funding sources. And I do preclinical
16 work for some pharmaceutical companies to basically do
17 biochemistry on their beta-lactamase inhibitors.

18 So Acinetobacter. You know, in my mind, when
19 you think about this and you have to talk about an
20 organism that you've studied for 20 years, I sort of
21 got a little philosophic. I thought about this, and I
22 said, my god, this is one of the most complex

1 pathogens.

2 And when you look at it, you can make a
3 statement like that because this organism has a really
4 sordid past. It went by the name "Mima," then it went
5 by the name "Herella," and then it went by "Bacterium
6 anitratum." It even picked up a letter and a number.
7 It's almost like somebody trying to avoid the police.

8 (Laughter.)

9 DR. BONOMO: And high diverse, it's a very
10 diverse organism. There are more than 50 species that
11 are known. Some species cause infections. And it's
12 really difficult in this field because the microbiology
13 labs often identify something as Acinetobacter X, Y, or
14 Z, when in reality it's Acinetobacter A, B, C.

15 And there's a lot of mystery and
16 misconception. The term "Acinetobacter" comes from the
17 term "akineto," and everybody knows those are the
18 actual Greek letters, I can't read Greek, but I'm told
19 they're really Greek, and where this comes from, and
20 this means that it's a nonmotile rod.

21 And probably one of the most dubious
22 distinctions is that the organism loves an environment

1 that is warm and wet, so I don't know what you want to
2 think about that, but it's probably not something that
3 other organisms actually go into.

4 And thinking about Acinetobacter over a number
5 of years, I hate to use the phrase, it's characterized
6 by some quantum spookiness. And you have an organism
7 that when you look for images of what it looks like on
8 electron microscopy or scanning electron microscopy,
9 the red image that you see looks nowhere like the green
10 image that you see, and both of them are Acinetobacter.

11 This is almost one of those things where we
12 really can't tell what we're studying sometimes because
13 its genetics are so complicated, its classification is
14 so complicated, and its morphology changes.

15 And it's fraught with misconceptions. It's
16 supposed to be nonmotile, yet the images that you see
17 on this slide, and if you shine blue light on it,
18 Acinetobacter moves. Believe it or not, it moves to
19 photo stimuli. It moves when you change the
20 temperature in an environment. And it also moves when
21 you change the consistency of the agar that it's being
22 plated on. So there are a variety of complexities that

1 we have with this organism.

2 And, in addition, it causes a variety of human
3 infections, with increased attributable mortality:
4 hospital-acquired or health care-associated pneumonia,
5 and it even causes community-acquired pneumonia. It
6 has a mortality of up to 70 percent. And if you are in
7 parts of the world where there is heavy alcohol use,
8 even in the community setting, it can cause significant
9 disease. It is characterized by bloodstream
10 infections, and in some areas of the world, neonatal
11 sepsis. It can cause burn infections, skin and soft
12 tissue infections, meningitis, osteomyelitis,
13 endocarditis.

14 And when the clinician is faced with these
15 challenges, the most difficult thing is not only are
16 you not certain which type of Acinetobacter you have
17 because the lab is not 100 percent sure, MIC testing is
18 challenging. You get things like skip-wells, that you
19 will see the cutoff point is at 4, and then all of a
20 sudden you pick up the pathogen again at 8, and at 16
21 you lose it, at 32, and you pick it up again at 64.

22 The organism, if you put an Etest on, you find

1 out that the organism that was susceptible demonstrates
2 heteroresistance, and there are a lot of
3 inconsistencies with the measurement of colistin.

4 So this singular successful pathogen brought
5 this in my mind unique combination of resistance and
6 virulence. And in *Acinetobacter baumannii*, you have a
7 resistome I think that you have to face when you
8 develop an animal model, and you have a virulosome.

9 And in this, you have to keep in mind that
10 this organism has this remarkable capacity to acquire
11 and rearrange genetic determinants that play a critical
12 role. The *Acinetobacter* that you have at the beginning
13 of the infection may not be the same *Acinetobacter* that
14 you have at the end of the infection because you have
15 these mobile genetic elements that are hopping around.

16 So how do we know that *Acinetobacter* is
17 virulent? What are the clues? Well, good observation
18 is important. Finding models and defining virulence
19 traits are the key to this. So a long, long time ago
20 in a kingdom far, far away when we first started
21 working with the Walter Reed Army Medical Center, Dr.
22 Colonel Kraft there sent us these isolates, and we were

1 very, very fortunate to get these isolates from him,
2 and we did a genetic determination of the antibiotic
3 resistance genes.

4 It occurred to us in a separate manuscript
5 that, you know, it's actually funny that some of these
6 resistance determinants were associated with
7 particularly bad outcomes. So we didn't know what this
8 meant at this time because we were very young, a lot
9 younger than I am now, almost a decade or more, we
10 didn't know that carbapenem resistance was associated
11 with the need, not the success or failure, but with the
12 need for mechanical ventilation.

13 We also discovered that certain particular
14 carbapenemase genes were associated with ventilation,
15 longer hospital stays, ICU stays, complexity,
16 durations, and changes made to the antibiotic regimen.
17 We had no clue. We had no clue what this meant. This
18 was an observational study, but it sort of got the ball
19 rolling.

20 So we thought that, well, maybe, just maybe,
21 blaOXA-23, or the carbapenemase gene, is a marker, and
22 we started thinking about the link between bacteria of

1 proteins in the periplasmic space and the cytosol, and
2 could there be any virulence determination that comes
3 from that? But regrettably at the time, we focused
4 more on the resistance side of Acinetobacter than we
5 actually looked at this sort of interesting virulence
6 thing.

7 But the rest of the world went on luckily.
8 And then Acinetobacter started being described as doing
9 some really strange things, like developing outer
10 membrane vesicles where part of its outer wall forms
11 another little bubble, and that bubble gets popped off
12 the Acinetobacter, and in that bubble is a resistance
13 gene, and then people started looking further, and not
14 only were resistance genes in these little lipid
15 bubbles called outer membrane vesicles, but other
16 proteins associated with pathogenesis and virulence and
17 specialized secretion systems for the delivery of
18 virulence factors.

19 So what's emerging here is an incredibly
20 complex organism. Resistance is the center of what
21 defines it in the lab. Its genetics change constantly
22 due to mobile genetic elements that are hopping around.

1 And it's put together in probably a way that -- I don't
2 understand *Pseudomonas* as well as I should -- but in a
3 way that's probably very unique, and similar to
4 something I've had to think about.

5 So how do you put together an understanding of
6 models of infection? Well, we all recognize here that
7 they are important to identify virulence. These help
8 us identify the factors that are important between host
9 and *Acinetobacter*. But there is a caveat, the in vitro
10 assays, including adherence to human cells, cell
11 invasion, biofilm formation, have often lacked
12 correlation in the current models with in vivo
13 virulence in *Acinetobacter* when studied head to head.

14 And I think that this observation or this
15 statement actually made by Brad Spellberg, in a
16 publication in *Clinical Microbiology Reviews*, speaks
17 not because the models are bad, because the organism is
18 very complex. And the models of infection that we
19 have, this is a pictorial representation, a mouse, rat,
20 a waxy worm, and *C. elegans*.

21 Some of the mice models, they're useful in
22 some ways, but they're challenging. You have to give

1 sometimes a high inoculum infection at 10. That's not
2 really relevant to what patients actually face. To
3 make mice neutropenic to actually study an
4 Acinetobacter infection, well, clinically, or at least
5 in the real world -- in the clinical world -- the
6 clinical world is the real world sometimes -- in the
7 clinical world, neutropenic patients don't get
8 Acinetobacter infection, they get other things. So
9 making a mouse neutropenic to give them an
10 Acinetobacter infection is limiting.

11 The diabetic mouse may be a little bit more
12 relevant because diabetes is one of the risk factors
13 and it can be used for antibiotics. To inject
14 Acinetobacter into the intraperitoneal cavity using
15 porcine mucin is a stretch, is a stretch, because,
16 first of all, Acinetobacter doesn't really cause a lot
17 of peritonitis in humans.

18 It's rarely recovered from a belly infection
19 or spontaneous bacterial peritonitis. It's got other
20 niches, it's more the lung. And so giving it an
21 irritant and recovering it from a belly infection
22 doesn't really help us understand virulence all that

1 well.

2 But there are strains of mice that are
3 intrinsically susceptible due to diminished cytokine
4 responses, and these are actually probably a good
5 model. And there is also another strain of mice that
6 is also a very good model, but we're not sure.

7 Rats actually have little bit better models of
8 infection. The pneumonia model in the rat, you can
9 give a rat pneumonia and non-immunocompromised. There
10 have been rat models of skin and soft tissue infection
11 to study burn. And there have also been wound models
12 using to make the mice a little bit immunocompromised
13 with cyclophosphamide and using particular strains.

14 And there are non-mammalian models. And it's
15 really interesting that the waxy moth, even though it's
16 non-mammalian, actually for some studies, like in
17 assessing virulence and for some studies, assessing
18 antibiotic efficacy, has done reasonably well. I can't
19 speak to C. elegans or zebrafish larvae, but I
20 understand they perform similarly in this way. We have
21 had experience in our lab with the waxy moth, and once
22 you get a handle on how to deal with it, it's actually

1 pretty good.

2 But these models lead us to define virulence.
3 And when you think about virulence in Acinetobacter, I
4 wish I could say it's one thing, but just like the
5 complexity of naming the complexity of the genome,
6 there are a lot of virulence factors. It can persist
7 in dry environments. It expresses motility when it's
8 not supposed to.

9 The virulence genes get turned on by ethanol.
10 Now, your mind is not supposed to go to the spot, but
11 just like humans, I guess.

12 Biofilm mechanisms are at play. Iron
13 acquisition pathways. Polysaccharide membrane.
14 Alteration in penicillin-binding proteins. And pilus
15 formation. And these are all complex things that
16 unfortunately we can't put together in a single model
17 yet as to why all these different factors are working.
18 It's more like there's a constellation of factors
19 working at the same time. And I'll show you a paper at
20 the end that shows this really very well.

21 And then there's the essential role of LPS.
22 And I love this figure about LPS because when you go to

1 medical school and you study biochemistry, and you have
2 to memorize all these little sugars and how they go
3 around in circles and how they get chained, and it's so
4 complicated. Just look at a molecule of LPS, and you
5 say, "I'm done."

6 (Laughter.)

7 DR. BONOMO: There are too many chains, too
8 many O's, too many circles. It's hard for us even to
9 understand this on a chemical level and its
10 modification, but be certain that LPS has a critical
11 role in Acinetobacter in evading the host immune
12 response and triggering the host inflammatory response.

13 And then there's the central role of OmpA, and
14 this is one of the most important proteins that has
15 been studied so far. On this slide, I have a summary
16 of the things that it's been involved in: serum
17 resistance, biofilm formation, adherence. And the
18 Spellberg lab has shown that recombinant OmpA conserved
19 across 90 percent of strains generates a humoral immune
20 response that is protective. So this is an important
21 protein and the genesis of it.

22 So when you start looking at all the papers

1 that are written and you start identifying virulence
2 factors, the complexity begins. You have what I've
3 mentioned, LPS and OmpA, and then you have superoxide
4 dismutase. And then as you begin to go through those
5 virulence factors, you see that some of these virulence
6 factors are also involved in antibiotic resistance,
7 OXA-24, pmrB, which is involved in colistin resistance.
8 You have a variety of other genes involved in this, and
9 even aminoglycoside-modifying enzymes, as well as
10 efflux pumps.

11 So this is an organism that has its virulence,
12 its virome sort of interacting with its resistome. But
13 we do have immunologic factors that can go against it:
14 cytokines, avoidance of polys, macrophages. Zinc and
15 magnesium sequestration are important.

16 And to lastly put it together, the sort of
17 integrated view is that there is a very important role
18 for the capsule in *Acinetobacter baumannii*. The
19 capsule is the primary defense against complement. It
20 helps ward off white cells. You have the LPS. You
21 have the fact that in many, many infections, it has
22 been observed that there is a large infectious

1 inoculum, so the more Acinetobacter you have together,
2 the more virulent it can become. And this is almost a
3 predictable consequence of not being able to treat this
4 organism with an effective antibiotic. You can't get
5 rid of it in the wound, and the numbers grow, grow,
6 grow, grow, then you get these quorum-sensing signals
7 that are triggered, and you go into sepsis.

8 So effective therapy helps the host rapidly
9 clear the bacteria, avoids damage, whereas ineffective
10 therapy enables the bacteria to persist at higher
11 levels, become more dense, and triggering host damage.

12 And what about targeting virulence and
13 resistance? Inhibiting LpxC protects mice from
14 resistant Acinetobacter by modulating inflammation and
15 enhancing phagocytosis.

16 A very important paper that asks the question,
17 Can LpxC inhibition block the ability of bacteria to
18 activate the sepsis cascade and enhance opsono-
19 phagocytic killing of bacteria and protect mice? And
20 the answer is yes, and it was based on very important
21 science that was published in Cell by Christian Raetz a
22 number of years ago, who developed this approach to it.

1 This was unappreciated at the time, how important this
2 pathway was. Now I think that people are beginning to
3 think about LpxC inhibition in the -- my screen just
4 went away. It went white.

5 (Technical interruption.)

6 DR. BONOMO: So basically what I was going to
7 get to is that, yes, this actually works, and you can
8 interfere with the inflammatory cascade by interfering
9 with LpxC inhibition. And this is a way to sort of get
10 at sort of a novel approach and to get to the punch
11 line basically.

12 When you start to integrate all these various
13 pathways together, you find that, well, when you look
14 at the genomic plasticity that this organism has, and
15 you look like at its responses to therapy, I think it's
16 time to start developing a novel way of looking at
17 Acinetobacter, and I think that's the role of this
18 committee today, because there is significant urgency.

19 And the urgency is here, a very important
20 outbreak that was described. I think Dan is going to
21 talk about this later. This was a huge outbreak of
22 Acinetobacter strains. They found that the strains

1 were genetically related to strains that had previously
2 went around the world. In murine models, these strains
3 were very, very virulent. They had a high virulence.
4 They used iron metabolism -- they discovered iron
5 metabolism genes, protein secretion, and they also
6 developed a PCR assay in this paper that could help
7 them identify this.

8 So we come back to this sort of synthesis in
9 this organism where many, many genes have been found,
10 about 300, that were required for survival and for
11 growth of *A. baumannii*, and there are many
12 transcription factors also required for this. And the
13 subset of these transcription factors that are involved
14 in virulence are also involved in resistance.

15 So I think this is a way to look at the
16 virulosome of *Acinetobacter* and to begin to think of it
17 in different ways.

18 So in conclusion, resistance and virulence I
19 think actually are very linked in *Acinetobacter*. I
20 think the way to approach this is to start to delve
21 into systems biology approaches that can reveal these
22 incredibly tight associations between what's happening

1 on the outside of the organism and what's happening on
2 the inside.

3 I think we need to start thinking about
4 different ways, antisense therapies, or siRNAs. They
5 have genes that are involved in resistance have dual
6 roles. We need to begin putting our heads around what
7 is the role of outer membrane vesicles in transporting
8 information across.

9 I think there are unexpected patterns of
10 infections that we have to be aware about, and in one
11 strain of Acinetobacter, in one infection in a patient in
12 Cleveland, we discovered that the patient was actually
13 infected with two genetically different strains but was
14 bacteremic with Acinetobacter by two genetically
15 different strains circulating in the bloodstream. This
16 is a way to think about this. And actually that was
17 published by Mark Adams in an mBio paper. And I think
18 that we have to link resistance to virulence in novel
19 strategies.

20 So the take-home point, what I think is the
21 future for Acinetobacter. Well, I think we have to
22 take a three-pronged approach -- we have to think about

1 immunotherapy, we have to think about biologics, and we
2 have to think about drugs -- because it's a very
3 cunning pathogen.

4 And I made a very simple figure, you have your
5 resistance genes on this side, you have your virulence
6 genes, you have the link between, and I think it's a
7 teeter-totter how to think about this. And I encourage
8 this committee, this group, to think about
9 Acinetobacter in a broader sense.

10 Thank you.

11 DR. FARLEY: For folks on the WebEx, we are
12 having technical difficulties, and you'll be able to
13 see the screen after lunch, hopefully. But you should
14 be able to follow along with the slides that are
15 available on the meeting website.

16 We'll now turn our attention to short formal
17 public presentations. These were requested in advance
18 per the meeting announcement.

19 I would like to invite Dr. William Weiss, from
20 the University of North Texas Health Sciences Center to
21 the podium.

22 Public Presentations

1 DR. WEISS: So 5 minutes to put my 2 cents in
2 on this subject of animal models for Pseudomonas and
3 for Acinetobacter. And Joanna and Robert just did some
4 excellent presentations on pathogenesis of both these
5 strains, so I won't belabor the point on this first
6 slide other than to say that the organisms share common
7 clinical infections and indications.

8 And the main areas of concern would be UTI,
9 pneumonia, bacteremia, and skin and skin structure
10 infections. And along those lines, there are
11 resistance determinants in the strains we're
12 encountering today that are of big concern.

13 In the case of the Acinetobacter, we're
14 talking about a whole host of beta-lactamases, Class A,
15 B, C, and D, particularly the Class D with the OXA-23
16 that Robert just mentioned.

17 In the case of Pseudomonas, it's a high
18 percentage of infections seen in the hospital settings
19 they cause with pneumonia, UTIs, and bloodstream
20 infections, and, in particular, eye, ear, nose, and
21 throat. And, again, wound infections and multidrug
22 resistance is a bigger issue.

1 Now, the Preclinical Services Group at the
2 University of North Texas runs a host of these animal
3 models in evaluating new therapies for treating these
4 types of infections, and I've been doing this for 35
5 years. I wanted to share some of the ways if you're
6 developing a new animal model or the way we've
7 developed the animal models and have run them that I
8 feel are very important, particularly for these two
9 organisms.

10 So in running these animal models, there's a
11 need to have representative current clinical
12 indications. You're not going to run a Pseudomonas
13 against some type of infection where it doesn't occur.
14 And this goes back to the UTI, the pneumonia, the
15 bacteremia, and the wound. These are the models of
16 concern, these are the models you want to have running.

17 You want to make use of relevant clinical
18 strains. ATCC strains are great, but if you're going
19 to test a new therapy, a novel therapy, you want to do
20 isolates that are of clinical relevance, that they came
21 from a site of infection.

22 If you want to develop a UTI model, you're not

1 going to take a Pseudomonas that came from a
2 bloodstream infection. The best possible case of
3 success in developing one of these models is to use an
4 isolate that came from that indication and to acquire
5 that and put that into the model, and that's what we
6 do.

7 The other need is to use current strains of
8 concerns. Again, you want resistant strains. You want
9 something expressing an OXA or an NDM-1. You want
10 something that maybe has an efflux mutation in it.
11 This is what you're trying to treat. A susceptible
12 strain, whereas it might develop an infection, is not
13 that relevant to evaluating new therapies. So there is
14 a need to acquire those strains. And this is where I
15 would encourage people to share some of these strains
16 if they have them and not hoard them. We need to put
17 these into the models to develop the proper efficacy
18 study.

19 We need to involve proper doses and dosing
20 regimens. Now, for a lot of the evaluations we're
21 doing early on, we don't know humanized doses. It's
22 hard to do so. You want to have a dosing regimen that

1 you can show a cause and effect. We always try to have
2 a dose range that gives a maximal effect and minimal if
3 we can do it. That's a true indication that the model
4 is working.

5 The humanized PK or adapting to PK needs to
6 come later on after you've done your initial screening.

7 You need to define the measure of efficacy.
8 What is your endpoint? And in a lot of these cases,
9 it's bacterial titers. Efficacy is defined as a
10 reduction in those bacterial titers at the site of
11 infection following therapy.

12 Survival is good, but it's an all-or-nothing.
13 You can't really tease out any little idiosyncrasies of
14 the model if you're just doing survival.

15 So with that in mind, I would like to go over
16 four of the models, the common models, but it's four of
17 the models that we work with on a regular basis, and we
18 work with on a regular basis with *Pseudomonas* and
19 *Acinetobacter*, and how it can be done, and different
20 ways to do it.

21 Robert talked about different strains of mice,
22 and, yes, there are different strains of mice that work

1 better than others. He talked about neutropenic versus
2 non-neutropenic. In the case of the lung model, you
3 can do both. You can do normal mice in a lung model,
4 Pseudomonas in particular works really well.
5 Neutropenic is usually needed for Acinetobacter.
6 They're a little bit tougher to establish that
7 infection.

8 Intranasal inoculation. Other people can use
9 tracheal. Intranasal inoculation, again, it's a common
10 route of infection for people. So we try to do it by
11 intranasal route.

12 Treatment can be delayed. We don't want to do
13 a lung model where you treat immediately. That's
14 really just knocking down the inoculum that you're
15 putting in. So minimum of 4 hours out to 24 hours,
16 depending on the etiology of your strain, is
17 acceptable.

18 Single/multiple dosing ranges over time. What
19 that will tell you with multiple ranges is if the
20 compound you're testing with will accumulate in the
21 lung to a high enough percentage to inhibit, it's more
22 clinically relevant.

1 In terms of endpoints, again, lung titer.
2 Survival can be used. In a mouse model, a lot of these
3 strains will go bacteremic and cause death.

4 PK/PD in the lung model is very common. You
5 can measure both plasma and ELF to get a measure of
6 efficacy. And, again, we have this working with
7 several strains that came from endotracheal aspirates
8 or bronchial lavage from a clinical study. The
9 relevant strain works much better.

10 The UTI, or what we run is an ascending
11 pyelonephritis. It can be done in normal mice. It can
12 also be done in diabetic mice. Particularly for
13 Pseudomonas, the diabetic mouse model works very well.
14 It's transurethral inoculation, so it really is a
15 source of infection, and ascends to the kidney to cause
16 infection.

17 Treatment, again, we don't start until 4 days
18 later. We're talking about an established infection.
19 You don't go to the physician just getting a UTI, you
20 already have the UTI, it's already there, you already
21 have an issue. So it's important to wait that amount
22 of time.

1 Your endpoint isn't just kidney. We want to
2 measure different aspects of it. Where does the
3 compound go? Where is it most effective? So we're
4 looking at kidney, we're looking at urine, and we're
5 looking at the bladder tissue itself in case there was
6 a biofilm type formation maybe with the Pseudomonas
7 there. And, again, we have urine clinical isolates we
8 have obtained and put into the diabetic model that give
9 very good reproducible results for both new therapies
10 and common molecules.

11 Skin and skin structure, there are a couple of
12 different ways to do skin and skin structure. One is a
13 superficial, the other is a subcutaneous abscess.
14 You're looking at bacteria titers, you're looking at
15 wounds, you can delay infection, you can delay
16 treatment of infection, and then start. We have wound
17 isolates that we're using. You could also do mixed
18 infections, which are common, Pseudomonas and a Staph
19 aureus to do wound infection models.

20 Then, lastly, septicemia. It can be done by
21 IP infection, which delays the onset of it that
22 produces a steady infiltration of the bug. Robert

1 alluded to it, gastric mucin in the GI tract is not
2 quite the way to do it. You could also hematologically
3 provide this infection.

4 Treatment has to be a little bit quicker
5 because this goes pretty fast. You can do a survival
6 endpoint. I know I said survival endpoints aren't
7 necessarily great, but we also do time studies where
8 you can track CFU in the blood and the spleen to look
9 at efficacy of your agent.

10 And here again, we have this working with
11 Acinetobacter and Pseudomonas of various resistance
12 mechanisms, including the ones provided.

13 So I think that was my 5 minutes. Thank you.

14 DR. FARLEY: Thanks. Dr. Jennifer Hoover,
15 from GlaxoSmithKline.

16 DR. HOOVER: Thank you. I want to thank the
17 workshop organizers for giving me the opportunity to
18 speak today. I lead the Bacterial Infection Model
19 Group, which consists of seven scientists, including
20 myself, in Antibacterial DPU at GSK.

21 What I wanted today was give a brief overview
22 of the pneumonia model that we use to evaluate our

1 compounds against Pseudomonas and Acinetobacter.

2 We induce the pneumonia by placing a bacterial
3 suspension in molten agar deep into the lung using a
4 nonsurgical intubation technique. The technique can be
5 a little tricky for someone to learn, but it is very
6 doable, and once someone is skilled, they can perform
7 it quickly and easily.

8 We did recently publish an article in the
9 Journal of Visualized Experiments which details this
10 model. It includes both a written manuscript as well
11 as a video demonstration of how to perform the
12 technique in both rats and mice.

13 One of the advantages of this model is that
14 many different isolates will actually establish
15 infection, and this gives us a lot of flexibility
16 because we can choose and change the isolates that we
17 put in the model based on an MIC for a particular
18 compound or a particular resistance phenotype that
19 we're most interested in.

20 In the graphs shown on the slide here, you can
21 see the growth of representative strains of Pseudomonas
22 in the top panel and Acinetobacter in the bottom panel.

1 The lighter colored bars represent the CFU from the
2 lungs of the animals at baseline, which, in this case,
3 was 1 or 2 hours post-infection, but that could be
4 delayed to give a higher bacterial burden at baseline,
5 as desired.

6 The dark colored bars represent the CFU from
7 the lungs of the animals at the end of the experiment,
8 which, in this case, was either 48 or 96 hours. We
9 typically do not see bacterial clearance of these
10 organisms within 48 or 96 hours using this model. And
11 the model is highly reproducible and it's very
12 consistent both between animals as well as from
13 experiment to experiment. Typically, we use
14 immunocompetent animals for this work as well.

15 In terms of validation, we have tested
16 commercially available antibiotics and shown that they
17 do not work against isolates which are resistant, and
18 they work against isolates which are susceptible, and
19 this is using doses in the animals that are relevant to
20 the PK that you would get in humans using relevant
21 clinical doses as well.

22 We've done a little bit of histology work in

1 rats, which shows that the pathology using this model
2 does appear to be similar to that seen in human
3 pneumonia. What we would really like to have would be
4 some additional validation work based on achieving
5 PK/PD targets. We have a little bit of that data, and
6 it looks very good, but we would like to have more of
7 that for additional compounds.

8 We would also like to see some additional
9 pathology work to, for example, look at mice to look at
10 the time course of infection as well as to better
11 understand the impact that the agar has on the
12 infection and the disease progression.

13 Because of the time limitation today, I'm not
14 actually going to show you data from the model. I
15 would refer you to our JoVE, where we do have
16 representative studies that you can go and look at.
17 And I'm happy to speak with anyone either today or
18 sometime after this workshop to share any data that we
19 have.

20 In summary, we feel this model offers another
21 approach to evaluate compounds against Pseudomonas and
22 Acinetobacter preclinically. And it does have

1 advantages over some of the existing models. Our goals
2 from the presentation today are threefold. First, we
3 would simply like to raise awareness of the model.
4 Second, we would like to see collaboration with other
5 scientists who might be interested in either this model
6 or other animal models. And, third, we would like to
7 offer our expertise and continue to be part of the
8 ongoing dialogue regarding these animal models.

9 In my group at GSK, we have been doing these
10 types of models for over 20 years, and we would really
11 love to share our experience as well as our industry
12 perspective.

13 We are very committed to high quality animal
14 work and robust models, and we fully support using
15 those models which will best help us translate from the
16 lab to the clinic. Thank you.

17 DR. FARLEY: Thanks. Dr. Lynn Miesel, from
18 Eurofins Panlabs.

19 DR. MIESEL: Hi. I'm Lynn Miesel, and I'm
20 from Eurofins Pharma Discovery Services. And I'm going
21 to tell you about our Acinetobacter and Pseudomonas
22 infection models.

1 So Eurofins Pharma Discovery Services is a
2 preclinical contract research labs. It's an
3 international network of labs in the United States, in
4 Europe, and in Taiwan, and we offer in vitro and in
5 vivo testing services to evaluate the safety and
6 efficacy of test articles. And we service multiple
7 therapeutic areas and have over 40 years of experience
8 in contract research. And our infection models are
9 performed at the AALAS-certified or -accredited
10 laboratories and Panlabs in Taipei, Taiwan.

11 Can you hear me? Okay.

12 So Eurofins Panlabs performs anti-infective
13 drug discovery services in areas from target ID and
14 validation through to candidate selections. It
15 includes both in vitro and in vivo testing services as
16 well as the safety, testing, in vitro, and in vivo non-
17 GLP.

18 So we have over 40 models that are already
19 validated and ready to go, and we readily develop
20 custom models upon request. And we work with over 160
21 Pseudomonas and Acinetobacter strains for these models,
22 including 130 strains that we just recently obtained

1 from the FDA-CDC AR Bank, and we're very grateful to
2 the CDC and FDA for this great resource. The infection
3 models that we work with include a variety of infection
4 types, and we work with both susceptible and MDR
5 organisms, Gram-negatives, including KPC, NDM-1, and
6 MCR-1 strains, Enterococci, Gram-positives, and fungi.

7 So the lung and thigh infection models are the
8 workhorse models that we offer to clients for
9 evaluating initial efficacy as well as PK/PD analysis.
10 And examples are on the left-hand side, a model with
11 Pseudomonas, a cystic fibrosis carbapenem-resistant
12 Pseudomonas strain, LES-431, that we use for both the
13 lung and thigh infection model.

14 And with all of our models, we perform
15 validation studies to demonstrate an increase in
16 bacterial counts between the initial inoculum and the
17 final data point at 24 hours after treatment. We like
18 to see at least a 2 log increase in bacterial counts.
19 And we strive for minimum data scatter as well as
20 reproducibility from day to day, and dose-responsive
21 efficacy of a standard of care agent over realistic
22 concentration ranges.

1 And, again, we have these models with MDR
2 strains, Pseudomonas and Acinetobacter.

3 We also perform the survival and infection
4 models, such as the peritoneal model. And I agree with
5 the comments raised before about the rapid loss of
6 survival in untreated animals with these models, but
7 these models offer the benefit that they're performed
8 with immune competent animals, and in that way, it
9 allows us to evaluate efficacy of vaccines and immune
10 modulatory agents, that are not so effective in the
11 thigh and lung infection models with neutropenic
12 animals.

13 Again, these models are optimized to
14 demonstrate dose-responsive efficacy. And we have 160
15 MDR strains available for testing in this model,
16 although the optimization is done with classical
17 strains.

18 So I am here to discuss any questions that you
19 may have or any inquiries about our services. And I
20 want to thank the organizers for the opportunity to
21 present.

22 DR. FARLEY: Thanks. Our final presentation

1 is by Dr. Craig Rayner, from D3 Medicine.

2 DR. RAYNER: Thank you very much for the
3 opportunity today. So just in terms of disclosures, I
4 am the President of D3 Medicine, A Certara Company. We
5 work with many, many biotechs and pharmaceutical
6 companies as well as the life science investment
7 community, and also with governments in providing
8 strategy and stewardship on complex drug development
9 programs. But today I'm here in the capacity of
10 representing the Australian Department of Defense, the
11 Defense Science and Technology Group, or DST.

12 And it's quite a wonderful opportunity to
13 announce something proactive and progressive in this
14 area, and that is, as part of the Australian Government
15 Next Generation Technology Fund, with about \$750
16 million appropriated, there has been approximately \$40
17 million which has been allocated for the support of the
18 development of medical countermeasure products, of
19 which clearly multidrug-resistant bacterial pathogens,
20 of which we're talking about today, is well and truly
21 in scope.

22 So it's the intention that this initial fund

1 will be leveraged to more than \$100 million, and also
2 to create a self-sustaining public-private partnership
3 so that this will be something which will continue into
4 the future.

5 So firstly I would like to thank and
6 acknowledge a number of people in this room and also
7 others on the phone because we've been working on this
8 for quite a long time. It's involved quite a lot of
9 advocacy over a large number of years, and we've been
10 able to get to this point.

11 And what I'm here to do today is to really
12 just acknowledge the community and, second of all,
13 encourage you, if you're interested in finding out more
14 about it, if you're interested in collaborating,
15 becoming involved, is to reach out directly me. My
16 email address is up on the website. And I would just
17 like to thank the organizers for the opportunity to
18 present today.

19 DR. FARLEY: Thanks very much. We will turn
20 the meeting now back to Dr. Miller and Dr. Bonomo for
21 an opportunity for some panel discussion.

22 Moderated Panel Discussion (with Audience Q&A)

1 DR. MILLER: I thought I would start out by
2 making a few comments about the morning since it's been
3 so informative.

4 First of all, I think if we can contrast the
5 animal model development and the FDA approval that
6 we've done for plague and anthrax compared to what we
7 hoped to do as a group or a community for these
8 pathogens, this is obviously a much more complicated
9 problem.

10 In terms of the bugs, both plague and anthrax
11 are very highly evolved pathogens. They maintain their
12 stability on plates, because they have evolved to cause
13 pathogenic disease, and we could easily develop,
14 relatively easily develop, new animal models.

15 Now, with these pathogens, they're unstable on
16 plates. We know that they lose their genetic integrity
17 and develop deletions as they're passed on rich medium,
18 probably because they're environmental organisms that
19 live in a nitrogen- and carbon-poor environment in the
20 soil and water, and when they move either to a hospital
21 to adapt or to human tissues, there is more food and a
22 specialized environment that causes them to change and

1 adapt.

2 So not only are they diverse because all the
3 environmental sources out there are extremely diverse,
4 so we've got all this diverse genomic and
5 characteristic features of these organisms because of
6 their diversity in nature, but then they become more
7 diverse.

8 And if we look at clinical trials and think
9 about clinical trials that we might seek where these
10 are causing greater diseases at a greater incidence, we
11 know that these organisms have the ability to cause
12 epidemic outbreaks where a single clonal organism
13 evolves over 10 or 12 years, changing its genetic
14 material in the hospital, perhaps adapting to the
15 hospital environment to adhere to plastic, to patient
16 lung tissue.

17 Then when we think about the clinical disease,
18 we've got this huge diversity of disease as well where
19 we sort of have two classes of patients. There are
20 many, many more classifications we could do, but if we
21 think about how we might classify them, there are the
22 immunosuppressed patients with typical -- they're on

1 chemotherapy or they're neutropenic, who are highly
2 susceptible to these organisms. And then there's the
3 class of barrier integrity loss, which is where they
4 may be extremely healthy people, the person who gets
5 Pseudomonas pneumonia after intubation for a routine
6 surgical procedure that's an elective surgery, the
7 person who gets Acinetobacter due to getting a
8 catheter.

9 And so any animal models that we want to
10 develop or try to take into account have to take into
11 account this organism diversity and at least probably
12 have to fall into these two categories of barrier
13 function, loss of integrity, and immunosuppression if
14 we want to accumulate that data.

15 And I think that a point of discussion that we
16 could hear more about from other people and begin to
17 think about is how we could combine some clinical
18 efficacy data in humans with the animal model data.

19 Of course, we've known for a long time that
20 many organisms are susceptible in vitro to an
21 antibiotic, the classical example being Salmonella
22 being susceptible to first-generation cephalosporins on

1 a plate but totally resistant in vivo because we know
2 that microorganisms change when they get into the
3 environment of animal or human tissues.

4 So we can't exactly reproduce in these animal
5 models human tissue, but it's closer, and if we use
6 some diverse animal models, I think we can get a lot of
7 good data about this that might be more consistent in
8 many ways than some of the human trials because the
9 human trials are going to have extremely diverse
10 patients in them, and that is going to confound some of
11 the data.

12 So this is a very thorny problem. And I'll
13 turn it over to anyone else who wants to comment about
14 these difficult issues that I've raised.

15 DR. COX: We're going to bring you a
16 microphone so folks can hear you. There are some folks
17 online, too.

18 DR. MAIRA-LITRAN: Thanks. This is Tomas
19 Maira, from the Brigham and Women's Hospital in Harvard
20 Medical School. So basically I was going to talk a
21 little bit about our experience with Acinetobacter and
22 the animal models primarily. We have been working with

1 lung infection models on bacteremias. So although
2 Acinetobacter has been considered for a while I guess
3 as a low virulent pathogen, we've seen in our
4 experience that obviously depending on the strain you
5 use for infection, the LD90s can vary dramatically. So

9

6 we've seen the strains in the 10 range, but we've seen

4 7

7 also many strains in the 10 and 10. So I guess you've
8 seen one of these fairly virulent strains is going to
9 help in these types of infections.

10 Also, in the mouse strain, we've seen also
11 like it's very important, and we compare a panel of
12 different strains, for example, in our studies, and we
13 clearly see that this has a great impact in the outcome
14 of infection, for example, strains like C57s are much
15 more susceptible than C3H or (inaudible) in mice.

16 And, again, also I agree with the fact that
17 using neutropenic model of infections are not really --
18 I mean, they are not clinically relevant since we know
19 neutropenia per se is not a risk factor for infection.

20 And, finally, we've seen that working with
21 mouse models of infection, that sticking to the same
22 vendors and even sticking to the same rooms in the

1 vendors help us a lot to get consistent results. So
2 the microbiome might play a role as well here.

3 PARTICIPANT: Can you identify yourself?

4 DR. MAIRA-LITRAN: Yes. Tomas Maira, from the
5 Brigham and Women's Hospital, Harvard Medical School.

6 PARTICIPANT: Thank you.

7 DR. REX: So as a mental model, I guess, it
8 feels like we've got a choice between two poles. One
9 pole is that you say to yourself, I'm not going to get
10 happy with Pseudomonas or Acinetobacter until I can do
11 something with the clarity of plague, you know, you say
12 that's what you want. Your other pole is to say that
13 no matter how many variations I do, every one of them
14 is going to have something wrong with it. It's going
15 to be not enough strains or the strain varied or it's
16 only in the lung or it's not in the -- there are going
17 to be lots -- there are going to be quirks around each
18 one of them.

19 And it feels to me like if you sort of lay
20 those two things out, you could spend a long time
21 trying to get -- and hearing the presentations, I think
22 you could spend a long time trying to get to the

1 clarity of the plague with Pseudomonas or
2 Acinetobacter. It's not obvious to me that you would
3 get there. It would be nice if you did, but everything
4 we're hearing says you won't.

5 And so rather than drive ourselves berserk
6 trying to achieve that level of clarity, it does feel
7 -- you know, the great value of this conversation is
8 that it says that in fact what you need to do is do 10
9 different animal models with Pseudomonas, with your
10 drug, just do it a bunch of different ways. And if
11 each way, if it's all consistent across all of those,
12 then great.

13 And also, I don't get too hung up -- you
14 commented a second ago about neutropenia. Neutropenia
15 for me is not meant in an animal model to mimic
16 neutropenia in a human being; it's simply a tool to
17 enable the organism to become aggressive. And I just
18 view that as yet another way to set it up so that I can
19 do something more sophisticated than work just in a
20 test tube. And I think use a variety of models and
21 look for parameters, PD parameters, that seem to cut
22 through them, and you include in those models reference

1 drugs, sort of standard benchmarks, standard
2 candlesticks, and make it all line up. Because I feel
3 like otherwise we're just going to spend forever trying
4 to get these models to work beautifully.

5 DR. MILLER: I think that's right. I think
6 you could today design -- How many? is the question,
7 and how many bacteria? Because you're going to have to
8 use some diverse different bacteria that you know
9 bacteria that have caused major outbreaks, bacteria
10 from the environment, bacteria that are current
11 clinical isolates. You're going to have to use -- and
12 they will need to be well characterized to understand
13 what's different about them so that that data can be
14 applied in the future if things change.

15 So you start getting this matrix of, how many
16 bugs and how many animal models and much is that going
17 to cost? Now, it's way cheaper than clinical trials,
18 and maybe things would have to make it through some
19 sort of hierarchy like that before people would spend
20 the money on a more limited clinical trial which would
21 show enough efficacy that people would use it or used
22 in a different way.

1 I mean, getting -- I don't know how the FDA
2 has dealt with, say, stool transplant in C. diff, even
3 where there's a clinical trial showing its efficacy,
4 whether we would start having to give some of these
5 drugs an ID after they were effective in an animal
6 model unless there's a better pathway to get them
7 approved.

8 DR. COX: Yeah, so the goal here really would
9 be to study the drug and gather the data that would
10 support an application that would lead to approval to
11 get out there. What we talked some about, too, is some
12 of the tools that something like LPAD offers, which
13 would help to identify the drug as being a product of a
14 more limited database.

15 But recognizing that for patients with
16 Pseudomonas aeruginosa or Acinetobacter who don't have
17 other options, it's a reasonable risk-benefit scenario
18 to consider using a drug when alternatives are not
19 available for patients who have those serious
20 infections.

21 DR. ZURAWSKI: So I would like to second
22 everything that John just said. I think it's really

1 important. Our experience with the Army with
2 Acinetobacter, the goal of our program was basically to
3 take a strain that we felt comfortable with and we
4 showed it established an infection across seven
5 different animal models. And so the real key is seeing
6 this consistency across all the models and doing all
7 the models, like John suggested. You can't just do
8 one, you've got to do multiple ones so you can feel
9 good about the drug or whatever therapy that you're
10 testing.

11 The second thing I would like to say is about
12 the neutropenia. I again second what he's saying.
13 It's a temporary neutropenia. Anybody who has done
14 these models can tell you that the white blood cell
15 count comes back on day three, both max and neutrophils
16 comes back on day three. And all it is, is a tool to
17 allow you to start with a very low inoculum and then
18 build up to what is a classical infection.

19 So what we see in the animals, what we call a
20 classic infection, is anywhere from 10, 10 program of
21 tissue. So to get to that point, you want to start out
22 with a lower inoculum, and what we do for our wound

8 9

4

6

1 models 10 we do for our lung models 10.

2 We're allowing the bug to go through its
3 normal stages of pathogenesis. How does it attack a
4 cell? attach to a cell? disrupt maybe the barrier,
5 epithelial barrier? things like this that are involved
6 in the pathogenesis that then allows it to establish
7 that infection and get to that amount.

8 So by having models that start with a lower
9 inoculum and then build, I think that really has to be
10 incorporated in.

11 And, finally, I would like to make a comment
12 about strains. One thing, as a microbiologist, as a
13 Ph.D. researcher, you're always kind of limited to the
14 strains you get from people. Right?

15 So when we get strains that we want to
16 research, oftentimes that comes from patients that may
17 have passed or had a serious infection, and somebody is
18 pulling that isolate maybe a week, 10 days, after the
19 infection is established. It's usually from the
20 bloodstream where you've got massive sepsis and that
21 patient is going down. That's not really the isolate
22 we want to study.

1 Oftentimes, that isolate, especially with
2 these two organisms, where their genomes are very
3 plastic, they change rapidly, and certainly in the
4 stress of the host they're actively changing, you want
5 earlier isolates that are involved in again that early
6 pathogenesis and how they establish an infection.

7 So I think you can get lucky and sometimes get
8 those isolates when you're looking at a wide range of
9 strains that you're getting from numerous places, but I
10 do want to caution that just taking a bloodstream
11 isolate from a patient that's 14 days old, it may not
12 be the same bug when you started, from the beginning.

13 DR. GUINA: I would like to make a comment. I
14 agree that it's really important to look at many
15 different animal models at this stage if you, as a
16 committee, are deciding on what animal models may be
17 most appropriate, but I think it will be more clear
18 after the afternoon's presentations how well
19 characterized are these models. I think that
20 eventually hopefully the field will come to several
21 models reflecting back to the monkeypox and smallpox
22 models that were used to approve drugs and vaccines.

1 I think that disease progression could better
2 characterize some of these models. Pathology has
3 almost been done to almost an extent in some of these
4 models. The committee may want to agree what are the
5 important disease biomarkers that are going to be
6 quality checkpoints. So there is still lots of work to
7 be done.

8 So while I agree that at this point if you're
9 a researcher, it's good to test your strains in
10 different models, but I believe that if you approach
11 this systematically, we may end up with two or three
12 models that may represent different stages of disease
13 or different maybe even to some degree patient
14 populations.

15 And, of course, strains are absolutely
16 important and where they're coming from. So that's why
17 we have basic researchers here at the panel, because
18 they have to impress that upon us, that it's really
19 important. We can have totally different disease if
20 you use different strains.

21 DR. MILLER: Just to underscore Tina's point,
22 even when you take a classical pathogen, like

1 Salmonella typhimurium, and you take an animal model
2 such as the (inaudible) mouse where one organism will
3 kill that animal, if you get 10 clinical isolates from
4 people, they all have different pathogenicity in
5 systemic infection model in terms of how many it will
6 kill.

7 So you're looking at -- and this is something
8 where we understand the pathogenesis pretty well, and
9 we don't know why that's the case for these organisms
10 and what the basis for any of this is. And so we are
11 going to have to pick some models and standardize them
12 to some degree, and this is going to be particularly
13 challenging with these organisms because of their
14 plasticity and because they're not used to living on
15 plates, on growth media, and stuff, and they will adapt
16 very quickly to that.

17 DR. MARRA: I'm Andrea Marra, from Melinta
18 Therapeutics. And just building on Dan's point -- and
19 I think the discussion is coming around to this -- but
20 I've been doing this a long time, developing animal
21 models of infection for antibacterials, and I think the
22 key thing is the strains, and this is what we've been

1 talking about. And I think the most helpful thing,
2 especially with these two organisms, is a repository
3 that we all have access to.

4 So those of us in biotech, we don't have
5 access to the strains that people in other areas do.
6 And I can't get the clinical isolates that, say, Dan or
7 other people in government can get, and we don't have
8 the resources and budget and time to put lots and lots
9 of strains through these models. So I think the best
10 way to move forward would be to have access to the
11 strains that we can actually use to test our compounds.

12 DR. BONOMO: I know they are developing right
13 now biorepositories of strains that have been supported
14 by the NIH through the Antimicrobial Resistance
15 Leadership Group. There are at least 100 strains of
16 *Acinetobacter* and at least --

17 DR. MARRA: (Off microphone.)

18 DR. BONOMO: Well, they were the same ones
19 that came from the wounded soldiers at Walter Reed Army
20 Medical Center. So you could check what happened to
21 them, but that's all published data, whether they were
22 bloodstream infection or wound infection or pneumonia,

1 it's all listed as part of the metadata that's part of
2 that collection.

3 DR. MARRA: No, I appreciate that point, but I
4 know that if I get 50 strains in, I might find one that
5 is actually mouse virulent. And like I said, we don't
6 have the time or the money or the resources to do that.
7 And I know from Dan's experience that that's the case.
8 So a repository of mouse-virulent strains would be the
9 most helpful thing.

10 DR. BONOMO: Well, mouse virulence and human
11 virulence are different. Mouse virulence and human
12 virulence, there could be a different nuance there, and
13 how some of these drugs act in a mouse are very
14 different than how they act in a -- they could be
15 different than how they act in a human.

16 DR. MARRA: Yeah, they need to add to the
17 mouse.

18 DR. COX: Yeah. It seems that both are
19 agreeing on that, that there are differences in the way
20 the bacteria may behave as you move from the human to
21 the mouse. And I understand. So the idea was to have
22 a repository of strains that could be available to

1 folks developing drugs.

2 Is it directly relevant to the last comment?

3 PARTICIPANT: Yes.

4 DR. COX: Okay. Is yours?

5 PARTICIPANT: Yes.

6 DR. COX: Okay. Then we'll go in order.

7 We'll be right back with you in a sec.

8 DR. CAMPBELL: I guess what I was wondering,
9 and we talked a lot about animal models, but I know
10 there are more and more people are developing organs on
11 chips. I'm Joe Campbell. I'm a program officer in
12 Judy Hewitt's section. Developing organs on chips that
13 do start with human tissues. And I was just wondering
14 if relevant to some of this -- and especially Dr. Rex's
15 comments got me thinking about this -- that we're going
16 to have multiple models which all maybe have some
17 weaknesses, if human organs on chip models are
18 something that should be discussed.

19 DR. MILLER: I mean, I think there are
20 advantages, particularly for Pseudomonas and
21 Acinetobacter, particularly for even just polarized
22 epithelial cell models or tissue wound models that are

1 -- because it's human tissue derived. So, I mean,
2 those would be early stage, but it probably isn't going
3 to substitute for animal models or lead to actual
4 approval of a drug, but I think they could be useful
5 models for early testing of compounds that wouldn't
6 involve animals, which is advantageous.

7 DR. ZURAWSKI: I think you just have to do
8 both. I mean, I think it's your compound or whatever
9 you're bringing forward, you have to do as many things
10 as you can to feel good about it. We are personally --
11 like our lab now is moving towards doing some human
12 cell work, tissue culture cell work, and the goal would
13 be to correlate what we're doing in animals with that.
14 So I think if you can have a correlation again across
15 the board and feel good about it, yeah, do it and feel
16 better about your drug. I don't think it's a bad thing
17 to do.

18 PARTICIPANT: I just wanted to point out the
19 antibiotic resistant bank offered by the CDC and FDA.
20 It's a collection of 130 Pseudomonas and Acinetobacter
21 organisms that are serious, a lot of different
22 antibiotic resistance mechanisms. The genome sequence

1 is known. I think it's a fantastic resource that the
2 FDA and CDC group are offering. Oh, and available for
3 free in the United States.

4 DR. COX: Yeah, we're aware of that. I don't
5 know the full extent of it, but we can certainly get
6 you a contact, too. We'll try and do that before the
7 day is out.

8 And then another comment? No. Okay.

9 DR. MILLER: We're going to have a lot of
10 discussion later, and we were running a little bit
11 late. So maybe we should break for lunch and we'll
12 continue the discussion later.

13 (Lunch.)

14 Approaches to Animal Model Development, Future
15 Direction/Next Steps

16 DR. KNISELY: Welcome back from lunch,
17 everyone. It's 1:35, so I think we better go ahead and
18 get started, and hopefully others will trickle in. So
19 this afternoon we're going to have a kind of whirlwind
20 tour of what's out there, at least a glimpse of what's
21 out there in terms of existing animal models for
22 Pseudomonas and Acinetobacter. And then we'll have a

1 panel discussion about the features of those models and
2 where we might need to go.

3 So our first speaker this afternoon is Dr.
4 David Andes. He is a professor in the Department of
5 Medicine and Medical Microbiology and Immunology and
6 Head of the Division of Infectious Diseases at the
7 University of Wisconsin, and Director of the Wisconsin
8 Antimicrobial Drug Discovery and Development NIH Center
9 of Excellence. His research programs are
10 multidisciplinary and strive to identify strategies to
11 combat antimicrobial drug resistance.

12 PK/PD Consideration for Animal Model
13 Development

14 DR. ANDES: Great. Well, thanks very much for
15 the invitation to come today. This has been great so
16 far.

17 Can you hear me back there? All right. Now
18 can you hear me? Great. All right.

19 So I've been asked to talk about use of mouse
20 infection models to answer PK/PD questions. Here are
21 my disclosures. I primarily work with a variety of
22 drug companies doing PK/PD. And here's what I would

1 like to discuss. So first, what PK/PD questions can
2 these infection models help address? What study
3 variables can impact the PK/PD answers we get? And can
4 these models and PK/PD analysis be used to predict
5 clinical efficacy in patients?

6 So first, why do we conduct PK/PD infection
7 model studies? And simply put, it's to improve the
8 probability of a positive therapeutic outcome in our
9 patients.

10 So what do we do? Simply put, we tie drug
11 potency, in this case, MIC, to antimicrobial exposure
12 looking for a relationship between exposure and effect.

13 You've already seen the two workhorse models
14 introduced during the public comments earlier today.
15 These include the murine lung and thigh infection
16 models. They roughly mimic soft tissue infection,
17 sepsis, and pneumonia respectively.

18 They are neutropenic. This allows the growth
19 of organisms that otherwise are not pathogens in these
20 models. With neutropenia, they support the growth of
21 most bacteria. We utilize organism burden at the site
22 of infection as the primary endpoint. And I can tell

1 you that this correlates very closely with survival in
2 these animals using a much lower number of animals.
3 You would have to use anywhere from three to five times
4 the number of animals for statistical significance
5 using survival as an endpoint.

6 A large number of comparator antimicrobials
7 have been examined in these models. And, importantly,
8 as I hope I'll convince you in a bit, that outcomes
9 from PK/PD analysis in these models have been useful
10 for forecasting efficacy in patients.

11 So this is roughly our study design. Here on
12 the left, we have an image of a mouse getting a thigh
13 infection. And we initiate therapy in these animals 2
14 hours after infection. This allows the organisms to
15 grow into the log phase of growth.

16 These are both acute models. And the endpoint
17 after therapy is at 24 hours, where bacterial burden is
18 assessed, followed by an analysis of the relationship
19 between the pharmacokinetics at the infection site to
20 outcome.

21 So how do we determine how much and how often
22 to administer an antibiotic? the first PK/PD question

1 we ask.

2 So to do this, we, in these infection models,
3 vary not only the dose level, but the frequency of
4 administration, varying in what's called a dose
5 fractionation design.

6 Here's an example of data output from one of
7 these studies. This is with a cephalosporin antibiotic
8 in the thigh infection model, and you can see here on
9 the right, on the X axis, we see increasing doses. And
10 in these dose fractionation studies, we've administered
11 five total doses of drug fractionated into four
12 different dosing intervals. And what you can see is as
13 the dosing interval is shortened from once daily to
14 every 3 hours, you see a shift in the dose-response
15 curve to the left, indicating enhanced efficacy. So
16 administering smaller doses frequently would be the
17 most effective dosing strategy.

18 We then examined these exposures
19 pharmacodynamically. So each of these dosing regimens
20 is expressed as one of the three traditional
21 pharmacodynamic parameters, percent time above MIC,
22 Cmax/MIC, and AUC/MIC, using a Sigmoid Emax Model. And

1 you don't need to be a mathematician to see that in
2 this case, the tightest data fit is with time above
3 MIC, as you would expect with a cephalosporin.

4 And these types of analyses have, I would
5 argue, been completed for every antibacterial that has
6 come to market. And this study design has been,
7 without an exception that I'm aware of, been useful for
8 discerning the pharmacodynamic driver. Is it time
9 above MIC, AUC/MIC, or Cmax/MIC?

10 So the first question, again, is, Which is the
11 driver? And I think it's clear from the published
12 literature that dose fractionation in these models
13 reliably defines the PK/PD driver. This works with
14 Pseudomonas and Acinetobacter as well.

15 The second critical question is, How do we
16 define the pharmacodynamic target, or how much drug do
17 I need for efficacy? So to do this, we used the same
18 infection models and the same type of analysis, in this
19 case, introducing additional bacterial isolates,
20 preferably isolates with MIC variation. And then we
21 calculate the amount of drug required for a variety of
22 endpoints, varying from stasis, which is the burden of

1 organisms in these tissues at the start of therapy, to
2 killing endpoints, 1 and 2 log kill relative to the
3 amount of drug required relative to the burden of
4 organisms at the start of therapy.

5 As I mentioned, I would also like to discuss
6 some of the pharmacodynamic variables that can impact
7 the pharmacodynamic target, and I'll discuss a few of
8 these. I'll discuss those related to the organism and
9 some of those related to the host and how the host
10 handles these antibiotics.

11 Let's first start with the organism. And so
12 here is data again with the cephalosporin with a
13 Pseudomonas infection, in this case, the thigh model.
14 And we have a treatment study with two organisms.

15 So the Pseudomonas strain on the left you can
16 see with over this time above MIC exposure, the
17 response curve has shifted to the left, compared to the
18 Pseudomonas isolate number 2. What this results in is
19 a stasis target for the strain 1 of 16 percent, and
20 almost 40 percent for strain 2. So which of these, if
21 either, is the pharmacodynamic target? And how do we
22 address this?

1 To address this, we add additional strains, in
2 this case, 14 strains, again in the same model. And
3 you can see here in doing so, we reduce the variability
4 and identify the pharmacodynamic target for stasis, in
5 this case, is a time above MIC of 30 percent, moving to
6 40 percent for a 1 log kill.

7 So how many strains do you need to incorporate
8 into these models to robustly define the pharmaco-
9 dynamic target? I would say that's a difficult
10 question to answer definitively, but you would
11 certainly like to have enough isolates where your
12 median and mean approach each other and have the lowest
13 coefficient of variation as possible. I probably
14 wouldn't put less than 8 to 10 of these strains in
15 these models because of strain-to-strain variability to
16 define the pharmacodynamic target.

17 We would also like to examine the impact of
18 MIC variation. And here this slide represents a very
19 large number of studies, so this is 65 dose-ranging
20 studies, 65 organisms, several cephalosporins,
21 penicillins, and carbapenems with MIC range for each of
22 these drug classes varying more than 1,000-fold.

1 And in this case, each of these data points
2 represents the time above MIC exposure needed for a
3 stasis target. And what you can see is within drug
4 class, that the pharmacodynamic target is in each of
5 these situations relatively similar across the
6 different MIC phenotypes.

7 We can dive deeper and look at the impact of
8 specific drug resistance mechanisms on the
9 pharmacodynamic target. Here's an example with strains
10 expressing -- producing extended spectrum beta-
11 lactamases, a large variety of them.

12 This is data with 20 organisms and 4
13 cephalosporins. And you can see the relationships are
14 very similar on the left with the ESBL-producing
15 organisms, and on the right, and, in fact, if you
16 superimpose these two graphs, you see that the
17 pharmacodynamic target in this case is the same
18 regardless of whether or not an ESBL produced or you
19 have a wild type strain without ESBL production.

20 Let's move to the host and how the host
21 handles the drug as a PK/PD variable, in this case, the
22 impact of protein binding. So this is data from the

1 mouse thigh model with seven fluoroquinolones. So for
2 the fluoroquinolones, the PK/PD driver is the 24-hour
3 AUC/MIC. And what you can see when one looks at total
4 drug levels, it would seem that the amount of drug
5 needed for, in this case, stasis in the thigh model is
6 quite a bit higher for gemifloxacin and garenoxacin,
7 but what you also see is that the mouse protein binding
8 for these two drugs is quite a bit higher than the
9 other fluoroquinolones studied in this case. However,
10 when you normalize for free drug levels, you get a
11 level playing field, and that across the board, you
12 would need an AUC/MIC in this case. And this is a
13 study against pneumococcus, you need a 24-hour AUC/MIC
14 of about 25.

15 So it's important to consider protein binding
16 in these studies. It's also important to realize while
17 most commonly the degree of protein binding in mice is
18 similar and approximates that in humans, there can be
19 differences. So this needs to be accounted for in
20 translation of these animal model PK/PD studies to
21 patients.

22 Infection site. So for Pseudomonas, and

1 Acinetobacter, as we've heard earlier, the lung is an
2 important site of infection. We are able to look at
3 the impact of infection site and infection site PK in
4 these models. This is data in an MRSA infection model,
5 both the thigh and the lung, with an oxazolidinone, and
6 each of these vertical bars represent the oxazolidinone
7 AUC/MIC needed for on the left, the stasis endpoint,
8 and on the right a 1 log kill.

9 And what you can see is you needed quite a bit
10 more drug for the same endpoint in the thigh compared
11 to the lung. These are from two different labs. And
12 we speculate that the reason for this is because of the
13 higher ELF concentrations relative to blood
14 concentrations of the oxazolidinones in these infection
15 models and in patients.

16 We can look at that more specifically in each
17 of these infection models. Here is data with an anti-
18 infective that's under development where we would
19 predict efficacy would be the same in the lung and the
20 thigh. And I say that because the ELF pharmacokinetics
21 approximate the free drug plasma pharmacokinetics of
22 the same antibiotic in the same mice. And, indeed,

1 that's what you see in treatment studies with this
2 antibiotic where the AUC/MIC in ELF and free drug
3 plasma is the same for stasis and 1 log kill are very,
4 very close.

5 Now, as with protein binding, it's important
6 to recognize that, again, while ELF pharmacokinetics or
7 infection site pharmacokinetics can be similar in the
8 mice and in patients, there can be differences as well,
9 so you can't rely solely upon the mouse ELF
10 pharmacokinetics to predict what's going to happen.

11 Patients, I think the best example of where
12 that was a problem is with ceftobiprole, where in the
13 mice, the EFL to plasma penetration ratio was close to
14 .7, and it was much lower in patients, and I think most
15 of us know how that drug fared in those pneumonia
16 trials.

17 So the value, an additional value, of these
18 particular models is that there is a large amount of
19 experience in defining the pharmacodynamic target. In
20 fact, there is experience with more than 100 individual
21 drugs, more than 2 dozen drug classes, with a
22 standardized panel of organisms, including clinical

1 isolates, ATCC isolates, and those with defined
2 resistance mechanisms.

3 One of the points that came up earlier was the
4 importance of studying these clinical isolates and the
5 debate between whether or not you should study ATCC
6 strains or clinical isolates. I think studying both is
7 important.

8 The value of the ATCC strains is we have a
9 large amount of experience across a wide variety of
10 drugs. So if you've got your new drug, we can tell you
11 how that performed against these other 100 drugs and
12 how those did in patients.

13 So what I hope I've convinced you now is that
14 these mouse models can define the PK/PD target, but,
15 again, there are important variables to consider,
16 particularly protein binding and infection site
17 pharmacokinetics. But does this mean anything for our
18 patients? Can we use the answers from these mouse
19 models to forecast efficacy in patients? Why might
20 this work?

21 Despite the fact that the mice are smaller and
22 the pathogenicity of these organisms in the mice is

1 somewhat different, as long as we account for infection
2 site PK and recognize and remember that the drug target
3 is not in the mouse or in the patient, but in the
4 organism, so if we express the exposure
5 pharmacodynamically relative to the MIC, we should get
6 the same pharmacodynamic target in the mouse and in
7 patients.

8 And there is actually data to suggest that
9 this is indeed the case. This is data that some of you
10 may have seen before, and Dr. Ambrose presented this in
11 the summer. And this is a comparison of the answer we
12 get from the animal models and the answer we get from
13 treatment trials of these same antibiotics in our
14 patient.

15 So on the left here we have data from the
16 mouse thigh model with an antibiotic called
17 tigecycline. And you can see here as we increase the
18 AUC/MIC, we see stasis and then we see up to a 2 log
19 kill with AUCs/MIC greater than 100.

20 When we can then do, or what ICPD folks did
21 nicely, is to look at the exposures with tigecycline in
22 patients. So they look at infection site

1 pharmacokinetics from these clinical trials, and in
2 this case looked at the MICs of organisms from these
3 clinical trials, and you can see here that the exposure
4 of tigecycline in the HAP/VAP studies would have been
5 enough for the stasis endpoint in this infection site.

6 It's a bit worse when you break this out for
7 ventilator-associated pneumonia than it is for
8 hospital-acquired bacterial pneumonia. And it's not
9 surprising that with these lower exposures and large
10 amount of PK/PD variability that you might expect
11 treatment failure, as was observed in this clinical
12 trial.

13 The models can also predict success. So this
14 is data in the mouse lung model. This is from Arnold
15 Louie and George Drusano's group where with meropenem
16 against *Pseudomonas aeruginosa* in this model, you can
17 see a nice relationship between the free drug, in this
18 case, infection site time above MIC, so the ELF time
19 above MIC, with maximal efficacy up near time above MIC
20 values at greater than 75, somewhere between 75 and 100
21 percent.

22 What were the meropenem exposures in the

1 treatment trial? In this case, I believe this was 2
2 grams every 8 hours, and one sees that exposure, while
3 there is a large amount of variability, the mean
4 exposure was up near the plateau for efficacy in this
5 treatment trial, and one would have predicted in this
6 case treatment success, and treatment success was
7 observed.

8 So just so that you don't think that they were
9 cherry-picking with these examples, here is a group of
10 data that they pulled together from treatment trials
11 for community-acquired and hospital-acquired pneumonia.
12 So 20 different drugs, all of them but one studied for
13 hospital-acquired pneumonia. There are 14 of these
14 antibiotics for which treatment was successful and
15 regulatory approval obtained, and six that failed to
16 gain approval.

17 What does this data look like when you look
18 back at predictions from the infection model PK/PD? So
19 if you're a visual person, look on the left, and this
20 is the relationship between the probability of PK/PD
21 target attainment in the animals and the probability of
22 NDA approval, with the solid symbols representing those

1 treatment trials for which the drug was approved, and
2 the hollow symbols representing those failures.

3 So as you move up and increase the likelihood
4 of target attainment, you see more drug approvals.
5 Now, there are some drugs that had high likelihood of
6 target attainment for which the NDA was not approved,
7 in this case, due to, on the far right, safety, this is
8 with garenoxacin, on the left, below here, is the
9 daptomycin exposure.

10 And if you're numerically inclined, you can
11 see here the probability of target attainment. And so
12 by target attainment in this case, I mean you achieved
13 a 1 to 2 log kill in the lung model with these
14 antibiotics. And you can see if you achieve that
15 target, you had a very, very high likelihood of FDA
16 approval.

17 What have we learned from this type of
18 analysis? I think we've learned that these mouse PK/PD
19 models can be used to forecast efficacy in patients.
20 And we also get some sense of where we should be, what
21 the hurdles should be, in these infection models for
22 the infection site. So if one is going after hospital-

1 acquired pneumonia, one should be probably looking for
2 a 2 log kill in the infection site model in the mice.

3 But as you've heard in the discussion earlier,
4 a mouse is not a human. There are differences. These
5 infection models for PK/PD purposes are not meant to
6 study organism pathogenesis or virulence. These mice
7 are not susceptible normally to these pathogens. There
8 are occasional strains that can produce infection in
9 non-neutropenic animals, but most of these organisms
10 need the absence of neutrophils for recovery.

11 And there can be pharmacokinetic differences
12 between the mice and patients. But as long as you take
13 that into account, differences, potential differences,
14 in protein binding, potential differences in ELF, I
15 think it's clear that these models can be used to
16 forecast effective regimens in our patients.

17 And with that, I'll thank you for your time.

18 DR. KNISELY: Thank you, Dr. Andes.

19 Our next speaker is Dr. Matthew Lawrenz. He
20 is interested in defining interactions between
21 bacterial pathogens in the host immune system. In his
22 research, he routinely uses animal models to study both

1 bacterial pathogenesis and for vaccine and therapeutic
2 testing. Many of his efforts have focused on plague,
3 but since 2014, he has also been using the mouse model
4 for preclinical screening of novel therapeutics
5 targeting MDR *Pseudomonas aeruginosa*.

6 Mouse Model of *Pseudomonas* Infection

7 DR. LAWRENZ: All right. I would like to
8 start by thanking the organizers for the invitation.
9 It's great to be here in a *Pseudomonas* field instead of
10 just a *Yersinia* field.

11 The model that I'm going to tell you guys about
12 today was developed at the University of Louisville,
13 and this has been done in collaboration with a good
14 partner of mine, Jon Warawa, who is also in the
15 Microbiology Department. And we have a team at the
16 Center for Predictive Medicine that's shown on the left
17 there that is our animal core that runs all of our
18 animal experiments for us and allows us to do these
19 experiments, as they're very labor-intensive.

20 I also want to mention that this model was
21 designed in collaboration with NIAID, specifically to
22 start to go after and look at new therapeutics for

1 Pseudomonas.

2 The model that I'm going to tell you guys
3 about today, I want to highlight a couple things as we
4 go along, and I probably won't be able to hit all of
5 the different items that go into this model
6 development, but this has been published, just so you
7 guys are aware, in a couple papers that are on the
8 bottom.

9 What I'm going to highlight today is a little
10 bit on the installation method that we used to
11 establish a lethal infection. And this is a lung
12 infection, so we're looking at a pulmonary infection.

13 We have talked a lot today about the
14 differences between immunocompetent and
15 immunocompromised. We tend to use the
16 immunocompromised model for all of our therapeutic
17 testing, but I'll show you a little bit of comparison
18 between those two. More of this is covered in the
19 publication.

20 We spent a long time developing nonsubjective
21 bio endpoints, biometric endpoints, for this model, and
22 we did that because, as you saw, we have a large team

1 of people that we work with. We also have multiple
2 health check time points over the course of this
3 infection model. And so we wanted to be able to rotate
4 people in and out without losing or I guess gaining
5 variability based on behavioral characteristics that
6 can be used.

7 And then at the end, I'll highlight some of
8 the multiple parameters that we can use to monitor
9 therapeutic efficacy in this model.

10 When we first developed this model, again,
11 this is a pulmonary or lung infection model, and so
12 there are different ways that we can introduce the
13 bacteria into the lungs. And, of course, one of the
14 most common is intranasal. We do that a lot for our
15 plague model, but we have to worry about for certain
16 infections whether or not there is going to be some
17 complications due to involvement of the upper
18 respiratory tract.

19 There is also the potential for variability in
20 the inoculum as the intranasal or the droplet of
21 bacteria descends the upper respiratory tract into the
22 lower respiratory tract. And so we didn't want to

1 introduce those variables into the model.

2 The other method that's used widely is a
3 conventional intratracheal model that is usually a
4 surgical model. It can be a little technically
5 difficult. It can be slow. And we were worried about
6 the potential for blood contamination during that
7 surgical procedure.

8 And so the method that we came up with is an
9 intubated mediated instillation method, we call it
10 IMIT. Essentially we intubate the animals, the
11 anesthetized animals, and then guide the catheter down
12 the trachea using an otoscope. We then insert a blunt
13 needle into the catheter, and we instill about 50
14 microliters of bacteria through that using a Hamilton
15 syringe. We also include about 100 microliters of an
16 air pocket behind that, and so we're essentially
17 causing the animal to take a nice little deep breath
18 after the bacteria are instilled.

19 We can do this with a team of about two
20 people, and when they're well trained, we can do less
21 than a mouse a minute by this method. And so that
22 allows us to be able to do large groups of animals when

1 we're using this instillation method.

2 These two images here show some of the
3 benefits of IMIT. So one of the things that we notice
4 when use this is that we get a broad distribution of
5 the inoculum. So in the center, there are the lungs of
6 an animal that was instilled with Coomassie dye, and
7 then we harvested the lungs immediately after the
8 instillation process. And you can see the dye is
9 distributed throughout the lungs in this case.

10 The other thing about the IMIT method is that
11 it's highly efficient at its delivery. So the graph on
12 the right-hand side there shows the CFU that was
13 intended to be delivered to the lung on the X axis, and
14 then what we recovered in the lungs 20 minutes post-
15 infection or instillation on the Y. And you can see
16 with those different doses that on average we were able
17 to recover about 98 percent of inoculum. So we have a
18 very good idea of how many bacteria we're instilling in
19 the lungs each time we perform this.

20 Furthermore, it's very reproducible. At each
21 one of those doses, there are multiple animals in
22 there, and you can see that it's very tight in the

1 inoculum. So we feel very confident that at least as
2 we start out on the inoculation that we're not
3 introducing a lot of variability into this model.

4 So using the IMIT model, we were able to
5 establish lethal infection in both immunocompetent and
6 immunocompromised animals. All the data that I'm going
7 to show you from here on out is using a clinical
8 isolate of Pseudomonas called UNC-D, which is a lung
9 clinical isolate. On the left-hand side is just our
10 BALB/c model, which we consider our immunocompetent
11 model, and on the left is our leukopenic or neutropenic
12 model that is established using cyclophosphamide.

13 And what I want to highlight here is, of
14 course, as we've been discussing today, introducing
15 neutropenia allows us to establish an infection with a
16 much lower dose of bacteria. And, again, we tend to
17 use this for all of our therapeutic studies. There are
18 problems with the immunocompetent mice if we put large
19 numbers of bacteria in the lungs and then hit them with
20 antibiotic. The immune system doesn't really like dead
21 bacteria and LPS floating around, so there are some
22 complications based on that.

1 As I said, the other thing that we wanted to
2 do when we established this model was to establish
3 those biometric endpoints. And so I'm showing you data
4 here on the temperature. With these animals, they all
5 have transponders, so we monitor their temperature. We
6 also monitor the heart rate and oxygen levels using a
7 mouse ox system. And then we've developed a checklist
8 based on the kind of natural history of this disease.

9 So the temperature is on the right-hand side.
10 The colors match to the infectious doses in the
11 survival curve on the left-hand side. The symbols that
12 are open are animals that succumbed to the infection.
13 The ones that are closed are animals that survived.
14 And the grey box is kind of our normal range for
15 temperature. And we did this for both heart rate and
16 oxygen also.

17 Based on these, we knew that our primary
18 indicator of morbidity is temperature, and we know that
19 once we reach about 26.6 degrees, that those animals
20 won't make it till the next health checkpoint. And so
21 based on these criteria -- these are also I think
22 fairly stringent -- we're trying to get as close to

1 death as we can get, and these allow us to get there.

2 And so individuals that go in use this checklist in
3 order to monitor morbidity.

4 In addition to temperature, there are a lot of
5 other things that we can measure in this model to look
6 at therapeutic, potential therapeutic, efficacy. So,
7 of course, we have survival and mean time to death that
8 we can look at.

9 The temperature, that's all from a lethal
10 infection, but we have seen with therapeutics that we
11 get a nice rebound in the temperature if those
12 therapeutics are going to work.

13 We can also look at bacterial load in the
14 lungs. So at the site of infection, our primary place
15 where we want to look.

16 But we can also follow whether or not the
17 bacteria disseminated in the bloodstream from that site
18 by looking at the spleens.

19 And then, finally, for our animals, we also
20 harvest the lungs and we look at pathology, so we can
21 look at if there are differences in the host response
22 or the development of pneumonia in these animals.

1 For the last couple minutes here, I just want
2 to show you a couple of examples of some antibiotics
3 that we've run through this model. The two antibiotics
4 that I chose for today are polymyxin B and meropenem.
5 The data that's on the slide right now is the in vitro
6 EC50s of these drugs, and the MICs are shown at the
7 bottom.

8 You can see with polymyxin -- again, I'll
9 remind you guys, this is a multidrug-resistant UNC-D
10 strain of Pseudomonas. And the MIC for polymyxin was
11 at 1 mcg/ml, making it -- it falls into the sensitive
12 category. With meropenem, it's a little more
13 resistant, it falls into that intermediate category at
14 8 mcg/ml.

15 When we look at lung, the lung burden, and so
16 these animals were instilled with a lethal dose of the
17 bacteria. Three hours post-infection we began
18 antibiotic treatment by subcutaneous inoculation, and
19 we continued that treatment every 8 hours for 5 days,
20 and then continued to monitor the animals 2 days after
21 we ended treatment. The lung data here is pulled at
22 the time that the animals were euthanized, so either if

1 they succumbed to the infection or if they made it to 7
2 days post-infection.

3 You can see with the polymyxin, which is on
4 the left-hand side, that as we increase the dose of
5 polymyxin over the course, we begin to see significant
6 decreases in the bacterial load in the higher doses.
7 And we see the same trend in meropenem even though it
8 is in that intermediate resistance category.

9 I also want to point out on the meropenem side
10 that you can see that there are several animals, the
11 dotted line indicates the limit of detection, and so
12 there are animals in this case that we were unable to
13 recover detectable bacterial loads in the lungs.

14 So even though we were able to see a decrease
15 in the bacterial loads in some of the higher doses of
16 the polymyxin treatment, when we look at the survival
17 curve here now, we were unable to differentiate any
18 differences between treatment with polymyxin and the
19 vehicle-only controls. We also saw no change in
20 dissemination. So there was no control of getting to
21 the spleen, and there were no significant differences
22 in the development of pneumonia in these animals.

1 On the other hand, when we looked at
2 meropenem, we see a nice dose-dependent increase in the
3 mean time to death, moving from left to right, there is
4 from lowest dose to highest. We can calculate an ED50
5 in these studies. We also saw that the higher doses of
6 meropenem where we're seeing protection are protecting
7 the animals from developing septicemic infection by the
8 organism.

9 And I'm not showing you it, but the ability of
10 the bacteria to protect the animals also results in a
11 decrease in pathology in the lungs.

12 So I just want to leave you guys with a little
13 bit here. The mouse model is very amenable to many
14 different things when we look at it. So we can use
15 several different routes of administration for these
16 therapeutics in our hands. I showed you data from
17 using subcutaneous treatment, but we've also done IP
18 injection. We've looked at molecules that can be
19 directly instilled into the lungs. We can do that
20 either by intranasal, or we can actually go back and
21 reintubate the animals and treat them by IMIT also.
22 And we also have used nebulizers to look at aerosol

1 delivery into the lungs.

2 Importantly, I think this model has the
3 capability not only to screen monotherapies, which I
4 showed you today, but also combination or adjunct
5 therapies. So especially with meropenem, where we're
6 at that intermediate range for treatment, if there are
7 potential therapies that might be thought to improve
8 the ability of existing antibiotics to work against
9 these organisms, the meropenem, at least in our hands
10 and with this strain, allows us to do adjunct
11 therapies.

12 Using this model, so far we've been able to
13 test 11 different novel therapeutics, and I just wanted
14 to highlight that those have ranged anywhere from novel
15 antibiotics to small compounds or even biologicals.
16 And even though this is a leukopenic model at the
17 beginning, we're also able to test therapeutics that
18 may potentially target the host as opposed to just
19 targeting the bacteria, so an immunomodulatory type of
20 compound.

21 So I would like to thank you for your time,
22 and I guess I'll leave it up for the next speaker.

1 DR. KNISELY: Thank you, Dr. Lawrenz.

2 Our next speaker is Dr. Daniel Zurawski. From
3 2009 to the present, he has been contracted by the U.S.
4 Army to manage a laboratory in the Wound Infections
5 Department at Walter Reed Army Institute of Research.
6 And he is also an adjunct professor at the University
7 of Maryland Dental School in the Department of
8 Microbial Pathogenesis.

9 Mouse and Pig Models of Acinetobacter
10 Infection

11 DR. ZURAWSKI: All right. So good afternoon,
12 everyone. I'm going to try and keep you awake here in
13 the afternoon. After lunch, everybody is getting a
14 little sleepy.

15 So I'm in the Wound Infection Department
16 literally I think it's 8 years today, to the very day.
17 I started March 1, 2009. And the work I'm going to
18 show today was really the first probably 3 or 4 years
19 of work that we did there. And the typical disclaimers
20 here for a government employee.

21 One of the things that we care about obviously
22 with the Army are IED blasts and soldiers getting

1 wounded, and then the consequences of that oftentimes
2 is infection afterwards. And so these are just some of
3 the numbers on that. And the typical bad actors that
4 we see there are the ESKAPEE pathogens. I'm adding an
5 E there now because of E. coli, where we've seen a big
6 uptick of E. coli, but certainly Acinetobacter was a
7 big player in this with the Iraq War, and we needed
8 countermeasures, and we needed to understand the bug
9 better.

10 As Dr. Bonomo pointed out earlier, we still
11 don't, even to this day, understand the pathogenesis
12 very well and how Acinetobacter does its thing, but
13 we're learning more and more as more people are working
14 on it now. So that's what I decided to focus on when I
15 started.

16 But at the present day, our department is
17 doing quite a bit of things. We're still studying
18 basic science, pathogenesis. You can see that, it's on
19 the left there of the slide, and that funnels into all
20 these therapeutics that we're using and attempting to
21 use. A small molecule program we have that's run by
22 ET, Experimental Therapeutics. We have a pretty robust

1 phage program now. I'm working on monoclonal
2 antibodies. And then we also have the kitchen sink
3 there. And we also partner with pharma and academia
4 also testing their therapeutics as well, all funneling
5 into our animal models.

6 And I did want to bring up one point in the
7 little intro here about Acinetobacter because some
8 people have suggested that it's not a good pathogen or
9 it's a low virulence pathogen. I disagree. I actually
10 think if the situation is correct, it will take off and
11 cause quite a bit of problem, and clearly the amount of
12 patients where the mortality levels are so high, it's
13 definitely an issue.

14 And I wanted to bring up that the CDC numbers
15 are 750 deaths a year in the United States. That means
16 every day two patients die from Acinetobacter. Now,
17 that may not seem like a lot, but to me, it's a lot.
18 That means today, just doing this meeting, two people
19 died because of this bug, and it shouldn't be the case.
20 We should be able to get over this and really start
21 making new drugs and get on it. Those are people's
22 families that are being affected.

1 I'm showing this slide because I wanted --
2 this is a recent study from Brazil -- I wanted to show
3 that all these bugs are playing a role in wound
4 infections. This is actually a wound infection study.
5 But if you actually combine Acinetobacter species
6 together, so you've got baumannii there, and you've got
7 the other Acinetobacter species, it actually makes 12
8 percent of all the wound infections that they're seeing
9 in Brazil. And this actually holds true, if you look
10 at a lot of studies in Central America, South America,
11 Asia, this number actually holds very true most of the
12 time. So it's actually one of the things that from the
13 world's standpoint is very important. We're seeing a
14 lot of it in Third World countries as well.

15 So I'm going to go through model development.
16 I'm going to take this into three parts: so strain
17 selection, then talk about our murine pulmonary model
18 of infection, and then go through our wound models. We
19 have two wound models of infection, we have a mouse
20 wound model and a porcine model as well.

21 So strain selection. We were kind of getting
22 at this earlier. Which strain are you using? What are

1 you going to use? And so when I first started in 2009,
2 I had tried using the ATCC strains in a lung model of
3 infection, and I could never get the animals that die,
4 and I'm like, how are we going to do this? We don't
5 have a survival model to test anything. And I was
6 really interested in virulence. I wanted to find the
7 genes that were required for virulence so we can make
8 monoclonals against them, and we're still doing this to
9 this day. But if you don't have a strain that kills
10 the animal, it's really hard to do a survival study to
11 look at virulence.

12 So that really prompted me to go in and dig
13 into these other strains, certainly the clinical
14 isolates that we have the access to with the Army, we
15 were getting them from patients very routinely. And
16 then I set up basically a criteria of what I wanted
17 that strain to be.

18 So I wanted it to be clinically relevant, it's
19 got to be a recent isolate, it's got to have actually
20 shown to have an infection in a human. I want them to
21 be MDR/XDR to fit the current problem of drug
22 resistance. I want it to be genetically amenable so we

1 can actually look at virulence factors. So it had to
2 have basically some susceptibility somewhere so we can
3 actually use markers to knock out genes. So we put
4 that on the list. Cause some more infections across
5 all different animals of infection.

6 So I'm going to show you these models today.
7 But we've also done a rat wound model at one time. We
8 did a rat fracture model with some collaborators. And
9 this same strain carries through all these models.

10 We wanted something that's more virulent. So,
11 of course, you want a more virulent strain to kill the
12 animal if you're doing a survival study, but it's also
13 about enhancing the therapeutic window. So if you can
14 actually show a large difference between something
15 that's treated versus untreated, that's really
16 important. And with our wound model, I'll show you why
17 that's important.

18 Can we predict efficacy? So Matt just showed
19 some stuff where he took FDA-approved antibiotics
20 already through his models and shown that they actually
21 work and kill bugs. We can do the same with our
22 models. And can it be standardized across more than

1 one model? And as I said, we did that as well.

2 So early literature. ATCC strains. Those
3 strains are 60-plus years old now. They're from 1955.
4 They're just completely not relevant at all. They're
5 not virulent at all. It doesn't take into account any
6 recent evolutionary changes.

7 And as I mentioned earlier, the Acinetobacter
8 genome is extremely plastic. It changes within a
9 patient literally in hours. It can pick up DNA very
10 readily, incorporate it into its genome, picks up
11 plasmids from all over the place, it will pick up a
12 Klebsiella plasmid, it will pick up a Salmonella
13 plasmid, and utilize it. And it can go into its genome
14 or keep it as a plasmid. I mean, it's very, very
15 volatile as far as its evolution goes. So when you're
16 using strains that are that old, you're missing a lot
17 of these recent events, and those strains are not --
18 they're literally susceptible to every antibiotic.

19 So we went into the recent literature, and
20 some French groups were looking at clinical isolates
21 for virulence. And then Tom Russo, at SUNY Buffalo,
22 was also looking at a rat pneumonia model as well, and

1 he was looking at some strains. So we kind of used
2 those folks to kind of set up what we did.

3 And so here is a list of 33 strains that we
4 looked at. These are all military isolates. They all
5 came from patients that actually had an active
6 Acinetobacter infection. And they're basically set up
7 here as far as their clade, and the clade is based on
8 pulsed field gel analysis.

9 And if you look at all the military data from
10 2003 to the present, you can basically put
11 Acinetobacter into 34 different clades. And there are
12 four major clades. And so that's the first ones at the
13 top there. And then there are 30 minor ones. And so
14 you can basically group them into that just based on
15 PFGE.

16 The PFGE is not necessarily the best way to
17 characterize strains, obviously we use MLST and all the
18 other things now as well, but this did give us a way
19 just to look at variability.

20 And then these isolates, I chose them for
21 their variability based on PFGE, but I also chose them
22 for where they were isolated from. So we have some

1 that are from bone infections, some that are from
2 blood, some that were from wound infections, to really
3 give a nice diverse set here that we can use and look
4 at.

5 And so this is just PFGE data that shows how
6 different they are. And clonal complex there on the
7 right is how the European groups originally started
8 classifying *Acinetobacter* into three clonal complexes.
9 Now there's a fourth complex, and you can kind of see
10 the four complexes there, how they're laid out. And so
11 these minor clades are actually little subtle changes
12 in the genome within the four major clonal complexes.

13 And if you evaluate these strains looking at
14 different in vitro characteristics, you can look at
15 biofilm diversity here. So you can see all these
16 strains make varying biofilms. Some make really great
17 biofilms, some don't, but this is all in vitro.

18 And Dr. Bonomo mentioned motility before. So
19 this is a slide showing motility, and it's also being
20 kind of superimposed on top of optical mapping. So
21 optical mapping is a way to chew up DNA and put it on a
22 glass slide and look at it, and so there's a company,

1 OpGen in Gaithersburg, that's doing that. And you can
2 actually sort your diversity that way just based on
3 what the DNA looks like via the optical mapping. And
4 if you do that and also put motility there, you can see
5 how diverse they are. They just all do different
6 things. They swim on plates differently, and there are
7 different patterns. So clearly this set is very
8 diverse.

9 But what we cared about was virulence, and so
10 here's virulence in the wax worms. This is the first
11 model that we started with because there was a
12 publication by Anton Peleg about it. And you can see
13 here that the strains all have varying virulence in
14 this model.

15 We also have a little bioluminescent
16 Acinetobacter down there. We use bioluminescent
17 Acinetobacter as well in some our models. I'm not
18 going to go into that as much as I probably should have
19 today, but if you want to ask questions about it, you
20 can ask questions later.

21 And this model is very black and white.
22 They're either dead or they're alive. And the worms

1 either turn black when they die or they stay white.
2 That's how it works. And you can see that there is one
3 strain, the square bar there, that's going across that
4 pretty much by 24 hours over 90 percent are being
5 killed or over 80 percent at least are being killed by
6 this strain. And that's AB5075.

7 We do like this model because sometimes it
8 does appear to translate into mice later on. And we
9 love the model because we can do tons of worms.
10 They're super cheap. You can buy 1,000 worms for like
11 \$50. So like our N group of 20, I mean, you can do
12 tons of stats on this and really evaluate and get some
13 good data.

14 Okay. So on to the pulmonary model. So once
15 we got an idea that the strain 5075 was more virulent,
16 in this model, we wanted to then follow it up and see,
17 does this really hold true into a pulmonary model?

18 So we're using an intranasal inoculation.

6

19 We're pretty consistent with this. We do 10 most of
20 the time. We lose about a log sometimes in the nose
21 and the areas, stuff like that, but we're pretty

5

22 consistent. We always get at least 10 into the lungs

1 every time. And we've measured at time zero.

2 So it is cyclophosphamide. It's a temporary
3 neutropenia. It allows us to start with a real low

6

4 inoculating dose, 5 times 10, and then we see disease
5 progress. And basically, with 5075, we see death in
6 just 48 hours.

7 We can do clinical scores, our endpoints, our
8 clinical scores, and CFU enumeration. We always take
9 CFU day two. This is right before the animals
10 basically start to perish. So we are getting our
11 control group, and then we're also getting our treated
12 groups as well at that point.

13 And I just wanted to show, here are bacterial
14 levels in lung tissue, just between the different
15 strains I showed earlier. So you can see 5075, the
16 white box, has a higher CFU burden in all these strains
17 than the other strains, and then that, in turn, leads
18 to what we see as dissemination, enhanced
19 dissemination, with that strain, and basically more
20 death, more death by day two.

21 The histopathology, if you look at the lung,
22 the lung sections here are A and B, and in B, there's a

1 small arrow there on the right pointing to basically
2 what we see are droplets, they're almost like droplets
3 of bacterium, which I think are actually biofilm-like,
4 probably in the middle, and then you have planktonics
5 on the outside as they're growing in the lung.

6 Typically, the bacteria are on the sides of
7 the lobes of the lung that are closest to the trachea.
8 So *Acinetobacter* is strictly aerobic. It does not do
9 so well in low-oxygen conditions. It does okay, but it
10 doesn't do great. So as far as the actual pathology of
11 the model, you're actually seeing the *Acinetobacter*
12 focus more in those lobes closer to the trachea.

13 However, after about 24 hours, getting into
14 that day 2, we start to see dissemination from the
15 lung. It then goes to other organs in the body. On
16 the left there, that is the adrenal glands. On the
17 right, D, that is the kidney. So it goes to both of
18 those places, colonizes both organs. We also see a
19 colonized spleen, liver, heart as well. So we looked
20 at all the organs of the animal. And that basically
21 leads to organ failure, and then death.

22 I would like to think that that's what's going

1 on in patients, in human patients. I don't know if we
2 really know for sure. I don't know if a lot of work
3 has been done clinically on how we looked at organs
4 after patients have died and what kind of colonization
5 we see. It's something we can maybe talk about later.

6 We also put through rifampin as a proof of
7 concept, so we've got varying doses of rifampin here.
8 And you can see that 5075 with sub-MIC treatments or
9 subclinically relevant treatments will still kill the
10 animal at 48 hours, but if you increase the
11 concentration up to 10 mg/kg, we start to see
12 clearance, and the animals survive. And so we can use
13 that to our advantage when looking at things.

14 And so one point that I want to show is show
15 that advantage as an application. We partnered with
16 Spero Therapeutics and looked at their compound,
17 SPR741. This is a new compound that potentiates, it
18 actually pokes holes in bacteria and allows other
19 antibiotics to get into the bacteria much more readily.

20 And in this case, we actually took advantage
21 of the rifampin data that we had where at 5 mg/kg we
22 only see 50 percent survival, but if we take that

1 concentration and then mix it with Spero's compound,
2 you can see we push that up to 95 percent survival in
3 this situation.

4 So understanding how the antibiotics work with
5 your model strain, you can then use that to your
6 advantage and always have clinical comparators
7 throughout.

8 And then if you look at CFU, we can also
9 measure CFU, and the combination there are the pink
10 animals, and we see about a 5 to 6 log reduction with
11 the combination, whereas the rif alone, it's about 4
12 logs. And so the combination is definitely allowing
13 for a better hit on the animals, which, in turn, is
14 leading to this clearance.

15 Okay. So that's the lung model. We're going
16 to move to the wound model now. The same concept here
17 where we do a temporary neutropenia. We inject
18 cyclophosphamide day -4, -1. Concentrations there are
19 150 mg/kg, and at 100 mg/kg, that's basically
20 throughout the literature for most of these models.
21 Again, temporary neutropenia the first 3 days.

22 I wish I had brought the slide where we see

1 the white cell count just come up at day 3. It drops
2 to about 1,000 or less, by day 3, it's up to like maybe
3 5- or 6,000, like it's already starting to skyrocket.
4 Normal white blood count in a mouse is anywhere from 3-
5 to 5,000. So it actually goes above that normal count
6 with the infection there at that day 3 point, so it
7 really comes roaring back.

8 The other note I wanted to make about the
9 neutropenia is that there are other insults to injury.
10 With the soldiers, we see massive blood loss. They're
11 likely getting morphine because they have crush injury
12 or blast injury on top of the actual wound infection
13 and things. And we know that that systemically plays a
14 role in basically dampening the immune response.

15 Okay. So both *Pseudomonas* and *Acinetobacter*,
16 we know the innate immune response is clearing these
17 bugs out. That's the thing that is you're a normal
18 healthy human, clears these bugs out no problem, that's
19 what's doing it, it's neutrophils and white blood
20 cells. If you're getting morphine, morphine dampens
21 that immune response. If you lose a ton of blood and a
22 lot of blood replacement, dampens the immune response.

1 So all that neutropenia is doing is trying to
2 temporarily dampen that immune response to kind of get
3 something clinically relevant.

4 In this situation, so you can see the
5 endpoints up there, wound measurement, CFU enumeration.

4

6 In this situation, we're only doing 5 times 10
7 Acinetobacter, very, very low dose, we think very
8 clinically relevant. We can kick that dose up to 1

5

9 times 10 or go actually more than that, probably like
10 a log higher, we'll actually see dissemination from the
11 wound, they'll go septic, and kill the animals.

12 So we had to play around to find that dose.
13 If we went too little, we didn't see a nice wound
14 infection. If we went too high, we were killing the
15 animals via sepsis. So finding that dose was key. And
16 we can use this model, by the way, for all ESKAPEE
17 pathogens, not just Acinetobacter. And we had to do
18 the same thing for all of the strains that we're
19 working with.

20 We have an amazing team. They're rare. Our
21 animal team right now consists of four people, and so
22 it literally becomes like a factory assembly line where

1 each person has a different station.

2 And so one person anesthetizes and shaves the
3 animals, the next person wounds them, passes the mouse
4 on, where we measure the wound with an Aranz
5 instrument. This is the older instrument. We have a
6 better instrument now that fires a laser, actually two
7 lasers, to measure the wound, and then we measure the
8 wound over time with the instrument down the road. And
9 then the next team member is then inoculating.

10 We also inject with a small amount
11 buprenorphine to keep the animals pain-free, and then
12 we put a Tegaderm dressing overtop.

13 So basically there are all these stations, and
14 each person is doing their job. And we can roll
15 through 60 mice in about an hour and a half, 2 hours.
16 And it's amazing. Every week we're doing 60 mice.
17 It's 52 weeks a year. Our capacity now is up to 300
18 mice if we really wanted to, that our team is
19 expanding. So it's quite an effort.

20 And this is just some of the data that you can
21 get. So we can take punch biopsies out of that wound,
22 we can do SEM, we can do 16S for microbiome, we take

1 blood from the animal, look at systemic, if there is
2 anything systemic going on for the immune system. We
3 can certainly plate and do CFUs at different time
4 points. You can just do gross pathology, look at the
5 wounds itself.

6 So this time we've got antibiotic comparators
7 here. So on the left side you've got your untreated
8 nasty wound infection, goes all the way out post-day
9 21. We see it close maybe around day 25. Again, the
10 animal is not dying. The wound eventually closes and
11 heals. But if you treat with rifampin or you treat
12 with doxycycline, these are two antibiotics that this
13 strain is susceptible to, you start to see the wound
14 close around day 15. So you can see that there in that
15 picture.

16 And what that leaves is this big 10-day what I
17 call therapeutic window where if you have an antibiotic
18 or a new compound or something you want to test -- and
19 we test lots of things, we're testing predatory
20 bacteria now, we're testing bacteria phage, we're
21 testing lots of different antibacterial approaches --
22 but if you want to get an idea of how well it's

1 working, it may not be as good as rifampin in this
2 thing, your wound may not close at 15 days, but it may
3 close at 18. And so what that does is it provides
4 guidance back to our partners, hey, this worked well,
5 maybe not as well as rifampin, maybe you could tweak
6 your molecule a little bit, go back to the chemistry
7 drawing board, make it, I don't know, more soluble,
8 make it more efficacious, just give them more ideas to
9 work with. So that's how we kind of work with the
10 folks we work with.

11 For wound area, you can see obviously a big
12 difference in treated versus untreated, and, again,
13 that carries through those time points. And this is
14 all published, by the way, in AAC, and you can see the
15 reference there.

16 Histopathology, we can do the same thing and
17 track wound closure and the re-epithelialization. I've
18 heard some comments that, well, mice don't heal the way
19 humans do because they have contractile healing. That
20 is true. You can add a splint so there isn't
21 contractile healing with mice, and then they will heal
22 by re-epithelialization. All that being said, it still

1 is -- again, we're seeing efficacy and we can still use
2 this to look at efficacy.

3 I wanted to show this. It wasn't in the
4 original slide deck, but this is using a PNA FISH
5 probe. We're actually look at Acinetobacter throughout
6 the wound bed and even all the way down. So what's
7 kind of cool about this, all the way down here is
8 muscle and then bone.

9 And what we saw in patients, what we saw in
10 infected humans, was the Acinetobacter actually
11 progressed its way -- I was getting stuff from doctors
12 all the time over at Walter Reed telling me, look, we
13 see Acinetobacter going from the wound all the way to
14 muscle, it's progressing throughout the tissue. It's
15 not just staying in that wound bed.

16 And so when we saw the same thing -- and
17 that's not the greatest slide, but we were seeing
18 Acinetobacter in E, which is the basal bottom of that
19 muscle down there, and we were even seeing it sometimes
20 associated with bone. So we were seeing what we
21 thought was very close to what's going on in human
22 patients, and this is what I was hearing from the docs

1 over at Walter Reed.

2 Okay. So CFU. Obviously, we can take punch
3 biopsies out of the punch that we made and then count
4 CFU, and, again, there's a nice difference there. And
5 everybody, of course, talks about wound infection and
6 biofilms, and so we certainly wanted to evaluate
7 biofilms as one of our methods, and we just do this
8 SEMs, so we take that punch out.

9 You can see the biofilm is really nasty in the
10 placebo, but with treatment, it kind of clears out when
11 we use different treatments. What's really left there
12 is just it looks like polysaccharide and red blood
13 cells that are left when we treat properly.

14 So I want to give one example. This is not
15 published yet, but I hope to publish it soon. One
16 example reviews the wound model to look at something.
17 So in this situation, I'm looking at a monoclonal
18 antibody to a virulence factor of Acinetobacter, the
19 type six secretion system. We add the antibody
20 prophylactically day -1, and then we just run our wound
21 model the way we normally would, and you can see that
22 it actually curbs the wound size, it actually allows

1 for the wound healing to take place a little faster.
2 We're still working on this. We're actually making a
3 cocktail against the number of targets on the surface.
4 But the proof of the pudding is always actually looking
5 at the animals themselves, I think.

6 And if you just look on the left, these are
7 really nasty infected *Acinetobacter* wounds, and this is
8 actually at day 15, real nasty, but if you look at the
9 antibody treatment, you see much less swelling, you
10 don't see the necrotic tissue kind of expanding out
11 from the site, and we're kind of keeping that infection
12 more localized to the initial wound bed where we had
13 it. And this is just one antibody dose prophylactic.

14 And if you measure CFU at day 3, you can see
15 there is an effect on CFU. So it's only about a log,
16 maybe a log and a half tops, but that's enough that it
17 keeps that infection a little more limited. And so I
18 just wanted to show you an example of where we've used
19 the wound model in the past.

20 Endpoints of this model: time to close is
21 obviously the big one; CFU/g for tissue; biofilm; gross
22 pathology; histopathology. We can also do immunology,

1 animal weights we found to be very predictive. So if
2 we measure the animal weight in actually the lung or
3 the wound model, any infection, it doesn't matter what
4 bug it is, we see 20 to 25 percent decrement in animal
5 weight. Treated animals, if they look good, even at
6 day 1, we won't see that weight decrement, so it's
7 something to look into. And we can certainly look at
8 microbiome as well.

9 Further optimization of the model. We're now
10 starting to look at adding urinal nitrate to basically
11 humanize excretion. So if you add this, this actually
12 prevents the kidneys to work as well in the mice, and
13 then you get a little more PK/PD more like humans as
14 far as excretion is concerned. We've looked at other
15 strains of Acinetobacter because I thought some people
16 would ask about that. I said earlier if we increase
17 the dose, we can get dissemination and sepsis.

18 We're also looking now at other mouse strains.
19 We're using diabetic mice. Dr. Bonomo mentioned the
20 A/J mice and this other mouse strain that are more
21 susceptible. And we're also looking into humanized
22 mice now, and we've done some work with them just

1 recently, and that's something where I really want to
2 keep pursuing, because these humanized mice actually
3 have a human immune system, and we're going to be
4 utilizing those more. And that work is all funded
5 through a DARPA project on predatory bacteria. So
6 that's where we're going with that.

7 Finally, we want to look more at the immune
8 response. So that's the wound model. I'm happy to
9 answer questions about that in the mouse. I'm going to
10 move to the pig now.

11 The pig model, again, very similar to all
12 these other models except here we are lowering the
13 cyclophosphamide dose. So unfortunately, there is a
14 lot of, again, on-the-fly learning here on what's going
15 to work best for a pig. Now, when I say "pig," I'm
16 talking a Yorkshire pig. This is a 25-kilo, 30-kilo
17 pig. This is not a mini pig. This is a pig where it's
18 on a farm and you get bacon from them. That's how big
19 this pig is.

20 Walter Reed has an amazing facility. It's a
21 100,000-square-foot animal facility in our basement.
22 It's huge. Okay? No one has something like this. And

1 so it allows us to do all sorts of animals. We have
2 non-human primates, pigs, sheep. We have all sorts of
3 things going on there. But the pigs are really -- what
4 I like to say about them is if there is a drug that
5 you're interested in getting approved, there is an 80
6 percent correlation to FDA approval using a pig model.
7 So if you can get it to work in a pig, they've seen 80
8 percent FDA approval rate there. Now, I don't know if
9 it's going to hold true for this, I'm just saying that
10 that's what's out in the literature right now.

11 So we wanted to make this wound model
12 obviously in their Wound Infection Department, and it's
13 doing the same kind of idea where we do
14 cyclophosphamide, but what we had to take into account,
15 mice have very robust innate immune systems. They
16 clear everything. They live in the wild. They're a
17 dirty kind of animal. Pigs are actually a lot more
18 like us --

19 (Laughter.)

20 DR. ZURAWSKI: And so the cyclophosphamide
21 we've got to use is very, very small, it's only one
22 dose at 25 mg/kg. I told you before, we're doing 150

1 and 100 mg/kg in mice. So it's 4X, 6X in mice, and
2 pigs -- and it's only one dose in pigs, but still at
3 day -4. We based this off of a Haemophilus paper where
4 they're looking at Haemophilus infections in pigs, but
5 we had to really do some playing around with that dose
6 to get it to go.

7 Where we've seen infection, so we're dosing

5

8 with about 10 Acinetobacter, and, again, the numbers

9 10

9 rise to about 10, 10 in that wound site. If we go
10 too high, again disseminates sepsis, the pig dies
11 unfortunately. If we go too low, we don't get those
12 same high CFUs that would be associated with infection.

13 The other beauty of the pig is that we can do
14 multiple wounds on the back of the animals, so it
15 allows us to facilitate lots of wounding and lots of
16 trials. We basically take a number of wounds at any
17 given day. And it's a 12-millimeter punch biopsy, but
18 then we can do again smaller punches within there.
19 Those are 6-millimeter punches within the 12-millimeter
20 where we can then take it and then do other data
21 aspects afterwards.

22 This is what a layout looks like on the pig.

1 So you've got the actual layout that we have like in
2 our protocol. We randomize it. So some people were
3 complaining, well, if I do stuff on one area of the
4 back of the pig, how is that going to reflect to the
5 other area of the pig? So now we're just like forget
6 it, we're just going to randomize it, we just do
7 whatever.

8 And then you can see what the actual pig back
9 looks like there. Again, it looks a lot like human
10 skin. And, again, we can pull, we can do a punch
11 biopsy out. That's us pulling the punch out. We
12 basically set up a DuoDERM kind of layer on top where
13 the wounds are being made, and that allows us to keep
14 our inoculum localized to that area.

15 Once we do that, we put a dressing overtop.
16 So that's the bottom. Then we put a bandage kind of
17 over those dressings. And then a jacket so the pig
18 doesn't actually like try to scrape it off or shake in
19 his cage or whatever where he is. And, in fact, this
20 keeps the wound closed and basically monoinfected with
21 Acinetobacter.

22 I did want to mention that, too, a lot of

1 people say, "Oh, microbiome, you must have 200
2 different bugs in there when you're looking at this
3 stuff." While true, we do have other bacteria in there
4 for sure, Acinetobacter completely dominates. It's the

5

5 only one that's there present above 10. So it's there
6 at a huge level. It basically takes over that wound
7 site irrespective of the other things that are there.

8 So, again, with this model, this is what it
9 looks like. We can do punches out of that. And then
10 we can do -- in this situation, we're doing placebo
11 versus polymyxin treatment, which is typical, found in
12 Neosporin. And here we did like a polymyxin gel. You
13 can see that we see a CFU decrement over time.

14 And so to summarize, we're basically looking
15 at a pathogen that we actually think is much more
16 aggressive than people said in the past. Dr. Bonomo
17 mentioned earlier there is one clade that actually
18 killed people that weren't compromised at all. That's
19 Colonel Lesho's work and my postdoc's work, Crystal
20 Jones. And basically they had little wounds on their
21 arm, and in 24 hours those patients died. It went
22 septic and killed them. Thankfully, this is only one

1 clade of Acinetobacter. It's called Clade B. It's
2 only 10 percent of what's out there, but it's out
3 there. So it's something to take into consideration.

4 5075, the strain I'm using for all the work I
5 showed here and for the rat models, it's an ST2 strain.
6 ST2 is the most isolated ST group of all the
7 Acinetobacter and all the outbreaks in the world. So,
8 again, we're trying to use a strain that is clinically
9 relevant.

10 We developed two murine models with that
11 strain that rely on neutropenia, and we feel that that
12 reflects the pathogenesis that we see with the organism
13 when I talk to doctors over at Walter Reed. We also
14 developed a porcine model using similar techniques.

15 On the whole, we've tested 14 different
16 antibacterials in the last 2 years using our models and
17 compared them to the standard of care. And this is
18 just a list of them there. Some of them are blacked
19 out due to our people that we're working with, but the
20 bottom line is we've tested a lot of things in these
21 models, and we've been doing it now for quite some time
22 and know how things behave.

1 So I will end there. Any questions -- or
2 probably we just have to move on.

3 I do want to acknowledge our group, which is
4 amazing, and the former members who helped with all
5 this. This is not a one-person job; this is a multi-
6 person job. These animals take a lot of effort to do,
7 and as I said, it's quite an ordeal. So I'm very happy
8 and honored to represent them today.

9 DR. KNISELY: Okay. Thank you. Yes, we will
10 move on from pigs to bunnies.

11 Our next speaker is Dr. Binh Diep. He is an
12 associate professor at the University of California,
13 San Francisco. His research is focused primarily on
14 the epidemiology and pathogenesis of Staph aureus, but
15 he has recently adapted his rabbit pneumonia model for
16 preclinical testing of novel monoclonal antibodies for
17 Pseudomonas aeruginosa.

18 Rabbit Model of Pseudomonas Pneumonia

19 DR. DIEP: Hello. Thank you very much for
20 giving me the opportunity to share with you two
21 different rabbit models of Pseudomonas pneumonia.
22 These are my disclosures. We receive funding from the

1 NIH as well as various industry partners to develop,
2 validate, and use different rabbit infection models.

3 So I first would like to make some comments
4 on, why rabbits? Every year annually in the United
5 States, about 140,000 rabbits are used in research
6 compared to 10 to 20 million rodents. And so rodents
7 offer distinct advantages over rabbits, including the
8 fact that they are inexpensive, easy to handle. You
9 can really do cool genetic studies with mice that you
10 can never do with outbred New Zealand white rabbits.

11 And it's also long thought that lagomorphs,
12 which include rabbits, are more similar to Rodentia,
13 which include mice and rats, than they are to primates,
14 based on their sheer morphological characteristics. So
15 why go through the trouble of using rabbits? However,
16 it has been shown that primates and lagomorphs are more
17 closely related to one another when you align 91
18 autologous protein sequences from these different
19 species, that they're more closely relate to one
20 another than to the rodents.

21 And it's also known for many, many years that
22 rabbits are rather similar to humans and chimpanzees in

1 their susceptibility to LPS. So, for example, in
2 rabbits, 2 to 4 ng/kg of LPS injected intravenously is
3 sufficient to induce a threshold change, physiological
4 changes, like an increase in temperature as well as
5 TNF-alpha.

6 So compare that to 1 to 5 ng/kg for human and
7 chimpanzee, and you see it's quite similar. For mice,
8 one would need to go to 500 mcg/kg to see a threshold
9 change. And when you look at the lethal dose in
10 rabbits as well as in swine, it's 10 mcg/kg. In mice
11 and rats, it's 8 to 15 mg/kg. So you need 800 to
12 1,500-fold more -- 1,500-fold more LPS to cause
13 lethality.

14 So in my lab, we use about 1,000 to 1,100
15 rabbits annually, mostly for *Staphylococcus aureus*.
16 But recently we started working with *Pseudomonas*
17 *aeruginosa* as well as *Klebsiella pneumoniae*.

18 And we use many different types of invasive
19 models in rabbits, and they can be roughly categorized
20 into two different groups. The higher throughput
21 rabbit models for which we can do about 32 rabbits per
22 week, it doesn't seem much when you compare it to mice,

1 but 32 rabbits per week, and these sort of animal
2 models are suitable for initial lead candidate
3 selection and validation. You need the high
4 throughput. And this includes the rabbit model of
5 acute pneumonia, rabbit model of severe sepsis, rabbit
6 model of acute bacterial skin and skin structure
7 infection.

8 We also have lower throughput surgical models
9 for which we can only do 6 to 10 rabbits per week. And
10 this is more suitable for further efficacy testing or
11 mechanism of action type study. And this includes the
12 aortic valve endocarditis model, prosthetic joint
13 infection model, and more recently we started working
14 with a ventilator-associated pneumonia model.

15 So what I'm going to do today is share with
16 you data on testing the protective efficacy of a novel
17 monoclonal antibody developed by MedImmune in two
18 different rabbit models, the acute pneumonia model as
19 well as the ventilator-associated pneumonia model.

20 So this molecule, MEDI3902, from MedImmune, is
21 a multifunctional by specific antibody targeting
22 *Pseudomonas aeruginosa*. The Fab portion of the

1 antibody targets the virulence factor PcrV, and the
2 scFv portion of the antibody targets the persistent
3 factor Psl. It also has a typical hinge-Fc portion
4 that's required for OPK.

5 And I should mention that this molecule has
6 been tested extensively in mice already, and it has
7 been shown to be protective across multiple different
8 invasive mouse models. So here what we wanted to do
9 was to test it in a different species, in rabbits, and
10 we wanted to know if MEDI3902 can reduce mortality
11 and/or prevent major morbidity in a different species.

12 So first the rabbit model of acute pneumonia.
13 In this model, the rabbits, these are New Zealand white
14 rabbits, outbred, about 2.5 kilograms. They were
15 randomized for either prophylaxis at 24 hours before
16 infection or treatment at 1 hour post-infection with
17 different doses of MEDI3902 or a control antibody. The
18 control antibody is an irrelevant isotype matched
19 control antibody.

20 These rabbits were challenged endobronchially
21 with 9e7 CFU of Pseudomonas aeruginosa Strain 6077.
22 This is an ExoU-positive cytotoxic strain. The rabbits

1 were then monitored every 2 hours, at least every 2
2 hours, for the first 36 hours post-infection, and then
3 three times daily thereafter. They are then euthanized
4 at 96 hours post-infection. The humane criteria for
5 euthanasia is a respiratory rate greater than 90
6 breathes per minute, the animal is cyanotic and has a
7 cough. Death in these animals is imminent, so they
8 should be euthanized.

9 Here are the Kaplan-Meier survival curves.
10 You can see that the animals treated with a control
11 antibody have five out of six of those animals die --
12 unfortunately -- oh, there it is.

13 So between 12 and 24 hour post-infection, most
14 of the animals die, five out of six die, and then the
15 last animal die at 52 hours post-infection. At the
16 lowest dose of MEDI3902, at 0.3 mg/kg, what we see here
17 is 50 percent overall survival. And in animals that
18 were treated at 1, 5, and 15 mg/kg, they all survive.

19 And then when you look at the lungs of these
20 animals and take the weight of the lung, animals that
21 were treated with 15 mg/kg, they all die and they have
22 very large lungs. The lung weight/body weight ratio

1 for an infected rabbit is 4. That's like 10 grams, a
2 typical weight of 10 grams, for the lungs divided by
3 the body weight of 2.5 grams. So that's a 4. These
4 animals, the lung weight/body weight ratio is between
5 15 and 24. So the lung goes from 10 grams to 40 to 60
6 grams.

7 And so why is it so heavy? When there is
8 damage to the alveolar endothelial barrier, there is
9 this massive influx of fluid from the blood into the
10 air space, and that resulted in just respiratory
11 failure and death in these animals. So the lung
12 weight/body weight ratio is a direct measure of acute
13 lung injury.

14 Animals that were treated at .3 mg/kg, three
15 of the animals die. They're shown here in the closed
16 symbol. The three that survive are in the open
17 symbols. And you can see that the ones that die have
18 bigger lungs. Now, animals that were treated with 1,
19 5, and 15 mg/kg have very significantly lower lung
20 weight/body weight ratio.

21 So this suggests that MEDI3902, its mechanism
22 of action in this model, the reason it's protective is

1 it's protecting against acute lung injury and death.

2 That was data for prophylaxis. Here are the
3 data for treatment. What we see here is the treatment
4 was administered 1 hour post-infection, and all of the
5 animals die in the control group. Four out of six
6 animals survive at the lowest dose at 1 mg/kg. And at
7 5 and 15 mg/kg, all of the animals survive. And
8 survival again in this model was correlated with a
9 significantly lower lung weight/body weight ratio.

10 So these are the lung CFU count. And you can
11 see that at the highest dose of MEDI3902, you get quite
12 a significant reduction in CFU count. Remember, we put
13 into the lungs about 9×10^7 CFUs, so it's quite a drop,
14 and it's very significantly different from animals that
15 were treated with a control antibody. And that's all
16 consistent with data in the mouse showing that this
17 antibody enhances OPK.

18 So we also recently only in the past 6 weeks,
19 7 weeks, started working with another model,
20 ventilator-associated pneumonia. We worked with this
21 model for a while in Staph aureus, but we have adapted
22 it for use with Pseudomonas only very recently.

1 And so in this model, rabbits were randomized
2 for prophylaxis at 24 hours before challenge with a
3 control antibody or MEDI3902, and here we only have
4 four rabbits per group. The rabbits were mechanically
5 ventilated with a lung protective low-tidal volume of 6
6 to 7 ml/kg, for 2 hours, and then they were challenged
7 through the endotracheal tube with 2.5×10^7 CFU. So this
8 is three-, four-fold less bacteria than required for
9 the acute pneumonia model presumably because of
10 ventilator-induced lung injury that predisposes the
11 lung to this lower inoculum infection.

12 These rabbits were monitored continuously for
13 36 hours post-infection. Blood samples were obtained
14 every 2 hours. And you can do this with a big animal
15 like a rabbit. And we did comprehensive blood analysis
16 for each of the time points. We do a five-part WBC
17 differential. We measure blood gas, acid-base,
18 electrolyte, creatinine, lactate, glucose, and various
19 enzymes, markers of renal and liver injury. So I'll
20 show you those data. What I'll show you today, I'll
21 show you the rabbit.

22 So these rabbits were intubated under view

1 control with a pediatric endotracheal tube, a cuff,
2 endotracheal tube, and then they are connected through
3 a one-way breathing circuit to an anesthesia
4 ventilator. And we have six of these ventilators, so
5 we can ventilate six rabbits concurrently. And so the
6 ventilator is set at an FiO2 of 35 percent, isoflurane
7 1.5 percent. The peak inspiratory flow is 4 liters per
8 minute. Respiratory rate of 35. PIP, 15 centimeters
9 of water. PEEP, 6. I:E ratio of 1:2. So all of the
10 settings is really to achieve a low-tidal volume while
11 also achieving normal ventilation, normal carbon
12 dioxide in arterial blood of 35 to 45 mmHg.

13 So the carotid artery is cannulated for
14 invasive blood pressure, but it also has a port here to
15 be able to take arterial blood from which we then
16 measure all sorts of things.

17 The rabbit is also cannulated on the ear
18 artery for infusion of, in this case, a fluid with 5
19 percent dextrose. This is the basic setup for our
20 ventilator-associated pneumonia model. And we also
21 have a more advanced setup where we do transpulmonary
22 cardiac output measurement as well as mixed venous

1 oxygen saturation, but I'm not showing you those today
2 because those are what we do with Staphylococcus
3 aureus.

4 So here are the basic data. So the rabbits
5 that were treated with a control antibody, they all
6 die. Two of the rabbits die at 12 and at 13 hours
7 post-infection. And then one rabbit died at 17 hours
8 post-infection, and another one at 24 hours post-
9 infection. And they get different colored symbols so
10 you can track the chronology of events leading up to
11 death.

12 So all the animals that were treated with
13 MEDI3902, they all survive, they all survive to 36
14 hours post-infection, when we euthanize them.

15 So here are the lung weight/body weight ratios
16 for these animals. The two animals that die late, they
17 have huge lungs. This one has a 40 grams lung, and
18 this is 51 grams lung, and you can see it here. And
19 the lungs are huge, and they are necrotic. It's likely
20 that these animals die from respiratory failure, and
21 I'll show you the evidence for that.

22 But, curiously, there are two animals that,

1 the blue and the green animals, they have small lungs
2 that are not so much bigger than normal uninfected
3 lungs, and yet both of those animals die. When you
4 look at the lungs, even though the lung is small,
5 there's a lot of necrosis. When you look at the lungs
6 from MEDI3902, the lungs look relatively normal
7 compared to infected lungs, very few areas of necrosis,
8 so suggesting that, again, MEDI3902 protects by
9 preventing this acute lung injury.

10 So we took serial blood samples so we can do
11 serial blood cultures, and you can see that animals
12 that were treated with a control antibody all develop a
13 bacteremia that then peak at the time of death. Some
14 of these are in the 1,000 CFU/ml in the blood, so it's
15 quite high bacteremia.

16 Three of the animals in the MEDI3902-treated
17 group had no bacteremia, but one of the animals did
18 have a very high-titer bacteremia, but it did survive,
19 at least to 36 hours post-infection.

20 When you look in the lungs at the CFU count,
21 those animals that were treated with a control antibody
22 have significantly higher CFU count than those that

1 were treated with MEDI3902. In the spleen, kidneys,
2 and liver, no difference.

3 So what causes death in the four control
4 antibody-treated rabbits? Although MEDI3902, the
5 fourth rabbit that survived, what are the effects of
6 the persistent bacteremia on the host? And we want to
7 be able to answer these two questions. And so what we
8 wanted to do was to look at the blood for some clues as
9 to why these animals die.

10 And here these are complete blood counts.
11 This is the white blood cell count. And you can see
12 that animals that were treated with a control antibody,
13 the white blood cell count dropped rather dramatically,
14 especially at the time of death. Platelets remained --
15 platelets a little bit decreased. Curiously, one of
16 the animals that was treated with the MEDI3902, but
17 that survived, had high bacteremia. It has slightly
18 elevated platelet levels.

19 But look at neutrophils. Neutrophils
20 significantly decreased. There's neutropenia. And
21 neutropenia, again, there's neutropenia in the
22 peripheral blood, so the neutrophil is getting traffic

1 somewhere. And so often the case with ventilator-
2 associated pneumonia, they get traffic into the lungs
3 where the neutrophils actually participate in the acute
4 lung injury. And we'll be able to confirm that this
5 profound neutropenia in peripheral blood is actually
6 due to the trafficking of neutrophils into the organs,
7 and the histology will confirm that, which we don't
8 have right now.

9 The monocytes, also there is a dramatic
10 decrease in monocyte count.

11 Now, the pO_2/FiO_2 , this is a very reliable
12 clinical marker of hypoxemia. And you can see that
13 three of the animals that were treated with a control
14 antibody have very, very severe pO_2/FiO_2 .

15 And there is also a concomitant increase in
16 carbon dioxide in the blood, suggesting that these
17 three animals die of respiratory failure, but very
18 curiously, one of the animals, the animal in the blue,
19 the control-IgG animal number 2, it has normal
20 pO_2/FiO_2 , and yet it has -- the carbon dioxide tension
21 in the arterial blood is less than 10.

22 This is very severe hypocapnia. And

1 hypocapnia is, actually when you look at the old
2 literature, hypocapnia, very severe hypocapnia, is a
3 consistent feature of Gram-negative septic shock. So
4 we wonder if it is the case that this animal died of
5 multiple organ dysfunction, septic shock-induced
6 multiple organ dysfunction. And do we have any clues
7 to the multiple organ dysfunction in this animal?

8 So let's keep tracking of the animal in the
9 blue. It has very severe base deficit. There's a
10 massive increase in lactate level. So lactate, when it
11 gets to this range of 19, 20, it really indicates very,
12 very severe tissue hypoperfusion consistent with septic
13 shock.

14 And when we look at the potassium level,
15 potassium is filtered and excreted by the kidney. So
16 this is a marker of kidney injury, of acute kidney
17 injury, and potassium just increased very, very
18 sharply. Creatinine also increased sharply in that
19 particular animal, suggesting the involvement of acute
20 kidney injury in this animal.

21 We also looked at liver enzyme alanine
22 aminotransferase, and we see that it's also increased

1 for this animal, as well as the amylase. Amylase is
2 produced in the pancreas. So this is suggesting that
3 maybe there is also acute pancreas injury in this
4 particular animal.

5 So taken together, so this is the blue animal.
6 It has many of the features that are consistent with
7 septic shock. And so the cause of death in that one
8 particular animal seems to be septic shock. But for
9 the other three animals, control IgG-treated animals,
10 1, 3, and 4, they likely die of just profound
11 respiratory failure. It's pulmonary failure.

12 The animals that were treated with MEDI3902
13 look rather good when you look at these different blood
14 markers, except one that has this persistent high
15 bacteremia, but it didn't die, and it looks like
16 lactate at the very end looks pretty good. So there's
17 no evidence really of severe sepsis and septic shock in
18 this one particular animal.

19 This work was done by postdocs and graduate
20 students and undergraduate students in my lab, who are
21 very dedicated. You can see that this is a 36-hour
22 experiment continuous. And it's also done in

1 collaboration with Tony, Bret, and Ken at MedImmune.

2 Thank you.

3 DR. KNISELY: Thank you.

4 Okay. So from bunnies back to pigs, our last
5 speaker in this section is presenting remotely. He is
6 Dr. Gianluigi Li Bassi. Is he on the line?

7 DR. LI BASSI: Yes, I am.

8 DR. KNISELY: Wonderful. Great. So Dr. Li
9 Bassi is board-certified in anesthesiology and critical
10 care medicine. In 2013, he obtained his Ph.D. on the
11 management and prevention of infectious interstitial
12 and cancerous pulmonary disease. And he is the head of
13 the Division of Animal Experimentation and Attending
14 Physician at the Department of Pulmonary Critical Care
15 Medicine at the Hospital Clinic, Barcelona.

16 Okay. Your slides are up and we're ready to
17 go.

18 Ventilated Pig Models of Pseudomonas Pneumonia

19 DR. LI BASSI: Very good. Thank you, Sumathi,
20 for the nice introduction. Can you hear me well?

21 DR. KNISELY: We can.

22 DR. LI BASSI: Okay. Perfect. So in the next

1 15 minutes, my main objective is going to be to try to
2 convince you that we still need large animal models to
3 study these *Pseudomonas aeruginosa* models of infection.

4 These are my potential conflicts of interest
5 related to this presentation.

6 Next. So, of course, we learned from many of
7 previous talks the importance of animal
8 experimentation. And in my daily routine, of course,
9 the Declaration of Helsinki, we have this declaration
10 in our lab that clearly states the importance of animal
11 experimentation before translating any result into the
12 clinical setting.

13 Next. So in particular, the rationale for the
14 use of pneumonia models, these models, they clearly
15 elucidate the pathogenesis of the disease. They even
16 characterize the interaction between the pathogen and
17 the host, and, of course, even that we are in this
18 workshop organized by the FDA, we can test new
19 antimicrobials, new drugs, against these pathogens.

20 Next. So far, you guys have focused
21 particularly in small animal model of *Pseudomonas*
22 *aeruginosa* pneumonia, and we do have many models, say,

1 rats and mice and rabbits.

2 Next. I'm a critical care physician, and we
3 primarily focus on pneumonia that develops in patients
4 that are admitted in the ICU. And, of course, one of
5 the main challenges to develop a model of these
6 patients is that animals, and particularly small
7 animals, that there are many challenges in ventilating
8 this animal, even giving hemodynamic ventilatory
9 support is important to these animals for long period
10 of time.

11 Next. Many of the previous speakers presented
12 many models of pneumonia and even other infections.
13 I'm not going to go, of course, into any detail on this
14 model.

15 Next. But I would like to particularly draw
16 your attention on the number of publications throughout
17 the years in small animal models and large animal
18 models. As you can see in the top part of this slide,
19 there has been an exponential increase throughout the
20 decades of the number of publications in my mice, rats,
21 and rabbits. Instead, if you look at publication in
22 pigs, sheep, in general, in large animal models, there

1 was a steady decline in the number of publications.

2 And I was very happy to hear Daniel, from
3 Walter Reed, that we have a list, 85 percent of FDA
4 acceptance of new drugs, and when they are tested in
5 large animal models. And as I said, one of my purpose
6 here is try to convince you that irrespective of this
7 decline in the number of publications, we still need
8 these kinds of labs and these kind of animal models.

9 Next. Now, many of the previous speakers,
10 they show you the benefit of mice models of Pseudomonas
11 aeruginosa pneumonia. And we do know that these small
12 animals, they have limited cost, and this is very
13 important. They have potential for extensive genomic
14 manipulation. This is very important because you can
15 even create a specific condition that then you can find
16 in the clinical setting and to look at their response
17 of a challenge with this pathogen. However, there are
18 also limitations in these models.

19 Next. And in particular, very careful, there
20 are dissimilarities in the anatomy of these mice in
21 comparison with humans. Even the physiology of the
22 respiratory tract have some differences. And even the

1 immunatory system and their response to a bacteria
2 challenge sometimes is different than the real response
3 in humans.

4 Next. And some other limitations, in
5 particular, limitations in my specific field of
6 investigation, which is intensive care medicine, is
7 that long-term mechanical ventilation in these models
8 sometimes is absolutely unfeasible.

9 Also, you cannot model the same level of
10 severity of patients in the ICU because when you reach
11 a very high level of severity, these animals, they just
12 die, and this is not the case in humans in the ICU.
13 For specific diseases, like ventilator-associated
14 pneumonia, you cannot even replicate the exact
15 pathogenic mechanisms. And there are many scientists,
16 that they are just skeptical on the possibility of
17 translating these results in the clinical setting.

18 And one of the reasons in particular in the
19 ICU is -- next slide, please -- one of the reasons is
20 just that ICU patients are very complicated. There are
21 many co-existing diseases. They vary for age. There
22 are many supportive therapies. The severity of the

1 illness sometimes is so high they cannot even be
2 reproduced in mice. So, of course, we need models that
3 they closely resemble this condition.

4 Let me give you an example. Next slide. This
5 is an interesting study in which they measure the
6 growth of *Pseudomonas aeruginosa* with vasoactive drugs,
7 and without these drugs. And vasoactive drugs, like
8 norepinephrine or dopamine, are drugs that we daily use
9 in any ICU. And as you can see here, when you use
10 these drugs, for some reason, the bacteria growth was
11 even higher.

12 Next slide. And even the biofilm formation
13 was much higher when you use these drugs. And, of
14 course, if you cannot even provide all this hemodynamic
15 support on the small animals, then you don't have a
16 reliable model.

17 Next slide. One other limitation particularly
18 in the ICU is that you cannot use the same devices that
19 we are using in the ICU, endotracheal tube, the same
20 ventilator, and these, of course, are a limitation.

21 But particularly, my major concern -- next
22 slide -- is the length of the mechanical ventilation.

1 We do not have ICU patients highly severe that they are
2 ventilated just for a few hours.

3 And the only way to increase the length of
4 intubation and keep these animals alive -- next slide
5 -- is to prolong -- to change the model.

6 Next slide. And to change the model and use
7 large animals: dog, baboons, sheep, pigs. So when you
8 have doubts in science, it's always better to ask the
9 experts.

10 Next slide. Let me give you some examples
11 from highly brilliant mind. For instance, Traber,
12 Daniel, he was a brilliant physiologist from the
13 University of Texas, and he was very clear in his mind
14 in what kind of animals we should use to model the ICU
15 patient. Would you, as a critical care physician,
16 accept data from a drug study on intensive care
17 patients who was not only not resuscitated with fluid,
18 but who did not even have blood pressure and heart rate
19 monitored. And sometimes this is what happened. And
20 you cannot resuscitate or give vasoactive drugs to
21 these animals.

22 Next. And one of my mentors from the National

1 Institutes of Health, Theodor Kolobow, who was another
2 brilliant physiologist, one day he told me that it's
3 rather unreasonable to believe the results from small
4 animal studies, started right after breakfast in the
5 cafeteria and completed in time for dinner, could be
6 safely translated into valuable therapies for ICU
7 patients.

8 Next, please. So what are the ventilated
9 animal models of *Pseudomonas aeruginosa* pneumonia that
10 we use in our lab?

11 Next. Now, before starting with the models,
12 you need to carefully consider some features. And many
13 of the previous speakers, they highlighted the
14 importance of the burden of the bacterial inoculum, the
15 bacterial strain.

16 Mind you, unless you talk with an ID physician
17 or a microbiologist, many physicians in many hospitals
18 worldwide, they think that *Pseudomonas* is just
19 *Pseudomonas*, and all the strains are the same. This is
20 not the case. The bacteria strain, we know from many
21 previous presentations, they can completely change the
22 disease and the kind of burden to this animal.

1 And even you have to decide the right type of
2 animals, for instance, sheep, they produce a lot of
3 saliva, pigs, they do not. And even decide what the
4 proper length of mechanical ventilation.

5 Next. Let me give you an example based on our
6 data. For instance, we use many *Pseudomonas aeruginosa*
7 strains, and some of these strains, they have a
8 mortality of 20 percent, and some others are multidrug
9 susceptible, they do not have a high mortality rate.

10 Next, please. Even for the need of a
11 vasoactive drug like norepinephrine, some strains, they
12 produce huge septic shock, and they need
13 norepinephrine, and some others, they do not have these
14 requirements.

15 Next. I believe that first the model and the
16 gold standard for *Pseudomonas aeruginosa* models in
17 large animals was developed from the (inaudible) set by
18 Johanson.

19 Next. They actually -- this was (inaudible).
20 They were not supposed to develop a model of
21 ventilator-associated pneumonia. They tried to create
22 a model of acute respiratory distress syndrome

1 injecting oleic acid.

2 Next. But then after a few days of mechanical
3 ventilation, what they found was *Pseudomonas aeruginosa*
4 -- well, they found ventilator-associated pneumonia.

5 And when they looked -- next, please -- at the
6 positive pathogens, they found that the majority of
7 these pathogens of this pneumonia were caused by
8 *Pseudomonas aeruginosa*. So this is not a pure model of
9 *Pseudomonas aeruginosa*. And there are many advantages
10 and limitations of this model.

11 Next. Of course, I said that this is the gold
12 standard because they have the same anatomy, they are
13 very close in their response to the bacterial burden,
14 but they just aspirate whatever pathogen they have in
15 their oropharynx after intubation. So many times,
16 there is not even the right -- there are heterogeneous
17 amount of pulmonary challenge.

18 And, of course, using primates has high cost,
19 there is scarce animal availability, and there are
20 strict legislation. For instance, in our university,
21 we cannot even use these models.

22 Next. A model that is matched easier and has

1 had huge development in the last decade was the Luna's
2 Model. This was a model developed in pigs. These are
3 animals mechanically ventilated for 72 hours, and they
4 are managed exactly like in an ICU.

5 Next. So these are animals that they are
6 challenged with *Pseudomonas aeruginosa* through a fiber-

6

7 optic bronchoscope with 15 ml of 10 colony-forming
8 units per milliliter of a suspension of *Pseudomonas*
9 *aeruginosa*, and this 15 milliliter into each lobe.
10 They have five lobes, so a total amount of 75
11 milliliters.

12 Next. And after approximately 12 to 24 hours,
13 they already have the first sign of infection. The
14 upper part on the left, you can see the sharp increase
15 in temperature, and on the upper part of the right, a
16 decrease in $pO_2:FiO_2$ ratio, which is a marker of
17 pulmonary failure.

18 Next. And if you can at the end of this
19 study, when they dissected the lungs, they found
20 extensive severe pneumonia in all the lobes.

21 Next. So the main advantages of this model,
22 there is a rapid development of severe pneumonia. This

1 is a highly severe pneumonia. It's ideal to study
2 efficacy and safety of new drugs, but there is an
3 extensive pulmonary bacterial challenge, and many times
4 this is not the real pathogenesis of pneumonia because
5 patients, they do not have this kind of bacterial
6 challenge.

7 Next. So in 2014, 2013/14, we decided to
8 develop another animal model, in particular, of
9 *Pseudomonas aeruginosa* VAP.

10 And our goal -- next -- was specifically to
11 reproduce the pathogenic mechanisms of VAP. We choose
12 it through aspiration of pathogens across the
13 endotracheal tube cuff.

14 Next. So we use the same kind of pigs, which
15 were oro-tracheal intubated and mechanically ventilated
16 for 3 days. Standard sedation, analgesia.

17 Next. And this is very important.

18 DR. KNISELY: Sorry to interrupt. Can I ask
19 everyone who is not our speaker to please mute
20 themselves online? We're hearing someone else's
21 conversation. Thank you.

22 Okay. Please continue.

1 DR. LI BASSI: Yeah. So this is very
2 important, the position. When you keep the animal in
3 this position, they have the trachea in an oblique
4 orientation, so they start aspirating across the
5 endotracheal tube cuff, and this is exactly what
6 happens in humans who are mechanically ventilated and
7 intubated.

8 Next. So we challenged not the lungs, but we
9 challenged the oropharynx just 5 milliliters after 4
10 hours and 5 milliliters after 8 hours of a high
11 concentration of *Pseudomonas aeruginosa* multi-
12 susceptible. And then, as I said, they started
13 aspirating this pathogen.

14 Then after 72 hours -- next -- we performed
15 the autopsy. You can go ahead faster here because they
16 are just a picture of the autopsy.

17 These are standard method, straight
18 (inaudible). And then we obtained the lungs. In the
19 (inaudible) samples, we biopsied each lobe of these
20 lungs, and export the results.

21 Next. We found an exponential increase in
22 tracheal secretion colonization, and this is the proof

1 that these animals, they were aspirating throughout the
2 time on mechanical ventilation.

3 Next. But the most important data are
4 regarding the colonization. This is not a broad high
5 colonization by *Pseudomonas aeruginosa* like in the
6 previous model, just the most dependent region, right
7 medial lobe, right lower lobe, which are gravity
8 dependent in this model, gets the highest colonization,
9 and this is exactly like humans, that usually
10 ventilator-associated pneumonia develops in one or two
11 lobes.

12 Next. Histology confirm pneumonia in one or
13 two lobes.

14 Next. And there are many advantages, as I
15 said, in particular in this model reproduce exactly the
16 pathogenic mechanism, but there are also some
17 limitations: high cost, labor-intensive, and time-
18 consuming, and you need 3 or 4 days and a huge team of
19 investigators to perform this study. But it's ideal to
20 study particularly preventive measures for this
21 disease.

22 Now, briefly, just for the application --

1 please go ahead, and again -- we received consistent
2 funding by health care industry, government agencies,
3 and medical societies, but I would like to draw your
4 attention particularly on the health care industry. As
5 I said before, there has been a strong decrease in this
6 kind of lab, particularly in the U.S., throughout the
7 years.

8 And if you go to the next slide, among all the
9 industry that we receive or we are receiving funding,
10 the majority is from the United States because they are
11 looking for labs that could perform this study because,
12 as I said before, there are some limitations in small
13 animal models.

14 Therefore, in conclusion, many of the previous
15 speakers -- I'm sorry, go ahead -- many of the previous
16 speakers clearly explained the importance of animal
17 models of pneumonia. And several animal models, like
18 the Johanson model, is one that represents a milestone
19 in this field.

20 Next. But particularly for the pig model,
21 ventilated pig model, we still think it's the most
22 appropriate if you want to be 85 percent sure that

1 you're going to receive FDA approval or even you can
2 translate your findings closely into humans I think
3 because there are close anatomical similarities with
4 the humans, good survival, irrespective of the
5 severity, and this is the important possibility of
6 prolonged mechanical ventilation. And in the second
7 model, we presented reproduction of the main pathogenic
8 mechanisms.

9 Next slide. Thank you very much for your
10 attention.

11 DR. KNISELY: Thank you. That was
12 fascinating.

13 DR. LI BASSI: Thank you.

14 DR. KNISELY: Thank you very much.

15 We're running a little bit behind schedule.
16 Let's take a 10-minute break, come back at 3:40. Thank
17 you.

18 (Break.)

19 Research Support and Resources

20 DR. NAMBIAR: Our first speaker in this last
21 session is Dr. David Boucher, who is from BARDA, and he
22 serves on the NIH Adjudication Committee, Data Review

1 Committees for Actelion and Medtronic, and is the
2 Treasurer of the IDSC.

3 Dr. Boucher.

4 DR. BOUCHER: All right. Thanks a lot,
5 everyone, for the organizers. Thanks for giving me a
6 little time to talk up here. I'll try to keep it
7 brief. I'm going to go off my slides. I'm only going
8 to go into about the third one, so if it looks like it
9 paused if you're online, don't worry, you're fine.

10 I'm with BARDA. That's the Biomedical
11 Advanced Research and Development Authority. For those
12 of you not familiar with our organization, we are a
13 member of the PHEMCE.

14 Are typical mission space is to pick up
15 promising programs from our partner agencies -- the
16 NIH, NIAID, CDC sometimes -- at that IND phase,
17 Phase 1, area; bring those through what's commonly
18 called the "Valley of Death," this area of clinical
19 development characterized by high costs, high
20 attrition.

21 Our ultimate goal is licensure of products.
22 For products without a commercial indication, we like

1 to be able to extend that to procurement, and hand it
2 off to CDC for inclusion in the Strategic National
3 Stockpile.

4 I have a slide here labeled "CBRN Profile,"
5 that's chemistry, biological, radiological, and nuclear
6 countermeasures. I am personally within the biological
7 portion of that. And even within biologicals, I do
8 therapeutics, so this is a very biotherapeutics-centric
9 slide. If it was somebody from another area of my
10 division, you would see different countermeasures here.

11 But we are historically a biodefense
12 organization. If you look at our portfolio, our more
13 mature programs -- our anthrax, smallpox, botulism --
14 we have several countermeasures approved and in the
15 stockpile. Recently, particularly with the response to
16 Ebola and Zika, we've become active in the emerging
17 infectious disease area. And also in public health, we
18 have several antibacterials in late-stage clinical
19 development, and we're one of the drivers of the CARB
20 accelerator.

21 I think John Rex was one of the first ones to
22 mention that Tier C/Tier D area of the Animal Rule. If

1 you kind of focus on the upper two-thirds of this
2 slide, that's kind of where we spend a lot of our time.
3 We rely heavily on the Animal Rule. We do a lot of
4 animal studies.

5 The way we get that done is through a non-
6 clinical network. This is a network of private and
7 academic partners that we recompute every 5 years. We
8 are looking at capacity, we're looking at capabilities,
9 we're looking heavily at quality.

10 Membership into this network allows you to bid
11 on proposals or Request for Proposals that we would
12 issue in the form of task orders. Proposals from the
13 network come back to us. That's a competitive process
14 individually.

15 And for those individual task orders, whether
16 it's an NHP efficacy study, if it's model development,
17 if it's strain panel production, we're going to take a
18 look at the offerors' capabilities, their relative
19 experience in that area, we're going to pick the one
20 that we think might be able to help us the best, and
21 then we sign a contract with them. We work very
22 closely through these contracts on the execution of the

1 task order.

2 That's kind of where I'm going to go away from
3 my slides. I'm going to put this up. I'm just going
4 to talk very loosely. When we do animal development,
5 again because of the phase of development we're looking
6 at, we're not so concerned with downselection of
7 candidates. We're not looking at optimization of
8 leads. We are looking exclusively at studies that will
9 support licensure. We are going to be bringing these
10 studies to the FDA, so we might have a little bit of a
11 different slant on how we see the animal model
12 development.

13 Typically, what we're going to do is we're
14 going to start with the challenge material. We want
15 recent clinical isolates. If mortality is a suitable
16 endpoint for the pathogen that we're looking to develop
17 countermeasures against or a model for, we want strains
18 that were involved in recent clinical cases that ended
19 in fatalities. Again, in most of the pathogens we're
20 looking at, mortality is a suitable endpoint.

21 We're looking to push that model such that
22 when we're using it, an untreated control animal, we're

1 looking for as close as we can get to 100 percent
2 mortality. This raises the bar for therapeutics that
3 we're developing and also reduces the animal numbers
4 that we need to meet statistical objectives.

5 We will take isolates. If we're looking at a
6 pool of potential isolates, the first cut we make is
7 only those isolates that will be available and free to
8 use. We don't want to have restrictions on those. We
9 want to be able to share them with who we want to share
10 them with, and that's typically anybody who asks.

11 And we want, again, clinically relevant
12 isolates. We want recent isolates. For a specific
13 pathogen, we downselect further. I was involved with
14 C. difficile, and what we looked at was things like
15 ribotype toxin production, drug resistance, that type
16 of thing, to get down to a panel that we think is
17 clinically relevant at that time.

18 We produce master and working cell banks. We
19 do extensive characterization on this, including deep
20 sequencing, other things. And we put those on
21 stability. When we go back into liquid nitrogen a year
22 from now, we like to know what we're taking out.

1 When we go to animal model development, again,
2 we're looking at pushing those animal models so that we
3 will be able to do efficacy studies that stand up to
4 FDA scrutiny. And we are looking heavily at quality.
5 When we look at who can complete this work for us, we
6 want technical expertise, of course, but we are heavy
7 on quality, and we are kind of hammering documentation
8 constantly.

9 So in the interest of time, I think I'll
10 probably stop there. I think there are probably a lot
11 more people you want to hear about Acinetobacter and
12 Pseudomonas particularly.

13 If you're interested in the C. difficile
14 program, the Burkholderia slide that I had up just a
15 moment, just grab me. There are a couple other people
16 here from BARDA. Any of us will be happy to talk to
17 you more.

18 DR. NAMBIAR: Thank you so much, Dr. Boucher.

19 Our next speaker to talk about research
20 support and services is Dr. Tina Guina, who is a
21 program officer in Drug Development Section in the
22 Division of Microbiology and Infectious Diseases at

1 NIAID/NIH.

2 DR. GUINA: Thank you very much for inviting
3 me. And I think there have been a lot of good
4 discussions today. So, again, I won't also take much
5 of your time.

6 I just wanted to share some information about
7 important research and development resources, including
8 development and application of medical animal models
9 for testing therapeutics.

10 So I'm in the Division of Microbiology and
11 Infectious Diseases, and as you know, NIH and NIAID, we
12 cover basic research, early translational research, and
13 drug development in preclinical phase and through
14 Phase 1. And our division works on all infectious
15 diseases except for AIDS, so you can imagine there are
16 lots of programs and there are lots of models that we
17 are working on.

18 NIAID Antibacterial Resistance Program is
19 aligned with National Strategy for Combating
20 Antimicrobial-Resistant Bacterial Infections. And we
21 actually support development of new diagnostics,
22 therapeutics, and vaccines.

1 We also have published recently new
2 Antibacterial Resistance Program document that talks
3 about "Current Status and Our Future Directions," and
4 this document describe our intention to support new
5 types of therapeutics, such as non-traditionals,
6 including those that actually act on human immune
7 system, for example, bacteriophages, and also narrow-
8 spectrum antibacterials that are sort of topic of this
9 workshop.

10 Since we actually provide support and cover
11 development, both basic and translational and early
12 clinical research, we have a number of different
13 mechanisms to fund investigators and developers to
14 lower the risk of product development. So there are a
15 number of different types of grants that are available
16 for more early research and development.

17 And then we often enter into contracts with
18 sponsors or investigators that actually have some kind
19 of therapeutic candidates or clinical candidates that
20 are in more advanced preclinical development. We
21 typically establish those contracts and fund them
22 through early clinical and sometimes Phase 2

1 development, but most often after successful Phase 1,
2 we transition it over to our colleagues at BARDA.

3 In addition to developing individual
4 therapeutics and products, we also have a whole host of
5 preclinical and clinical development services. And I
6 just want to -- I'll take a moment a little bit later
7 to talk about them because apparently lots of
8 investigators are not aware of them, and I think they
9 should be, because we can test your therapeutics in
10 various different animal models and to help you with
11 many other stages of development at no cost to you
12 under confidentiality agreements.

13 So I'm not going to go much in detail on this
14 slide. I just provided this slide so that you see what
15 type of funding mechanisms we have, and also a couple
16 of useful links. For sponsors, they're kind of looking
17 ahead, and they already have some kind of, I would say,
18 therapeutic leads or clinical candidates, and they have
19 to put together very large proposals, and they're
20 looking for source of funding a year ahead or 2 years
21 ahead or 6 months ahead.

22 I encourage you to actually look at the NIAID

1 website on which we'll list our NIAID Council-cleared
2 concepts because often at NIAID Council, together with
3 external advisory board, we discuss potential funding
4 opportunities that are up and coming. So this actually
5 can help you to look ahead and plan your proposals.

6 In terms of product development services,
7 actually we have an ever-expanding host of services
8 that include various types of in vitro and in vivo
9 models for testing therapeutics. We also have some
10 additional chemistry support and development.

11 Then toxicology, we can do toxicology studies
12 for investigators, GMP manufacture for
13 biopharmaceutical products and vaccines.

14 We also can help you with regulatory advice
15 and help you put together documentation for IND.

16 And we provide these services through actually
17 establishing contracts similar to BARDA and some other
18 organizations. We establish a network of providers
19 that are either at different CROs or at different
20 academic labs that actually have the capacity, and we
21 heard about some of them today. And in the past, we
22 actually have worked with them very closely also to

1 develop -- in collaboration, to develop models for
2 testing of therapeutics for biodefense indications, as
3 you heard this morning. So we work with them very
4 closely. But we also use these contracts to either
5 develop new animal models, or we establish contracts
6 with providers that have these models in place to test
7 your therapeutics and vaccines and potential
8 diagnostics. So actually this is again at no cost to
9 you, and it's done under confidentiality agreements,
10 and you keep your IP, and all the data is yours.

11 And I should mention also that we also have
12 some Phase 1 units and vaccine testing and evaluation
13 units that actually we can provide support for Phase 1
14 testing of new therapeutics, but also we have abilities
15 to perform clinical trials in some special populations.

16 And Antibacterial Resistance Leadership Group
17 is actually on the network of investigators and
18 clinical trial sites that is looking into different
19 aspects of working in antimicrobial resistance space
20 such as potentially evaluating new diagnostics or maybe
21 new regimens or dosing for already existing
22 antibiotics. Those are just some of the examples.

1 So these resources are available to everyone.
2 They are actually gap filling. So, for example, if you
3 were going to do your entire development through these
4 services, it would take very long because there's a
5 process at every step. You have to provide some proof-
6 of-concept data and prove that you're eligible to go to
7 the next step of development and actually use the
8 resources. So they're not really intended as a sole
9 source of development funds, but they can fill really
10 important gaps that can help you get to the next stage
11 of funding either with NIAID or BARDA or some other
12 organization externally.

13 Everybody is eligible. It's open to academic,
14 investigators, and from any other organizations. And
15 also it's open to everybody around the world, so we are
16 not limited only to the U.S. investigators.

17 And you do not have to have current NIH
18 funding to be eligible. You just need to have some
19 proof-of-concept data and good ideas, and we will be
20 talking to you and helping you all along. And we also
21 actually have lots of experts in-house who are very
22 familiar with different stages of especially early

1 preclinical drug development, and they can provide lots
2 of advice as you go along. And, as I said, this is all
3 done under confidentiality agreements.

4 So NIAID has a website on which actually,
5 believe it or not, all of these resources are listed,
6 and I'm providing the website link here. When you go
7 through this website, you can go through different
8 resources and actually at every resource there is an
9 email, a name of an actual person who is a contact and
10 a program manager for that space. And they have been
11 very successful lately helping the ever-increasing
12 number of investigators in doing both development of
13 therapeutics and vaccines.

14 And that's it. Thank you very much.

15 DR. NAMBIAR: Thank you, Dr. Guina.

16 Our last speaker for the day before we move
17 into the panel discussion is Dr. Thushi Amini, who is
18 the Associate Director for Research in the Office of
19 Antimicrobial Products at the FDA.

20 DR. AMINI: So in 2011, FDA developed a
21 strategic plan for regulatory science to facilitate the
22 translation of breakthrough discoveries into

1 innovative, safe, and effective products for tomorrow.

2 On December 19 of last year, we issued a
3 Request for Information to develop animal models of
4 infection. The purpose was to solicit information
5 input from our external stakeholders to evaluate the
6 current state of animal models for different types of
7 pneumonia due to *Acinetobacter baumannii* and
8 *Pseudomonas aeruginosa*; and, secondly, to conduct
9 studies of an animal model or models of serious
10 infection caused by these two pathogens. We've
11 extended the deadline until March 22.

12 In addition, FDA has an ongoing broad agency
13 announcement. The purpose is to solicit research and
14 development to support regulatory science and
15 innovation. The deadline to submit white papers is by
16 March 31, and full proposals are due by June 26. And
17 this is an open announcement.

18 The Office of Antimicrobial Products research
19 area within this BAA is Research Area 2.4. And we
20 state that FDA's role in combating antibacterial drug
21 resistance are to facilitate the development of new
22 antibacterial drugs to treat patients and to advance

1 the science of clinical trial design.

2 Specifically in FY17, our research will focus
3 on Section 2.4.2, which is to advance the science of in
4 vitro animal model and/or PK studies to facilitate
5 antibacterial drug development. Our research funding
6 to develop animal models this fiscal year is
7 approximately \$5 million.

8 So what are the next steps? We will take all
9 the information that we receive from today's workshop,
10 as well as the responses from the Request for
11 Information and review them. We encourage potential
12 applicants to submit white papers through the BAA
13 process. The deadline for white paper submissions is
14 March 31 for funding.

15 We will then review the white papers on
16 technical merit and contribution to FDA's mission.
17 Those that meet the eligibility, we will then notify
18 the Office of Acquisition Grant Services, or OAGS, to
19 send a letter to submit full proposals. And the
20 deadline that OAGS will send these letters is on
21 June 5, and full proposals are due to the FDA by
22 June 26.

1 We will then evaluate the proposals. We will
2 rate and rank them. And then we will award the study
3 through a BAA contract. And we will try to do this all
4 during the summer so that we can initiate the research
5 study by September.

6 If you have any questions, please feel free to
7 contact me. My information is right here on this
8 slide. All the information I've discussed today can be
9 found on the Office of Antimicrobial Products research
10 web page, which can also be accessed through the OAP
11 main webpage.

12 That's it. Thank you.

13 Moderated Panel Discussion (with Audience Q&A)

14 DR. NAMBIAR: Thanks.

15 All right. So I think we have about 45
16 minutes for our panel discussion, and we're running a
17 few minutes late. So we do have four questions that we
18 were hoping to get input from the panel members.

19 So I think in the interest of time, what we
20 could do is maybe have a discussion around Question 1
21 and 2, and then we can move into Questions 3 and 4,
22 which sort of are more focused on what more work needs

1 to be done.

2 With Question 1 and 2, I think the main focus
3 really is that we've heard about different models
4 during the course of the day. We've heard the pros and
5 cons, the merits and demerits, of using the mouse or
6 using the pig model or using the rabbit model. So I
7 think we just want to get a feel for, are there any
8 other models that need to be considered when one is
9 developing or trying to understand infection due to
10 Pseudomonas and Acinetobacter other than the models
11 we've already discussed?

12 And I think another important point to discuss
13 would be whether or not we actually need to do studies
14 in large animals. Dr. Li Bassi's presentation, it did
15 appear that he is very much in favor of larger models,
16 studies in larger models, and not necessarily in the
17 smaller models.

18 So I think it would be very helpful to hear
19 from the different panel members on your thoughts of
20 what might be the role of smaller animal models versus
21 larger animal models in the context of developing drugs
22 that treat these specific organisms. So I will open

1 that up to discussion and see if somebody wants to
2 start.

3 So, Dr. Li Bassi, it sounds like you do have a
4 question for Dr. Diep about the rabbit model? Is that
5 correct?

6 DR. LI BASSI: Yes, I do have a question about
7 the rabbit model --

8 PARTICIPANT: He's on the phone. I'm not sure
9 if we're -- are we muted?

10 DR. LI BASSI: -- large animal model. So the
11 question is about you mentioned in your presentation
12 that you intubated these animals for the bacterial
13 challenge. After the challenge -- I didn't get from
14 your presentation, after the challenge, you extubate
15 the animals? You keep them alive up to 36 hours? Or
16 these animals are continuously ventilated?

17 DR. DIEP: The rabbits are continuously
18 ventilated for 36 hours post-infection. We also in our
19 Staphylococcus aureus study, the animals are
20 continuously ventilated for up to 60 hours post-
21 infection. And we can ventilate them as long as you
22 can do with pigs, so we can ventilate them out to 96

1 hours post-infection.

2 It just depends on the study. We don't have
3 so much experience working with *Pseudomonas aeruginosa*.
4 We only started working with *Pseudomonas* in the last 6,
5 7 weeks. But with *Staphylococcus aureus*, you can go
6 out longer because it's needed to look at a variety of
7 different parameters. But, no, so to answer the
8 question, the endotracheal tube is in place for the
9 mechanical ventilation for the duration of the study.
10 They're not taken out.

11 DR. LI BASSI: Okay. And what about the
12 septic shock of these animals? Do they develop such
13 septic shock that you need to provide vasoactive drug?
14 Or as soon as they reach this level of severity, they
15 are at the end and they die?

16 DR. DIEP: So fluid resuscitation is going to
17 be needed if we're going to prolong the animal, so keep
18 them alive longer so we can test the protective
19 efficacy of whatever it is, antibiotics or antibodies,
20 and so we do, do that. Right now we are taking a very
21 conservative approach to fluid management because it's
22 a double-edged sword, as you know. Too much fluid can

1 induce acute lung injury.

2 So in this model, we don't have so much
3 experience again with *Pseudomonas*, so we are very
4 conservative. We put in 3 ml/kg/hr. But in the
5 context of septic shock, perhaps it is necessary to
6 administer more fluid.

7 Shock is defined clinically as a 20 percent
8 decrease in cardiac output. Formerly, in the model of
9 *Pseudomonas aeruginosa*, we have not measured cardiac
10 output, but we do measure cardiac output with a thermal
11 dilution catheter in our *Staph aureus* model, and there,
12 there is an decrease in cardiac output as well as mean
13 arterial blood pressure, all of these parameters we can
14 measure. We just don't have enough experience with
15 *Pseudomonas*, so we don't know.

16 DR. LI BASSI: And do you use vasoactive
17 drugs?

18 DR. DIEP: No. We have not done that for
19 either *Staph aureus* or for *Pseudomonas*. But that could
20 be added to any treatment modality, of course.

21 DR. LI BASSI: Of course. Okay. And the
22 comments about -- one of the problems, particularly in

1 critical care medicine, now we are talking about in
2 general *Pseudomonas aeruginosa* infection, but
3 specifically in the infection that they are ultimately
4 treated in the ICU, in general, we had a lot of failure
5 in many medications, not just infection, acute
6 respiratory distress syndrome, septic shock, of many
7 drugs that were developed and tested specifically in
8 mice, and then they were translated in ICU patient.

9 So the ICU physician is particularly important
10 to highlight in this FDA-sponsored workshop, that we
11 still have a huge gap in this field of investigation.
12 Many of the drugs that they are very efficacious in the
13 mice model, they do not reproduce the same results in
14 ICU patients. We do not know the exact reason why. Of
15 course, we are a lot of (inaudible) because the
16 complexity of these patients, but this is something
17 that absolutely should be taken into consideration in
18 this field.

19 DR. MILLER: I'd make a couple of comments as
20 sort of a more neutral observer perhaps. First, I
21 think in terms of antibiotic drug development for the
22 FDA, the mouse models are not -- the anatomy is such

1 that I think that's going to be difficult to accept
2 mouse model data just because of the anatomical
3 differences. And that will be difficult to accept that
4 as part of the Animal Rule.

5 So then I think we're moving toward the
6 rabbits and pig models as reasonable models that have a
7 reasonable LPS type response similar to humans but also
8 have some anatomical characteristics similar to humans.

9 I think when you start to get to very high
10 levels of bacteria that you have to instill as part of
11 the model, then the model starts to get iffy, too,
12 because in some of these models, you're instilling the
13 equivalent of a dose of LPS that will kill the animal.
14 And so then you start to get into a very difficult
15 model as well.

16 What probably hasn't been explored enough, in
17 humans, there is probably some lung injury often
18 associated with the actual disease, and probably what
19 hasn't been explored is the ventilating animals
20 associated with some sort of lung injury as a way to
21 establish the infection more acutely.

22 And I don't think there has been a lot done

1 with that type of thing, but it's probably more likely
2 what's associated with the human disease at the time of
3 surgery or in a particular situation, there's a lesion
4 that occurs, a thromboembolus or actual damage from
5 surgery or something that has contributed to the actual
6 inciting part of the infection.

7 So I think there might be room for development
8 of lowering the infectious dose with a combination of
9 injury and ventilatory combination.

10 DR. LI BASSI: If I can just add, this is a
11 very interesting comment. We do have two pig models
12 for particularly acute respiratory distress syndrome
13 that we create, for instance, bacterial challenge or
14 saline lavage of the lung, and then we created the
15 second hit with ventilator-induced lung injury.

16 But this is absolutely a great comment.
17 Usually, animals, they many times in many diseases, in
18 reproduction of many diseases, they need a two-hit
19 model. That could be with the injury of the
20 ventilation or sometimes even they need not just one
21 single inoculum, but two or three inoculations in order
22 to have that kind of disease similar, even a smaller,

1 lower concentration of the bacterial challenge. Very
2 interesting comment.

3 DR. COX: Yeah, so just hearing the comments
4 have been very helpful information. Just my crew and I
5 were talking about this, and that's sort of the
6 difference in animal models that may look at sort of
7 antimicrobial activity/infection versus disease models.
8 So if you're actually trying to sort of model the
9 disease, and the greater role that an animal model
10 might take, to get into the space, to have sort of
11 similar physiologic conditions may help to get
12 something that may have a greater likelihood of being
13 predictive of a human response.

14 DR. MILLER: I like the way that you've
15 distilled that. I think these larger models seem to be
16 really impressive as far as pathophysiology and I think
17 provide really nice complementary information in drug
18 development. I think it would be hard to utilize them
19 alone for dose finding. So I still there is a lot of
20 value in the smaller models for the PK/PD studies and
21 then use these larger models for validation studies,
22 looking for a signal of, gosh, maybe this isn't going

1 to work.

2 DR. MILLER: And even these models tell you
3 something, particularly if you get bacteria in the
4 bloodstream, you're at least putting them in an
5 environment different than a culture plate and
6 different than the environment, and so you're getting
7 some information even in the mouse models, no question
8 about that. But for antibiotic development, you get --
9 but it's incremental.

10 DR. COX: Just to agree with your comment,
11 David, I mean, the idea of using small animal models of
12 infection, you know, try and work things out, learn as
13 much as you possibly can, and utilize the smaller
14 animal models, the activity models, as sort of the
15 earlier models to choose a compound, work on dosing,
16 all those sorts of things, and then as you've learned
17 enough from that, I mean, the paradigm of then moving
18 forward to the bigger sort of physiologic models that
19 are more difficult logistically and they use larger
20 animals, it seems completely reasonable and a very
21 rational way to approach this.

22 And the small animal stuff will add something,

1 but the bigger animals will -- or the disease models I
2 should say, it doesn't necessarily have to be a large
3 animal, but a disease model I think will help to get to
4 that physiology you're trying to replicate.

5 DR. LI BASSI: Yeah. If I can just add a
6 small comment. Usually, for instance, to give you some
7 kind of cost of these large animal models, just for one
8 animal, we usually -- the animal's sedation,
9 ventilation, staff, this experiment, just one
10 experiment, can cost between 3,000 and 6,000 euros,
11 which is very close to \$3,000, \$6,000 U.S. dollars.

12 So absolutely you need to first know -- when
13 the health care industry approach us for potential
14 collaboration, we cannot even start if they do not have
15 some kind of good results in mice, an idea, at least a
16 broad idea, of dosage, because, otherwise, it's just
17 unfeasible to test hundreds of these animals in a
18 normal setting, it's just impossible. So you can do in
19 one week 50 mice, 60 mice, but you can do just two or
20 three pigs per week in these models.

21 DR. GUINA: I would like to make a comment.
22 So I definitely agree, and I think we all agree, that

1 mouse models are very useful, and they're really
2 critical for evaluating PK/PD and studying clinical
3 doses and targets. I think maybe if we may could start
4 considering -- could we start maybe discussing what
5 sort of biomarkers we would look for in a larger model
6 or animal model that would be more close to human
7 physiology? I think there were a couple of great
8 presentations, and actually almost no presentations
9 people discussed that.

10 So if people are doing animal model studies,
11 would you like to comment on what you think would be
12 the critical biomarkers that would reflect more human
13 disease? And I would like to hear from clinicians
14 also, what is your opinion on that?

15 DR. ZURAWSKI: I think with the wound model
16 and with pigs, Stephen Davis, at the University of
17 Miami, has done quite a bit of work, I mean, over
18 25-years-plus work, looking at the host biomarkers as
19 far as wound closure and healing. So if you're going
20 for an SSTI indication for your FDA, I think you want
21 to look at those kinds of wound-healing markers. And
22 so there is matrix metalloproteinases and things like

1 that that are involved in wound healing that are
2 conserved even in humans from pigs. They're not the
3 exact same, but certainly you can use some of those as
4 markers for healing with wounds.

5 As far as pneumonia and HAP/VAP, I don't know.
6 I think I would be most concerned about sepsis because
7 I think -- I mean, certainly, lung function is
8 important, but we're clearly seeing this dissemination
9 out of the lungs going into the bloodstream, and I
10 think if you have markers for sepsis, which I know are
11 out there, I think that would be important to look at.

12 DR. DIEP: So I would like to comment on the
13 blood markers that can be used for ventilator-
14 associated pneumonia or septic shock or severe sepsis
15 in that case, and these are the standard blood tests,
16 biochemistry tests that's done in the clinic. You look
17 for, you know, if you think there is an acute kidney
18 injury, you look for creatinine, you look for
19 potassium, you look for BUN.

20 Now, these are the standard markers that's
21 used in the clinic. If you think there is liver
22 involvement, it's ALT/AST. And all of that can be

1 measured in any animal models. The biochemistry tests
2 are the same. The only problem is if you're using a
3 tiny animal like a mouse, there is only so much blood
4 that you can get through like submandibular blood.
5 That's only like 2-, 300 microliters that you can get.

6 And so the advantage of using something bigger
7 like a rabbit or a pig or a dog or any of these animals
8 is that you can take serial samples and look at the
9 chronology of events leading up to the septic shock,
10 leading up to death. And they tend to correlate very
11 well with what you would observe in the clinic.

12 And I'm not a physician, but from reading the
13 different papers on what are the predictors of
14 survivors versus non-survivors, and you see those same
15 correlates happening in the severe animal models, I'm
16 not sure whether that is observed in the ventilated pig
17 models.

18 It didn't seem like, from the data that was
19 presented here, that the infection got to the point
20 where it's very severe ARDS, because if I remember
21 correctly, the FiO_2 , the pO_2/FiO_2 in those animals,
22 it's still in the range of 200, and in that range,

1 there is not very severe -- it's classified, ARDS is
2 classified, using three different tiers. And so you
3 have very severe ARDS when the pO2/FiO2 is less than
4 100, and it's moderate ARDS when it's about 200, and
5 you have very mild ARDS when the pO2/FiO2 is about 300.

6 So it depends on how severe you want to get.
7 But these blood markers that are used in the clinic can
8 be recapitulated in the animal model, you just have to
9 do it.

10 The problem is again of course it's very
11 costly. Every time you do a blood sample and you look
12 at blood gas analysis and you do all of this
13 biochemistry, it's about \$100 at each time point. And
14 for the study that I showed you there, it's 16 time
15 points per rabbit. And so suddenly it's like \$1,600
16 for just the blood work. So it can get expensive very
17 quickly in these models.

18 DR. LI BASSI: Yeah. I'm sorry, I'm sorry.
19 Go ahead.

20 DR. WALLNOFER: I wanted to add to the
21 discussion. My impression from the presentations is
22 primarily I think that the large models will allow to

1 investigate a limited number of questions. It needs to
2 be focused with a clear plan in mind. And this can be
3 useful actually to validate what we have observed in
4 the smaller models, validate, for example, your PK/PD
5 modeling.

6 And then the other aspect where it could be
7 helpful is it could complement the clinical trials that
8 you do. Now, what is more difficult to understand now
9 from my perspective, how valuable that would be seen.
10 I think to the clinical real data that you generate,
11 those could be further substantiated, those specific
12 questions addressed. We stated that they have been
13 generating in such a large model. So that would be my
14 reading from this discussion.

15 DR. LI BASSI: Okay. So for our model,
16 usually we focus on the lungs. So these are models of
17 pneumonia, and we specifically look at inflammation and
18 (inaudible) and injury of the lungs. And one of the
19 main advantage of this model is that you can get
20 sequential bronchoalveolar lavage. And this give you
21 some data on the inflammation, local inflammation, that
22 you could even compare with systemic inflammation with

1 inflammatory markers in the blood and bronchoalveolar
2 lavage. Then you can measure the Pseudomonas
3 aeruginosa growth in the lungs through these
4 bronchoalveolar lavage. And at the end of the study,
5 you can even culture the tissue and do histopathology
6 of the tissue, and you can look at the severity of the
7 injury and severity of the bacterial burden in these
8 animals.

9 In terms of clinically valuable data, now,
10 many of the clinical trials on new drugs, they look at
11 the improvement at 48 hours, 72 hours. And when we
12 look at improvement, patient improvement, after 2 days
13 or 3 days of treatment, we look at lung function, and
14 usually pO₂/FiO₂ ratio is a good marker of lung
15 function. And bacterial culture. Many times we either
16 get tracheal aspirates or bronchoalveolar lavage of
17 these patients to corroborate the good response. So
18 these are the things that usually we can obtain from
19 these models.

20 DR. NAMBIAR: To answer your question,
21 Andreas, I think our main focus here, as we discussed
22 today, is try to get the best clinical data we can

1 because that would really be ideal. But then we all
2 realize from a practical standpoint that that might be
3 doable or might not be doable, and there might be
4 practical difficulties in getting to the numbers you
5 had set out to do.

6 So I think this discussion is around, what is
7 the best we can do with the animal models that we have?
8 And what more needs to be done? What are the areas
9 that we need to focus on so that at the end of the day,
10 if someone tries to do a clinical trial and only once
11 you attempt it will you know how successful you're
12 going to be, how difficult it's going to be.

13 And if the trial is just not feasible, so
14 we're not talking about a trial where the drug has
15 shown it doesn't work, I mean, then the drug is dead,
16 but if you have a drug that has the potential, but you
17 just cannot do the human trials, then we want to have
18 the best body of information we can get for how the
19 drug performs in animals. So I think all kinds of
20 animal models have their different rules. The smaller
21 animal models play a different role.

22 So I think that's the purpose of this

1 discussion. It's not that these are to replace human
2 data, but it's to sort of complement whatever human
3 data you can get, which I think we all have to be
4 practical and think that there might be a situation
5 where you're really not going to get human data that's
6 going to be interpretable.

7 And then you cannot start planning what next,
8 you start planning now. And that's the purpose of
9 having this discussion.

10 DR. ANDES: I think that before you can use
11 these larger animal models to try and predict what's
12 going to happen in patients therapeutically, it would
13 be nice to see -- I saw some examples where people took
14 a drug that was approved, treated the animals, and they
15 did well. It would be nice to see, try and like has
16 been done in the mice, take a drug that failed, take a
17 drug that doesn't work, mimic the PK in patients and
18 show that it failed, show that it's predictive, and
19 look at then, what of those endpoints tracked along
20 with that failure?

21 DR. NAMBIAR: That's a very valid point,
22 something we've certainly discussed, having both two

1 kinds of controls, ones that you know. Unfortunately,
2 we have a few examples of drugs that haven't worked in
3 humans, so we can use those examples. And we also have
4 examples of drugs that really do well in humans. So
5 having both, I think, and testing them in animals is a
6 good idea.

7 DR. MILLER: Since we were asked, one of the
8 questions was other models, and so I think that we
9 should also be working on bacteremic models because
10 bacteremic models are very reproducible usually if
11 you're injecting bacteria directly into the bloodstream
12 in animals, and they have a lot of -- they're short
13 term, there are good endpoints. Particularly with
14 rabbits, the LPS aspect is very predictable for humans.

15 So I think bacteremic models have a lot of
16 appeal. It's a short-term model compared to the
17 ventilatory models, which are really complicated, which
18 we need, but I think there are a lot of advantages to
19 bacteremic models.

20 DR. NAMBIAR: Any other comments from the
21 panel members for Questions 1 and 2? Dr. Rex, you have
22 a comment?

1 DR. REX: I'm sort of thinking about the
2 intersection of what David and Andreas were talking
3 about, and trying to think also about the way that --
4 you know, the standard we have for drugs, about
5 substantial evidence of efficacy based on adequate and
6 well-controlled evidence.

7 And the words are not defined numerically.
8 And we've talked a lot about justification for you
9 could say larger NI margins or a different alpha. I
10 mean, all those are sort of functionally equivalent
11 manipulations of the statistical boundaries.

12 And maybe this is saying that one way to look
13 at this is that if you've clearly developed your PK/PD
14 argument in mice, and maybe do a couple rabbits, and
15 then you do a tiny number, which is all you're going to
16 be able to do, of pigs, and prove to yourself that in
17 fact when I treat a 40- to 50-kilo pig, which is a
18 reasonable fraction of the size of the human being and
19 a lot of the same anatomy, it worked again, then that
20 actually would permit you, if you could not do adequate
21 clinical data, to say that a different dimension
22 statistically -- it's sort of like saying it's Bayesian

1 prior, it's another way to say it, it's actually
2 creating that sort of an argument.

3 And I actually do think it's important that we
4 get down to discussing that because another part of
5 sort of the whole scenario, game-playing this all the
6 way out to the end, is that even being approved doesn't
7 mean that other people will understand the basis of
8 approval or why they should pay for it or use it.

9 So the fact that this very sophisticated group
10 sits down with an agency and says, "Yes, you've done
11 these studies, and, yes, you've got this little bit of
12 data," it actually needs to be something that others
13 can see reasonably well in terms of justifying whether
14 or not they would reimburse for it.

15 So, again, it feels like that's the kind of
16 logic that other people could get behind. It steadily
17 adds up. So I'm very cognizant of the other
18 stakeholders that have to ultimately decide that, yes,
19 not only was it approved, but that it makes sense to
20 me, too. The agencies do not have the last word in
21 that regard; there are many others whose opinions
22 really matter.

1 So I think I came in today not as certain that
2 I knew why you would do the big pigs. And I had looked
3 at Dr. Li Bassi's slides, and I thought, wow, that is a
4 huge amount of work, but maybe there is a reason for
5 doing a small set of studies there, particularly if
6 you've really run that model well, if you've really
7 characterized it and you know that a humanized exposure
8 of X doesn't work when it shouldn't work and it does
9 work when it should work, you've put in all your
10 standard candlesticks. You've actually -- you've
11 really measured it --

12 DR. MILLER: You have the controls --

13 DR. REX: You have the controls, you really
14 know.

15 DR. MILLER: -- of antibiotics that work and
16 antibiotics that do not work, and you have a few
17 surrogate markers --

18 DR. REX: Yeah.

19 DR. MILLER: -- that are fairly equivalent,
20 then I think you could approve it for an indication
21 when there was not something else available that was
22 approved, you could include that in the approval.

1 DR. REX: Well, but now, you've put in
2 something that I'm sure I would be careful about that,
3 something -- nothing else approved. I --

4 DR. MILLER: Well, not -- when there is no
5 other agent available.

6 DR. REX: Well, for use when there is no one
7 there to let it run.

8 DR. MILLER: Yes.

9 DR. REX: But I would be careful about saying
10 that we can't approve something else unless there is
11 nothing else anywhere in the universe that --

12 DR. MILLER: No, that's not what I'm saying.

13 DR. REX: Yeah, that's -- be careful about
14 that.

15 DR. MILLER: Because there are clinical uses
16 where approved drugs that would work cannot be
17 clinically used for various reasons.

18 DR. REX: Right. Yeah. Dr. Boucher showed us
19 one of those today.

20 DR. MILLER: Human allergy or many sorts of
21 situations. So it would just be when another approved
22 antibiotic is not available.

1 DR. LI BASSI: Yeah, if I can add to
2 something. I think we should put all this discussion
3 in the context of 2017. And as a clinician, we are
4 very worried that many agencies, like the Food and Drug
5 Administration, the European Agency for Drug Approval,
6 and even health care industry, they are -- considering
7 that we do have an increasing number of pathogens that
8 they are becoming drug resistant, there is not a
9 parallel improvement in the research, development, even
10 approval by these agencies to facilitate the
11 development of new drugs.

12 As a clinician, every day I go to an ICU where
13 there is a patient with a *Pseudomonas aeruginosa*
14 resistance to everything except colistin. So I think
15 that one of the goals that Food and Drug
16 Administration, and Europe as well, should have in
17 mind, is to try to not make the entire approval process
18 more difficult than it has been throughout the years,
19 but much more easier, because if there is the
20 development of drug, then we wait for mice, then we
21 wait for drugs, and the multi-institutional randomized
22 clinical trial, this just make the development of new

1 drugs so difficult that the health care agency and
2 health care industry, they just shift to other kind of
3 business that they are more proficient in terms of
4 money. And so this is a very important conversation
5 particularly in the era of multidrug resistance.

6 DR. KNISELY: Okay. Thank you. Oh, Ed, go
7 ahead.

8 DR. COX: I was just going to say, I mean, a
9 lot of what today is about is trying to balance
10 benefits and risks, and recognizing the unmet needs
11 that are out there for patients with serious infections
12 who need new options.

13 So I think really what you're describing,
14 Dr. Li Bassi, is consistent with what we're talking
15 about here, which is trying to find feasible pathways
16 here so that there are options out there for patients,
17 recognizing the tremendous need.

18 DR. KNISELY: Right. So now let's move on to
19 discuss Questions 3 and 4, which are kind of more
20 forward-looking questions on what we need to do moving
21 forward.

22 These have already come up, but what are kind

1 of the key highlights of research questions that need
2 to be addressed in order to move this idea forward,
3 including other sites of infection that should be
4 prioritized? Dr. Miller already brought up bacteremia.

5 DR. DIEP: I'll make a comment. So in the
6 Staph field, Staphylococcus aureus, the gold standard
7 model for testing antibiotics is the rabbit model of
8 aortic valve endocarditis. This model would produce a
9 persistent bacteremia.

10 And the reason that this model is the gold
11 standard model for testing new drugs against MRSA is
12 because it's a biofilm-based model. It's very
13 difficult to treat. And the rabbit model of aortic
14 valve endocarditis also exists for Pseudomonas, for
15 Klebsiella, for A. baumannii. And it's for the same
16 reason, it's the biofilm. It's very difficult to
17 treat.

18 And it's very easily adaptable for any bugs,
19 and that's because of the way that the model is done,
20 it's a low inoculum model. And the reason that it's a
21 low inoculum model is the carotid artery is cannulated
22 with a catheter, and the catheter is placed across the

1 aortic value, and that cause valvular damage, providing
2 this deposition of platelets and fibrin, and it sets up
3 a niche for bacteria to bind to. So you can use often
4 5

4 10 or 10-fold less bacteria to cause the endocarditis.

5 And this is also a relevant infection for
6 opportunistic pathogen like a Pseudomonas. It occurs
7 in injection drug users. Right.

8 DR. COX: Can I ask, in the last question, we
9 were talking about the things that you might do early
10 on, and as you move from sort of activity models, you
11 would then move to disease models. Where would you put
12 the model that you're describing, biofilms, aortic
13 valve? Is that something you would do early or is that
14 something you're thinking about doing later on just in
15 the overall development program?

16 DR. DIEP: I can actually comment on that. So
17 the sort of model that like a rabbit bacteremia model
18 or a severe sepsis model, those are really easy to do,
19 just like they are in mouse. It's just an intravenous
20 injection. The surgical models are complicated, and
21 they cost a lot more to do. For example, it was
22 mentioned that for the pigs, it's 3- to 6,000 euros to

1 do a ventilated pig model. To do a rabbit ventilated
2 model, it's \$6- to \$8,000 U.S. dollars. It's extremely
3 expensive, more expensive than the pigs it seems, maybe
4 because labor in the United States is higher than it is
5 elsewhere.

6 (Laughter.)

7 DR. LI BASSI: That's a good point.

8 DR. DIEP: But I think cost is the key issue.
9 And so if you can do -- you know, it depends on how
10 much money is available to fund the study. An
11 endocarditis model is, I would consider, a later stage
12 type mechanism of action study. And I would use, for
13 example, a bacteremia model first because it's a lot
14 cheaper.

15 DR. ZURAWSKI: I would like to comment about
16 the biofilm aspect. So when we talk about drugs that
17 fail, oftentimes it could be because of resistance that
18 we see. And one of the things that I used to often
19 banter with Jared Silverman about was there is really
20 no good model for resistance when it comes to animal
21 models and when we're looking at antibiotics. We can
22 do as much hollow fiber as we want, we can do a lot of

1 PK/PD in these models, but a lot of that is short term.

2 And I think one of the things that isn't --
3 that we should just invest more in are some longer term
4 models, something like this, where we've got a biofilm
5 that's going to change your -- actually, it's going to
6 change your PK/PD because some of those biofilm
7 bacteria are just not going to be able to get hit by
8 the drug that you're looking at. And so we need
9 something that's like a week long where a mutant can
10 arise, all those kinds of things, and we just don't
11 have good -- we're not addressing that very well right
12 now.

13 There's a rabbit ear punch model that my
14 colleague Kylie (ph) Young was doing at USAISR for
15 Klebsiella, but you could probably adapt that to any of
16 these ESKAPE pathogens if you used the right strain
17 again. There you actually have a biofilm growing on
18 the ear of the rat making a wound, similar to our wound
19 models where we see biofilms.

20 We ourselves have not addressed that very well
21 even in our models where we've looked at mice and pigs
22 over a prolonged period of time where it would be nice

1 to do a study where we use rifampin, something where we
2 know resistance pops up routinely at a certain number,
3 see if we can recapitulate that. And then maybe where
4 we've seen failures in terms of resistance, also see if
5 we can recapitulate in the animals as well, that we've
6 seen in humans.

7 I don't want to throw stones, but, I mean,
8 like the Anacor compound, for example, that failed, it
9 failed because of resistance reasons. I think if that
10 company had done more work up front in animals and saw
11 resistance crop up, it may have never gone to clinical
12 trial, or it shouldn't have. So just something to
13 bring up there. But the biofilm component is a huge
14 component of pathogenesis that we're not really
15 discussing, and it's a big deal. It's literally a
16 1,000-fold change as far as how some of the antibiotics
17 work.

18 DR. COX: Can I ask another one? So we've
19 been talking about activity in disease models, and it
20 sounds like we've got disease models for *Pseudomonas*
21 *aeruginosa* in the lung. And what I'm not so clear on,
22 there are some nice public presentations, but sometimes

1 it's hard for me to tell sort of when we're talking
2 about activity and when we actually move to disease.
3 And I welcome comments from any of the speakers that
4 are available to talk about this that presented
5 earlier.

6 How are we doing for Acinetobacter for a
7 disease model in the lung? Dan, you presented some
8 nice models, but they were skin models, if I'm
9 remembering.

10 DR. ZURAWSKI: Well, we have a mouse lung
11 model that's similar to all the other ones that people
12 are running for Pseudomonas that works very similarly.

13 There is a rat pneumonia model that Tom Russo
14 developed at SUNY Buffalo that works with fairly low

7

15 inoculum. I think the inoculum is 10 I want to say.
16 So the inoculum is still pretty high, but you don't
17 have to do neutropenia, so you're taking that element
18 out because the rats have less of an innate immune
19 response than mice.

20 So I did want to bring that up because
21 Question 1, we're talking about other animals that
22 should be discussed. I think rat is left out quite a

1 bit. I like the rabbit quite a bit, but rats I think
2 maybe should also be included. We've done a rat wound
3 model that I didn't talk about today. We've kind of
4 done that low frequency, but it recapitulates
5 everything that we're seeing in mice and pigs, and
6 certainly in humans, where we see this penetrative
7 infection of SSTI. But as far as long goes, really
8 it's just mouse and rat at this time.

9 I'm sure the models we saw for *Pseudomonas*
10 lung today could be adapted to *Acinetobacter* if the
11 right strain were used and you get the damage that Dr.
12 Miller was talking about. I'm sure you could get
13 *Acinetobacter* working in that setting.

14 DR. COX: Do you think that the rat model,
15 lung infection, *Acinetobacter*, is it a disease model or
16 are we looking more at activity there?

17 DR. ZURAWSKI: I think it's a disease model.
18 I mean, what Dr. Russo showed, you have the
19 *Acinetobacter* disseminating from the lungs into the
20 bloodstream and killing the animal. I mean, I really
21 think that's what's happening in ICU patients as well.
22 So it's not perfect, but I think it's a very good first

1 step, even looking at disease.

2 I think where things go wrong as far as
3 efficacy go is when we just do like a mouse thigh or a
4 rat thigh, and, "Oh, I see a 2 log drop. My compound
5 is great. We're moving on." That is not -- you need a
6 pathogenesis piece because these bugs do something
7 differently in every different part of the body. There
8 are different stresses in every part of the body. I
9 feel like you have to have a biofilm component. Some
10 of that gets addressed in the rat pneumonia model.

11 I believe even when we do a mouse lung model,
12 there are components of biofilm that are going on there
13 with those bugs. I wouldn't call it a true biofilm,
14 but you get these droplets, like I mentioned, that you
15 probably have biofilm-like or stationary phase-like
16 bugs and then planktonic around them. And we see that
17 even within 2 days, 1 to 2 days pathology-wise. So
18 they are disease models. They are not necessarily just
19 efficacy.

20 DR. MILLER: But I think even for Pseudomonas,
21 where there has been a lot more work done, the
22 reproducibility of these models and their

1 standardization with specific bacteria, it just has not
2 been there over the years.

3 And so there needs to be more work done with
4 both of them if the models are going to reach the
5 standard that you're probably looking for in more than
6 one site and very specifically designed experiments I
7 think to develop these models that could be accepted
8 with the right bugs and developed so that there could
9 be a specific model where you could point to and say,
10 "This is what we think needs to be accomplished,"
11 because they haven't been using drugs that work or
12 don't work, or they're a specific strain or a specific
13 mouse strain, or just --

14 And any animal model, anything involving host-
15 pathogen interactions can be difficult to reproduce
16 biologically, and so you're going to have to be
17 convinced that you can biologically reproduce it in
18 more than one site. Just like in clinical trials,
19 right?

20 DR. DREIER: I'm Tom Dreier, from BARDA. Just
21 a question. It's not per se some of these questions
22 that you have here, but who's going to decide what

1 bacteria strain you use for the models? I look at this
2 and I thought -- and we've done a lot of work with
3 BARDA and the FDA, but the first step is always you've
4 got to define the strain so you can define your
5 problem. So who's going to define the strain? Who's
6 going to grow the strain? And who's going to put it on
7 distribution?

8 DR. COX: Since I don't develop animal models,
9 I guess I'm free to answer that question.

10 (Laughter.)

11 DR. COX: No, I'm just kidding around. It's
12 getting late in the day. And I'll welcome the comments
13 from folks who actually do develop animal models, but I
14 would think that it seems like the host that you're
15 studying and the strain go together. And we heard some
16 discussions earlier about picking a strain that has
17 certain properties based on its clinical behavior. And
18 then it sounds like that strain needs to be well
19 pedigreed in the animal model of infection and such.

20 But maybe some of the animal model developers,
21 who actually do this, will tell me how embarrassed I
22 should be for what I just said there.

1 DR. ZURAWSKI: I'll speak for Acinetobacter.

2 I mean, even though I laid out those criteria, we just

3 don't know enough how this thing is causing disease.

4 Right? So, I mean, I would like to say that -- you

5 know, I haven't -- we have data that we haven't

6 published yet that we're working on where we've

7 identified virulence factors that we know are pretty

8 important. And there are some that I think may be

9 important that we identified that could be important,

10 let's say, and one of those might be barrier function.

11 So breaking the tight junctions in the epithelial

12 barrier, it may possess a toxin that does that.

13 So you don't want to use a strain that doesn't

14 have that toxin. Right? So if that's a key part of

15 its virulence and how it's -- there are going to be a

16 percentage of strains that don't have that toxin. We

17 know by looking at the 1,000 sequenced Acinetobacter

18 that not all of them have it or they have different

19 variations of it.

20 So how are you going to -- it's hard, I think,

21 to get at this, to crack the nut, because we're still

22 so early -- I mean, Pseudomonas, there's much more work

1 on that that's been developed on the pathogenesis side
2 where we know a lot of the toxins, we know a lot of the
3 things that it does pathogenesis-wise that I think we
4 can exploit, but with Acinetobacter, it's more of an
5 open question.

6 DR. GUINA: Well, I would like to just add to
7 that. I think it's really important to pick strains
8 that are obviously very low passage, they've been very
9 well characterized, and also those that reproduce as
10 close as possible to human disease in any of the animal
11 models, that we pick based on some agreed upon
12 biomarkers and endpoints that actually are the quality
13 checkpoints for the model. Because there are so many
14 strains, we'll never agree to agree.

15 DR. GOLDBERG: And I think you should not just
16 rely on one strain, but you should always look at a
17 panel of them to see how they're holding up to one
18 another.

19 DR. MILLER: And that's part of the challenge
20 of developing these models, is whoever is developing
21 these models will consult with experts and decide on a
22 set of strains, and that's what will get developed, and

1 once -- but they will need to be continually validated
2 that they haven't changed, just like stocks, just like
3 you would with any other biologic, there will have to
4 be endpoints that it still has that biological
5 characteristic when the animal --

6 DR. COX: It sounds like in part that speaks
7 to the importance of having control animals and
8 monitoring your strain over time, too, it seems like.
9 Thank you all for helping me.

10 DR. LI BASSI: I have a question. Should the
11 decision of this strain be also regulated by the
12 agencies based on the prevalence of the strain in the
13 human population?

14 DR. REX: No.

15 (Laughter.)

16 DR. REX: So John Rex says no. And you don't
17 want to write something down like that and create such
18 a hard rule because things may change over time. And I
19 think that as we go along, what you want for Drug B
20 will be different than what you wanted for Drug A
21 because of the existence of Drug A. So you've got to
22 be careful not to overspecify here.

1 DR. LI BASSI: Okay.

2 DR. KNISELY: Any other questions from the
3 audience? Okay.

4 DR. GELHAUS: Carl Gelhaus, MRI Global.
5 Previously, all the antibacterial products that have
6 been approved under the Animal Rule use non-human
7 primates. So we saw a non-human primate model briefly.
8 Is there any thought about the need for a non-human
9 primate model?

10 DR. COX: All right. Am I going to have to go
11 first again?

12 (Laughter.)

13 DR. COX: So really what we're trying to get
14 at are animal models that are predictive of human
15 efficacy. So I think the question sort of, you can
16 distill it down to, what are those potential animal
17 models? And can you do that in animals other than non-
18 human primates and do it in a way that's sufficiently
19 predictive for establishing the likelihood of efficacy
20 in humans?

21 So in some cases, it seems that the non-human
22 primate is in fact the model that gets you to that

1 point of having something that really you've got good
2 reason to think that it's likely to be predictive.

3 So I think it may depend upon the particular
4 bacterial species, how it interacts with the host, and
5 whether you can get information from -- or from which
6 animal species you'll actually be able to get
7 information that you think is based -- that's likely to
8 predict efficacy for humans. And it may not always be
9 a non-human primate, it may be something other than
10 that. In some instances, it may be a non-human
11 primate, but I think that's really sort of a scientific
12 question, and folks here have described a number of
13 different species and the animal models that they've
14 looked at.

15 DR. LAWRENZ: Keep in mind, too, when you look
16 at plague and tularemia and anthrax, there aren't a lot
17 of human cases that you can move then and do those
18 small clinical studies, where with these bugs, there
19 are availability to move to that next step. And so I
20 don't know that the requirement for a non-human primate
21 is going to be as high when you look at these guys in
22 the clinic.

1 DR. MILLER: And there is no evidence that
2 these bacteria would be more pathogenic or more like
3 humans in non-human primates than in pigs, whereas for
4 other human-adapted pathogens that are really human
5 specific, say like Francisella or something like that,
6 then that makes more sense.

7 DR. DIEP: I would like to make a comment on
8 that. Sometimes the non-human primate does not make
9 the best animal model either. It depends on what is
10 the target. In the field of Staphylococcus aureus,
11 where I come from, there is a particular kind of toxin
12 called Panton-Valentine leukocyte, and it's associated
13 with this epidemic of MRSA that we saw in the past
14 decade.

15 And this particular toxin targets a C5a
16 receptor on human neutrophils, and also targets at the
17 same level sensitivity to rabbit neutrophils. The C5a
18 receptor for rabbits and for humans are rather similar
19 to one another. And when you look at monkeys, monkeys
20 are very resistant to this particular toxin.

21 And so to test an antitoxin against the
22 Panton-Valentine leukocyte in the rabbit model is like

1 testing it in the mouse and the rat, which are also not
2 susceptible. So sometimes monkeys are not -- non-human
3 primates are not the best model. And it depends on the
4 pathogen.

5 Like Staphylococcus aureus and Pseudomonas,
6 those are natural pathogens of rabbits. There are
7 outbreaks, natural disease outbreaks, that occur in
8 rabbit farms. That's why it makes for a good model for
9 that, also for that reason. But it all depends on what
10 is the target and whether the host is susceptible to
11 the target or not.

12 DR. NAMBIAR: No other comments before we --
13 oh, there's one more comment.

14 PARTICIPANT: Thank you. So I wanted to make
15 two comments actually. First I want to address the 052
16 question because I was heavily involved with those
17 studies, and we did an enormous amount of animal work.
18 We did neutropenic mouse, lung, thigh. We did
19 competent mouse studies. We did rat thigh studies. We
20 did rat pneumonia studies. We did recreated human PK
21 profiles in rat pneumonia studies. We did almost
22 everything you can do. And we never saw the resistance

1 in those studies.

2 We even tried after the fact to recapitulate
3 the resistance, and we couldn't get it to happen unless
4 we spiked a certain number of mutants into the
5 inoculum. So anyone who has worked with trying to
6 resistance studies in animals, it's incredibly
7 difficult to develop those models. So I felt like we
8 really deserve a little bit of credit for doing a whole
9 lot of work.

10 DR. ZURAWSKI: I understand. And, again, I
11 wasn't throwing stones, it's just -- I understand.
12 That's what -- it's a high bar. I mean, that's -- if
13 we can get that, that would be wonderful, if we have a
14 resistance model.

15 PARTICIPANT: Yes, I agree. I think one of
16 the difficulties there is you need a high enough
17 inoculum. We've done a lot of work with rifampicin,
18 and even that notorious compound, you need to get at

8

19 least 10 bugs in there to really get any mutants to
20 come back out. So it's difficult, and the animals tend
21 to die when you get those high inocula, so you just
22 can't follow through.

1 So the other comment I wanted to make was
2 around this idea of picking a model and one strain. I
3 think that's incredible dangerous, and I really would
4 encourage us to not go that direction. Thank you.

5 Closing Remarks

6 DR. NAMBIAR: All right. So thank you,
7 everybody. It's 5:00, and it's been a long day.

8 I just wanted to thank all the panel members
9 for their participation and presentations today. Very
10 helpful.

11 I want to thank the audience for their
12 participation as well. Thank you for coming.

13 And I also want to thank people who are
14 joining us remotely. I think this was an extremely
15 helpful workshop, and we will take your feedback and
16 discuss it and hope to continue the dialogue because we
17 really need to find a way forward to get these products
18 to patients who need them. So thank you very much and
19 safe travels.

20 (Applause.)

21 (Whereupon, at 5:02 p.m., the meeting was
22 adjourned.)

1 CERTIFICATE OF NOTARY PUBLIC

2 I, MICHAEL FARKAS, the officer before whom the
3 foregoing proceeding was taken, do hereby certify that
4 the proceedings were recorded by me and thereafter
5 reduced to typewriting under my direction; that said
6 proceedings are a true and accurate record to the best
7 of my knowledge, skills, and ability; that I am neither
8 counsel for, related to, nor employed by any of the
9 parties to the action in which this was taken; and,
10 further, that I am not a relative or employee of any
11 counsel or attorney employed by the parties hereto, nor
12 financially or otherwise interested in the outcome of
13 this action.

14
15 
16

17 MICHAEL FARKAS

18 Notary Public in and for the

19 State of Maryland
20
21
22

1 CERTIFICATE OF TRANSCRIBER

2 I, DEBORAH ARBOGAST, do hereby certify that
3 this transcript was prepared from audio to the best of
4 my ability.

5
6 I am neither counsel for, related to, nor
7 employed by any of the parties to this action, nor
8 financially or otherwise interested in the outcome of
9 this action.

10
11 
12

13 MARCH 13, 2017

DEBORAH ARBOGAST

&	115:13 120:13	130 181:22 203:20	1:35 204:17
& 82:22	130:19 146:2,2,4	130,000 67:22	2
0	159:1 187:13	13th 24:11	2 16:18 29:17
0.25 60:20	190:6,7,7 192:8	14 114:16 197:11	35:15 50:19 71:7
0.3 269:16	195:20,20 196:1,1	211:2 219:13	77:17 88:12,15
0.5 109:10	196:18 199:3	263:15	114:3,3,4 116:19
0.5. 60:21	211:14 244:19,22	140 10:19 11:7	118:12,16 122:3
08 82:16	245:4 247:11	140,000 265:5	169:1 178:3
1	250:6,9 252:16	141 11:10	182:18 207:13
1 1:7 29:17 50:9	260:8,8,9,9 262:5	15 9:4,7 94:15	210:2,18,20
50:11,18 51:2,6	263:2 265:6	110:22 114:17	215:21 217:18
51:19,22 53:10	266:10 267:9	122:13 252:14	219:1 220:13
54:6,10 64:3	270:1,2,5 277:21	253:2 256:8	221:2 230:20
74:20 114:2,4,5	290:7 295:16	266:11 269:18,21	246:14 251:15
120:12 142:12	338:4,4 342:15	270:5,19 271:7	263:16 266:2
171:9 178:3 182:5	354:19	273:8 281:1 290:7	269:1,1 272:6,14
182:6 210:2,19	100 50:13 56:10	290:9	277:19 303:22
211:6 214:8 215:3	75:21 108:17	150 248:19 259:22	304:20 311:21
220:13 230:11	114:20 146:3	151 11:14	312:2 324:5
234:17 248:18	154:17 185:1	16 100:5 114:18	327:12 330:21
250:8 255:20	200:15 215:20	118:15 154:20	344:4,17,17
257:6 266:6	216:11 217:19	210:19 325:14	2.4. 309:19
268:16 269:18	218:20 225:15	16.5 54:17	2.4.2 310:3
270:18 271:4,6	248:19 260:1	160 118:4 181:20	2.5 268:14 270:3
279:10 296:17	300:1 325:4,13	183:14	2.5e7 272:7
302:14 304:1	100,000 33:18	168 11:16	20 31:20 40:5
306:12,13 311:20	67:21 258:21	16s 251:22	52:20 58:2 114:21
312:2 330:21	11 49:14 114:12	17 114:19 274:7	151:7,20 180:10
342:21 344:17	233:13	18 37:22 66:22	212:12 219:12
1,000 53:18 70:19	111 10:17	78:18 84:11	226:14 244:11
116:3,4,14 211:22	113 117:15	107:21 114:20	257:4 265:6
244:10 249:2	114 114:1	134:6 253:3	278:11 288:8
266:14 275:14	118 75:22	1800s 89:19	315:7
341:16 347:17	11:15 140:17	184 144:10	20,000 53:22,22
1,100 266:14	12 49:14 70:7	185 11:19	200 75:20 77:8
1,500 266:12,12	101:18 107:21	19 39:6 114:21	78:17 262:1
1,588 143:16	114:14 117:13	134:7 278:11	324:22 325:4
1,600 325:15	187:13 237:7	309:2	2000 142:19
1,700 150:13	260:17,19 269:13	1926 90:3	2000s 99:9
1.5 273:7	274:6 290:12	1954 143:3	2001 96:11 98:20
10 31:20 52:21	120 75:22	1955 240:3	103:7,8 106:21
63:2 73:15 114:5	13 114:15 274:6	1:1 75:21	2002 82:2 97:1
114:8,11,14,14	357:13	1:2 273:9	111:4

2003 82:7 97:1 241:10	250 53:7 84:5	33 241:3	247:10 327:11
2004 97:1	26 309:16 310:22	336 52:22	4x 260:1
2005 82:14	26.6 228:19	34 89:8 241:11	5
2007 82:16	264 13:7	35 76:14 170:4	5 31:6 33:11 73:15
2009 82:19 234:3	28 9:10 75:17	273:6,8,12	79:8 81:12 88:6
234:17 238:1	114:2	355 14:8	111:13 114:6,13
2011 308:20	280 13:12	36 269:2 272:13	118:16 120:13
2013 31:1 83:22	295 13:14,19	274:13 275:19	146:1 169:1
280:10	2:1 55:17	279:21 313:15,18	176:13 230:19
2013/14 291:7	2nd 1:13	3:40 295:16	244:21 245:4
2014 70:19 222:3	3	4	247:21 248:10
291:7	3 29:13 42:5 46:13	4 30:20 70:16,17	249:3 250:6,8
2015 67:8 84:1	46:21 47:2,3,4	70:20 84:11 100:4	260:7 262:4 266:6
2016 58:7 82:2	52:20 53:2 74:13	111:13 114:5	269:18 270:19
2017 1:7 40:17	75:1,5,9 77:7,17	117:14 118:16	271:7 273:18
335:3 357:13	78:4 81:11 88:6	142:1 154:19	292:9,10 298:7
204 11:21 12:8	88:16 92:5,8 96:1	173:15 174:17	310:7,21 338:3
205 12:12	100:4 114:4,4,5,6	190:6 196:1	5,000 249:5
20910 1:15	114:15 115:20	212:12 234:18	5,580 142:22
20s 89:21	116:20 118:12	248:11,18 250:5	50 96:15 109:5
21 40:14 114:22	120:12 208:14	260:3 266:2 270:1	152:10 201:4
252:9	234:18 248:21	270:3 273:7	225:13 244:11
21st 24:10	249:1,2,4,6	279:10 292:9	247:22 269:17
22 114:22 309:11	256:14 270:14	293:18 311:21	321:19 331:17
22,000 53:2	279:10 291:16	336:19 338:3	500 266:8
222 12:16	293:18 311:21	40 49:15 68:9	5075 244:15 245:5
23 156:21 169:15	315:4 327:13	76:11 89:4 181:7	245:15 247:8
234 12:21	336:19 338:22	181:18 184:16	263:4
24 78:18 87:21	3,000 53:2,8	210:20 211:6	50s 112:19 116:12
94:3 100:5 102:20	321:10,11	270:5 274:17	51 274:18
103:1 163:7	30 43:6 55:14 89:4	331:17	52 251:17 269:15
173:15 182:17	115:13 211:5	400 60:20 78:1	5:00 355:7
207:17 213:2,13	241:13 258:16	84:5	5:02 355:21
244:4 246:13	300 53:7 78:1	40s 112:13	6
262:21 268:15	166:10 251:17	42 142:2	6 59:19 94:2 114:5
269:13 270:5	324:5 325:5	43 9:17	114:7,13,21
272:2 274:8	300,000 115:19	431 182:12	117:18 118:1,16
290:12	3042 24:12	45 273:12 311:15	196:1 244:18
25 54:17 55:15	31 309:16 310:14	46 34:15 37:3	245:3 248:10
151:7 213:14	311 14:6	114:7	260:19 267:9
252:9 257:4	314.600 20:21	47 117:14	271:18 272:5
258:16 259:22	32 154:21 266:21	48 72:14,15 87:21	273:9 290:6
322:18	267:1	118:2 119:14	304:21 314:4
		178:8,10 245:6	

339:2 6,000 53:2 249:3 321:10,11 338:22 6.6 142:20 60 67:21 68:11 72:19 240:3 251:15,16 270:5 313:20 321:19 601.90 20:22 6077 268:21 60s 112:14,20 64 69:1 70:15 154:21 65 211:19,20 650 20:22 672 52:22 6x 260:1	8,000 339:2 80 10:10 60:21 68:10 76:10 87:4 244:5 259:5,7 800 266:11 83 87:4,10 85 283:3 294:22 8727 1:14 88 70:8	85:22 87:5 93:13 98:2 100:20 103:14 116:4,8 126:14,18 127:13 131:11,12 132:5 132:11 133:19,21 134:5,19 136:8,19 138:5,20 140:11 164:3 168:12,14 185:10 214:2 223:4 224:3 225:22 226:16 227:4 231:14 233:12,17 236:20 273:15 276:7 277:4 297:1 298:20 300:9 301:3 331:16 340:7 351:6	acceptor 142:4 access 200:3,5,10 238:14 accessed 311:10 accomplish 23:17 81:2 accomplished 80:18 345:10 account 73:14 107:9 188:10,11 217:1 221:13 240:5 259:14 accounted 213:19 accredited 181:9 accumulate 173:20 188:14 accuracy 110:7 accurate 356:6 acgme 29:3 achaogen 17:8 49:5 76:13 achievable 74:6 78:18 137:9 138:9 achieve 109:10 192:6 220:14 273:10 achieved 220:12 achieving 179:4 273:11 acid 272:17 289:1 acineto 151:9 167:11 acinetobacter 1:4 11:12 12:18 15:7 16:1 19:5,11 25:8 25:11 29:9 31:2 31:10 38:10 42:3 44:7,13,20 57:6 65:2 66:18 67:10 67:16,18 68:2,5,7 68:12,15,22 69:4 69:7,16,22 70:2,6 70:14,18 71:6 72:3,5,10,13,18
7	9		
7 32:4 107:21 114:8 117:18 146:1 190:6 215:14 231:1 271:19 272:6 314:5 342:14 70 154:6 71 32:7 72 64:13 85:17 86:10,21 87:19 119:14 290:3 292:14 327:11 75 218:20,20 290:10 750 184:15 236:15 76 87:19 79 9:20 84:10	9 114:10 159:1 190:5 195:19 260:8 90 52:21 60:21 68:13 162:19 244:4 269:5 91 265:17 915 55:17 95 20:22 248:2 96 86:22 178:8,10 269:4 313:22 979 143:17 98 226:17 99 70:19 9e7 268:21 271:13	aborted 113:3 abscess 175:13 absence 221:10 absolutely 55:12 198:15 284:8 316:17 318:16 321:12 abstract 51:18 abundant 112:18 113:12 academia 236:3 academic 43:10 43:10 298:7 305:20 307:13 accelerator 297:20 accept 18:11 54:10 57:14 128:12 286:16 317:1,3 acceptable 59:19 173:17 acceptance 283:4 accepted 345:7	
8	a		
8 59:19 114:9 130:18 154:20 195:19 211:14 219:2 230:14,19 234:16 266:11 292:10 354:18	aac 253:14 aalas 181:9 ab 51:10 52:12 55:10,15 ab5075 244:6 abdomen 35:14 36:13 abdominal 40:13 146:12 abilities 306:14 ability 19:22 77:15 164:17 187:11 232:9 233:8 356:7 357:4 able 54:3 57:2 70:3 71:5,14 78:7 81:2 82:17 85:9		

73:13,21 74:4 75:13 76:4 125:20 133:12 134:17 135:9 151:3,4,6 151:14,18 152:13 152:14,16 153:4 153:10,18 154:16 155:6,12,13,16 157:4,8,12 158:9 158:13 159:4,8,10 159:14,16 161:3 162:11 163:18 164:1,14 165:17 165:22 166:16,19 167:14,21 168:9 169:3,13 172:19 173:5 176:11 177:1,22 179:22 180:21 181:21 183:2 188:7 189:21 190:2 191:10 192:2 194:16 195:2 200:16 202:21 203:20 204:22 209:14 214:1 234:9 235:6,12 236:7,16 237:5,7 240:7 241:6,11 242:8 243:16,17 246:8,11 249:15 250:7,17 254:5,10 254:13,18 255:18 256:7 257:15 260:8 261:21 262:4 263:1,7 301:11 309:7 312:10 342:6 343:10,13,15,19 347:1,17 348:4 acknowledge 110:16 185:6,12 264:3	acquire 155:10 171:4,14 acquired 18:8 23:9 73:16,22 74:1 142:9 146:21 154:4,5 218:8 219:11,11,13 221:1 acquisition 161:13 310:18 act 17:15 24:11,12 45:4 147:22 201:13,14,15 303:6 actelion 296:1 acting 27:9 59:3 action 57:15,15 59:10,11 61:12 267:11 270:22 339:12 356:9,13 357:7,9 activate 164:18 activation 119:13 active 31:22 60:6 60:11 61:3 64:6 64:22 104:18 241:5 297:16 actively 197:4 activities 44:14,15 activity 50:16 51:7 69:14,15,15 70:13 121:18 319:7 320:14 338:10 341:19 342:2 343:16 actors 235:3 actual 32:5 53:4 82:9 83:17 105:3 152:18 203:3 246:10 249:12 261:1,8 308:9 317:18 318:4,5 acute 16:5 115:22 118:9 119:14	146:21 147:13 148:16 149:20 150:6 207:16 267:5,6,18 268:12 270:12 271:1 272:9 275:9 277:3 278:16,19 279:3 288:22 315:1 316:5 318:12 323:17 acutely 317:21 adams 151:13 167:17 adapt 149:1 186:21 187:1 199:15 340:15 adaptable 337:18 adapted 264:15 271:21 343:10 352:4 adapting 172:5 187:14 adapts 150:9 add 54:5 70:16 132:20 201:16 211:1 253:20 255:19 257:11 318:10 320:22 321:5 325:20 335:1 348:6 added 102:16 106:18 107:18 108:12,19 315:20 adding 235:4 257:10 addition 22:19 34:5 41:13 86:6 99:22 105:20 143:19 144:11 145:6 154:2 229:4 304:3 309:12 additional 16:6 20:9 22:5 40:21 57:22 82:15,17	83:5 105:12 138:16 179:4,7,8 209:19 211:1 215:17 305:10 additionally 19:4 additive 106:13 address 39:7 40:18 66:7 185:16 206:2 210:22 211:1 353:15 addressed 79:13 83:8 326:12 337:2 340:20 344:10 addressing 340:11 adds 132:14 332:17 adequate 23:11 41:3 331:5,20 adequately 81:16 adhere 187:15 adherence 158:10 162:17 adhesions 147:22 adjourned 355:22 adjudication 295:22 adjunct 233:4,10 234:6 adjust 60:15 administer 107:14 207:22 315:6 administered 106:2 107:20 208:10 271:4 administering 208:16 administration 208:4 232:15 335:5,16 admission 36:10 admissions 32:12 36:9 admit 102:22
---	--	---	--

admitted 282:4	267:22 268:21	164:22 192:14	222:18 225:22
adrenal 246:16	281:3,22 283:11	agree 183:4	227:15 233:10
advance 30:21	285:6 287:9 288:6	190:16 197:14	245:3 247:18
168:17 309:22	288:16 289:3,8,9	198:4,8 320:10	255:22 259:1
310:3	290:6,9 291:9	321:22,22 348:14	260:15 261:13
advanced 3:6	292:11 293:5	348:14 354:15	298:10
273:21 296:11	309:8 314:3 315:9	agreed 348:11	alluded 103:7,8
303:20	316:2 327:3	agreeing 42:17	176:1
advantage 75:10	335:13 341:21	201:19	alluding 64:4
76:14 247:13,15	affairs 2:20	agreements	alpha 266:5 331:9
247:20 248:6	affect 62:17	304:12 306:9	alt 323:22
324:6 326:19	affiliations 43:21	308:3	alteration 161:14
advantageous	african 23:5 81:8	ahead 40:19	alternatives
203:6	82:12 84:20 90:13	204:17 292:15	135:14 194:18
advantages 23:20	124:2	294:1,15 304:17	alveolar 270:8
44:5 177:13 180:1	afternoon 79:14	304:20,21,21	amazing 250:20
202:20 265:7	204:19 205:3	305:5 325:19	251:16 258:20
289:9 290:21	234:11,13	336:7	264:4
293:14 330:18	afternoon's	aids 80:9 302:15	ambrose 217:10
adverse 58:18	197:18	air 225:16 270:10	ambrose's 51:14
advice 305:14	agar 153:21 177:3	akineto 152:17	65:6
308:2	179:11	al 73:19	ameliorates 98:1
advisory 83:14	age 114:3,4	alanine 278:21	ameliorating 21:3
105:10,21 129:18	284:21	albeit 102:6	amenable 127:17
130:3 131:5 305:3	agencies 63:5	alcohol 154:7	238:22
advocacy 185:9	110:17 294:2	alginate 148:12	amendable 232:13
aerobic 246:8	296:15 332:20	149:6	america 237:10,10
aerosol 119:22	335:4,10 349:12	align 265:17	amerithrax 96:16
120:3 232:22	agency 64:2 95:22	aligned 302:19	amikacin 64:13
aerosolized	309:12 332:10	alive 243:22 286:4	amini 2:5 13:19
113:14	335:5 336:1	313:15 314:18	308:17,20
aeruginosa 1:5	agenda 25:2	allergy 4:10,15	aminoglycoside
15:8,22 20:3	agent 44:10 61:3	334:20	163:9
25:11 53:17 58:14	120:22 176:9	allocated 184:17	aminoglycosides
125:20 133:13	182:21 334:5	allow 195:17	34:6 36:17,18,20
134:17 135:9	agents 28:17 34:3	229:1 325:22	aminotransferase
139:4,9 141:3,14	39:13 41:20 69:6	allowed 116:7	278:22
142:12,15,18	69:8 80:6 142:7	allowing 64:12	amount 75:2 79:3
143:7 145:11	183:10	72:15 95:3 196:2	120:5 142:16
146:1,5,20 147:12	aggressive 192:17	248:12	143:11 144:1
148:5,22 150:4,9	262:16	allows 22:3 37:20	145:8 174:21
151:6 194:16	agms 23:11	59:10 120:19	196:7 209:21
218:16 222:5	ago 32:10 42:3	183:9 196:6	210:3 213:4
264:17 266:17	46:7 77:21 155:19	206:18 207:14	215:18 216:9

218:10 219:3	22:6,15,18 23:2,3	199:20 202:9	86:3,11,15,20
236:11 251:10	23:20 24:1 25:9	203:3 204:14,21	87:1,3,6,19 88:15
289:17 290:10	25:14 39:9,9,10	205:12 213:20	88:16 89:8 90:22
333:4 353:17	39:20 40:1,2,8	217:12 221:22	91:3 98:8 100:5
amr 48:20	41:12,13,16,17,17	222:17,18 225:17	103:11 105:15,17
amylase 279:1,1	46:15 47:8,9,16	226:6 236:5	108:9 113:2,4,16
anacor 341:8	77:12,14 79:16,20	238:10 239:12	113:20 114:12,19
anaerobe 142:2	80:7,11,15,18	246:20 247:10	114:21 115:2,2
anaerobically	81:3,6,14,20	250:21 252:1,10	116:1,7,17 117:1
142:3	82:10 84:2,6,17	257:1,2,4 258:21	117:13 119:1,16
analgesia 291:16	85:1,12 86:12	259:17 267:1	122:8,8 123:20
analyses 209:4	87:12,17 89:12	269:6,15 272:14	124:3,10,11,13
analysis 76:8	90:17 91:4,13,20	277:18,19 278:4,7	126:12 132:15
144:7,9 182:9	92:4,7,12,19	278:8,19,20 279:1	133:9 136:4
206:4 207:9,18	95:20 96:4 97:20	279:4,5,8,18	143:10 145:21
209:18 220:18	98:3 99:1,10	280:13 281:2,7,10	178:2,7,12,14,19
241:8 272:15	100:17 101:20	281:21 282:8,17	183:6,8,12 195:19
325:12	104:8 109:22	282:17,22 283:5,8	203:6,13 207:2,2
analyzed 76:5	111:1,6,10 112:5	287:4,9,22 289:19	207:4,13 219:21
anatomical 295:3	112:10 113:3	291:8 292:2	221:9 225:10,11
317:2,8	115:6,11,12,16,18	294:13,16,17	225:22 226:21
anatomy 35:15	115:20 118:5,8	297:22 298:3,4	227:6 228:4,12,13
283:20 289:12	121:5 122:4,10,13	299:4,11,22 300:3	228:19 229:19,22
316:22 331:19	125:6 126:5,7,9	301:1,2 302:8	230:16,20,22
andes 2:10 12:12	126:11,13,14	304:10 306:5	231:10,12,22
26:15,15 205:4,14	127:11,11,17,21	309:3,6,9 310:4,6	232:7,10,21 238:3
221:18 329:10	128:18,19 129:11	312:20,21 313:10	239:5 245:9
andrea 199:17	129:15,20 131:10	314:17 317:4,13	247:12 248:10,13
andreas 7:8 9:16	131:21 132:1,2,3	319:6,9 320:11,14	250:11,15 251:3
27:9 43:1 45:3	132:4,22 133:2,8	320:22 321:3,7,8	251:11 256:5
327:21 331:2	133:15,20 134:12	322:6,10 324:1,3	257:5 259:1
anecdotal 62:2	134:15,20 135:1	324:15 325:8	260:14 264:6
anesthesia 120:8	136:2 137:16	328:7,20,21	269:7,10,11,14,17
273:3	138:1,1,12,15,21	329:11 339:20	269:20,20 270:4
anesthesiology	139:3 140:10	343:20 345:14	270:11,14,15,18
280:9	144:17 145:4,20	346:8,13,19,20	271:5,6,7,14
anesthetized 87:3	150:4,22 155:8	348:10 349:5	274:12,16,16,20
225:11	169:2 170:2,6,7	350:6,14,16 351:6	274:22 275:1,3,11
anesthetizes 251:2	170:10 180:6,8,13	351:13 352:9	275:16,17,21
animal 1:3 9:19	186:5,14 188:9,18	353:17	276:9,12,16
10:6,13 12:5,10	189:3,4,6,22	animal's 321:8	277:13,17,18
15:6 18:2 20:11	192:9,15 193:16	animals 22:2,14	279:9,9,12 282:6
20:12,15,20 21:1	194:5 195:5	81:12 85:3,6,8,16	282:7,9 283:12
21:13,16,18,19,20	197:15,16 199:1,3	85:16,18,21 86:2	284:11 285:15

286:4,7,14,21 288:2,17 290:3,5 293:1 312:14 313:12,15,16,19 314:12 317:19 318:17 320:20 321:1,17 324:7,21 327:8 328:19 329:14 330:5,12 341:5,10 342:21 349:7 350:17 354:6,20 anitratum 152:6 annotation 144:6 announce 184:13 announcement 168:18 309:13,17 annually 265:4 266:15 anorexia 114:22 answer 164:20 205:20 211:10 217:11,12 258:9 276:7 314:7 327:20 346:9 answers 206:3 216:18 antagonism 108:22 anthraxis 95:17 96:14 97:14 98:15 anthrax 10:6 22:19 80:12 82:2 95:17 96:14 97:18 98:11 103:9,18 104:3 112:11 124:2,2 126:14 127:6,10 128:1 145:13 186:6,10 297:13 351:16 anti 6:19 15:10 25:5 28:16 46:11 61:2 67:2 105:10 181:12 214:17	antibacterial 16:20,22 24:6,13 27:8 126:20 127:2 127:5 129:8 176:20 209:5 252:21 302:18 303:2 306:16 309:20,22 310:5 350:5 antibacterials 199:21 263:16 297:18 303:8 antibiotic 29:16 58:14 60:13 66:8 106:20,22 107:4 107:10,10 108:10 108:17 109:4,6 117:9 123:10 142:5 143:15 156:2,16 160:18 163:6 164:4 188:21 203:19,22 207:22 208:7 214:22 215:2 217:16 227:20 230:18 240:18 252:6,17 316:21 320:8 334:22 antibiotics 31:8,21 34:1 35:10 36:14 36:19 48:13 59:8 61:11 82:4 106:3 106:13,14 107:14 107:20 108:3,6 142:14 159:13 178:16 210:10 217:13 219:14 220:14 230:2,3 233:8,15 239:19 247:19 248:4 252:12 306:22 314:19 333:15,16 337:7 339:21 341:16	antibodies 22:20 96:20 97:17 99:5 236:2 264:16 314:19 antibody 54:13 96:19 97:16 105:1 105:7 106:1,12 255:18,19 256:9 256:13 267:17,21 268:1,2,17,18,19 269:11 271:15,17 272:3 274:5 275:12,21 276:4 276:12 277:14 antifungal 24:6,13 antimicrobial 2:7 3:15 4:5 27:3,5 30:15 43:7 73:4 106:18 109:12 124:21 142:6 200:14 205:8,11 206:11 302:20 306:19 308:19 309:18 311:9 319:7 antimicrobials 96:19 207:6 281:19 antisense 167:4 antitoxin 98:14 103:18,20 106:17 352:21 antitoxins 107:19 126:20 anton 243:12 anybody 195:13 300:10 anytime 51:21 aortic 267:12 337:8,13 338:1,12 apparently 34:20 304:7 appeal 330:16	appear 179:2 244:8 312:15 applause 355:20 applicants 310:12 application 194:10 247:15 293:22 302:8 applied 128:18 193:14 applies 21:1 apply 62:10 appreciate 201:3 approach 20:16 77:20 79:4 113:11 134:21 138:19 164:22 165:10 166:20 167:22 179:21 198:10 211:12 314:21 320:21 321:13 approached 117:3 approaches 10:12 12:5 23:21 25:14 38:20 111:5 166:21 204:14 252:21 appropriate 100:21 137:22 197:17 294:22 appropriated 184:16 appropriately 31:1 approval 20:11 21:1 67:2 83:22 84:3 127:14 186:5 194:10 203:4 219:15,16,22 220:16 259:6,8 295:1 332:8 333:22 335:5,10 335:17 approvals 22:16 220:4
--	---	--	--

approve 197:22 333:20 334:10 approved 22:6,13 22:18,20 23:6 24:17,21 31:21 82:4 83:15,16 84:9 127:6,7 129:2 194:7 220:1 220:6 239:19 259:5 297:14 329:14 332:6,19 333:22 334:3,16 334:21 350:6 approximate 214:21 approximately 67:21,22 68:8,10 68:11 69:1 71:7 72:19 75:22 77:7 78:1 111:12 114:3 184:16 290:12 310:7 approximates 213:18 ar 182:1 arabidopsis 144:19 aranz 251:4 arbogast 357:2,13 ards 324:20 325:1 325:3,4,5 area 45:16 52:6 97:11 129:6,7 184:14 253:11 261:3,5,14 296:17 296:18 297:9,17 297:22 298:19 309:19,19 areas 23:22 38:1,3 45:17 154:10 169:8 181:7,13 200:5 244:21 275:7 328:8	arena 22:16 arginine 142:3 argue 209:5 argument 331:14 332:2 arm 23:14,16 49:22 50:3 51:6 52:7,22 64:5 75:22 76:22 77:1 77:8,10 113:15 262:21 arms 55:9 64:13 104:18 army 7:15 12:20 155:21 195:1 200:19 234:4,5,22 238:14 arnold 218:14 arrow 246:1 art 144:21 arterial 273:12,15 277:21 315:13 artery 273:13,18 337:21 article 123:9 177:8 articles 181:6 articulating 99:11 ascending 174:10 ascends 174:15 asia 73:20 113:3 237:11 asked 29:7 48:7 99:8 106:22 205:19 330:7 asks 164:16 300:10 asm 51:18 aspect 326:6 330:14 339:16 aspects 63:6 175:2 260:21 306:19 aspirate 289:14	aspirates 174:7 327:16 aspiring 292:4 292:13 293:1 aspiration 291:12 assay 104:6 166:6 assays 92:10 158:10 assembly 250:22 assess 19:7,9 109:17 assessed 60:5 101:16 207:18 assessing 94:21 108:22 160:17,17 assessment 128:10 134:15 assist 34:19 35:1 36:21 73:8 associate 2:6 3:11 3:19 5:17 264:12 308:18 associated 18:9 51:17 68:6 119:2 134:3 143:12 147:1,13 154:4 156:6,10,14 157:16 218:7 254:20 260:12 267:14,19 271:20 273:20 277:2 284:13 288:21 289:4 293:10 317:18,20 318:2 323:14 352:12 associations 166:22 assume 76:11 assuming 77:22 assumptions 75:18 assured 91:5 ast 323:22	astounded 90:9 atcc 170:18 216:1 216:5,8 238:2 240:2 attach 196:4 attack 97:8 196:3 attacks 96:16 attainment 77:19 219:21 220:4,6,11 220:12 attempt 328:11 attempted 34:10 attempting 235:20 attend 136:12 attending 280:13 attention 39:19 42:15 66:10 82:1 92:3 94:11 140:13 168:16 282:16 294:4 295:10 attorney 356:11 attributable 154:3 attributed 114:21 attrition 296:20 auc 208:22 209:9 213:3,12,13 214:7 215:2 217:18 aucs 217:19 audience 11:19 14:6 25:17 69:11 185:22 311:13 350:3 355:11 audio 357:3 aureus 28:15,16 36:4 38:5 175:19 264:14 266:15 271:21 274:3 313:19 314:5 315:11,19 337:6 352:10 353:5 australia 143:4 australian 184:10 184:14
---	--	---	--

authority 3:7 296:11 autologous 265:18 autopsy 292:15,16 availability 18:17 62:14 289:19 351:19 available 19:9,12 19:20,22 23:21 48:22 49:10,11 52:11 69:19 78:9 96:5,13 106:10 112:8,21 142:17 143:18 144:2,3,12 145:2,6,8 168:15 178:16 183:15 194:19 201:22 204:2 300:7 303:15 307:1 333:21 334:5,22 339:10 342:4 avenue 64:3 average 72:19 117:13,15 226:16 avibactam 34:4 avoid 152:7 avoidance 163:14 avoids 164:9 awake 234:12 award 311:2 aware 24:10 44:11 46:5 48:5 96:10 131:18 167:10 204:4 209:7 223:7 304:8 awareness 180:3 axis 102:17 208:9 226:13	baa 309:19 310:12 311:3 baboons 286:7 bacillus 95:16 96:13 97:14 98:15 back 29:13 32:13 33:2,7,13,16,22 35:2,7,17 36:2,15 40:14 42:9 52:22 83:5 84:18 112:19 116:11 124:12 140:14 166:8 170:14 185:20 195:15,16 197:21 202:7 204:16 205:17 219:18 232:20 249:7 253:4,6 260:14 261:4,8 280:4 295:16 298:13 300:21 354:20 background 16:12 16:15 20:20 78:22 123:18,20 141:8 bacon 258:18 bacteremia 85:10 85:14 88:11,12 93:8 102:16,21 169:9 170:15 275:13,15,17,18 276:6,17 279:15 337:4,9 338:17 339:13 bacteremias 190:1 bacteremic 85:8 85:17,19 87:20 88:15,16 167:14 174:3 330:9,10,15 330:19 bacteria 9:14 15:14 42:22 43:14 44:21 50:22 87:22 89:9 99:13 145:3 145:4,14 149:8,10	156:22 164:9,10 164:17,19 175:14 193:7,8,9,9,10 201:20 206:21 224:13,21 225:14 225:18 226:18 227:16,19,21 229:17 230:17 232:10 233:19 246:6 247:18,19 252:20,20 258:5 262:3 272:8 284:1 285:10 287:20 317:10 320:3 330:11 338:3,4 340:7 345:1 346:1 352:2 bacterial 7:14 10:13 15:13 16:5 18:9,9 94:16 111:6 119:1 143:13 146:6 159:19 172:9,10 176:18 177:2 178:4,9 182:16,18 184:19 207:17 209:19 218:8 221:21 222:1 229:13 231:6,13 231:15 245:13 267:6 287:14,15 289:13 291:3,5 302:20 313:12 318:13 319:1 327:7,15 351:4 bacteriophages 303:7 bacterium 141:20 152:5 246:3 bad 156:7 158:17 203:16 235:3 balance 336:9 balb 227:10	ball 156:18 ballroom 1:13 bandage 261:16 bank 182:1 203:19 banks 92:22 300:18 banter 339:19 bar 81:13 88:13 89:2 149:7 244:3 300:2 354:12 barcelona 6:7 13:12 280:15 barda 3:7 7:20 13:17 125:10,13 295:21 296:10 301:16 304:2 305:17 307:11 345:20 346:3 barda's 26:9 barely 55:18 barrier 188:3,12 196:4,5 270:8 347:10,12 bars 89:1 178:1,6 214:6 basal 254:18 base 55:4 272:17 278:9 based 17:19 19:6 22:13 23:7 39:8 49:2,11,19 54:12 55:13 68:1 75:12 76:5 77:13,18 78:8 97:19 101:3 106:21 113:11 120:4 122:4 129:3 144:14,14 164:20 177:17 179:4 224:5 227:22 228:8,17,21 241:7 241:14,21 243:2 260:3 265:14 288:5 331:5 337:12 346:17
b			
b 46:20 47:22 152:14 169:15 230:4 245:22,22 263:1 349:19			

348:11 349:12 351:7 baseline 75:4 86:6 178:2,4 basement 258:21 basic 56:19 198:17 235:18 273:19 274:4 302:12 303:11 basically 32:15 51:20 64:1,4 71:19 90:10 144:8 145:19 151:16 165:6,11 189:20 195:2 238:16 239:2 241:6,10,14 245:5,10,19 246:1 246:20 248:19 249:14 251:13 257:10 260:16 261:12,20 262:6 262:14,20 basis 50:4 68:20 69:1 71:8 73:17 101:11 103:15 172:17,18 199:10 332:7 bassi 6:4 13:11 27:21,22 280:6,7 280:9,19,22 292:1 295:13 313:3,6,10 314:11 315:16,21 318:10 321:5 325:18 326:15 335:1 336:14 339:7 349:10 350:1 bassi's 312:14 333:3 battelle 6:11 10:9 27:14 94:14 95:8 95:22 110:15,16 baumannii 1:4 15:7 16:1 25:11	67:18 69:5,16 71:6 72:3,5,10,14 75:13 125:20 134:17 135:9 139:4 155:6 163:18 166:11 237:6 309:7 337:15 bayesian 331:22 beautifully 43:18 193:4 beauty 260:13 becoming 185:15 335:8 bed 254:6,15 256:12 bedside 72:22 began 82:7 99:6 118:5 230:17 beginning 30:13 86:21 92:15 101:18 119:20 155:12 165:2 197:12 233:17 begins 163:2 behalf 58:12 behave 201:20 263:22 behaves 17:11 132:1 behavior 346:17 behavioral 224:5 belabor 169:5 believe 41:14,21 75:2 78:16 79:3 97:1 153:18 198:10 219:1 287:3 288:15 308:5 344:11 belly 159:18,21 benchmarks 193:1 benefit 21:21 22:8 62:4 106:18	107:18 108:12,20 183:7 194:17 283:10 benefits 226:3 336:10 berserk 192:5 best 19:9 42:1 47:20 48:22 49:10 49:11 96:15 136:1 136:2,2,4,7 171:2 180:15 200:9 215:11 241:16 258:15 298:20 327:22 328:7,18 352:9 353:3 356:6 357:3 beta 68:21 69:11 69:12,13,17,17,19 69:20 70:2,2,8,11 151:17 169:14 212:10 better 23:19 54:6 134:1 160:7 173:1 174:9 179:10 194:6 198:1 203:16 204:17 235:9 248:13 251:6 286:8 beyond 77:4 bfdmi 53:12 bid 298:10 big 169:12 235:5,7 252:16 253:11 256:21 258:18 272:14 333:2 341:15 bigger 30:15 40:8 169:22 270:18 275:2 320:18 321:1 324:6 bind 338:3 binding 161:14 212:22 213:7,15 213:17 215:5	216:16 221:14 binh 3:18 13:6 26:11 264:11 bio 223:21 biochemistry 151:17 162:1 323:16 324:1 325:13 biodefense 4:19 26:5 80:2 94:22 297:11 306:2 biofilm 148:14 158:11 161:12 162:17 175:6 242:15 246:3 255:9 256:21 285:12 337:12,16 339:16 340:4,6,17 341:13 344:9,12 344:13,15 biofilms 242:16,17 255:6,7 338:12 340:19 bioinformatic 144:3 biologic 21:6 349:3 biological 297:5,6 349:4 biologically 345:16,17 biologicals 233:15 297:7 biologics 20:22 168:1 biology 2:17 166:21 bioluminescent 243:15,16 biomarkers 198:5 322:5,12,18 348:12 biomedical 3:6 6:11 10:10 27:15
---	--	---	--

94:14 296:10	244:1	blunt 225:12	boucher's 28:13
biometric 223:21	blacked 263:18	board 203:15	boundaries
228:3	bladder 175:5	213:11 253:7	331:11
biopharmaceuti...	blaoxa 156:21	280:9 305:3	bounds 56:4
305:13	blast 249:12	body 15:15 18:6	box 47:7 228:14
biopsied 292:19	blasts 234:22	19:17 29:2 37:16	245:16
biopsies 251:21	blinded 87:8 92:9	39:16 40:11 41:10	boxes 82:5,9
255:3	block 164:17	51:11 55:1 86:2	brad 151:13
biopsy 260:17	blocks 46:8	101:10 102:3,17	158:15
261:11	blood 32:19 33:1	102:19 113:18	brazil 237:2,9
bioremediation	85:15 90:17 100:4	116:17,21 117:2	breach 145:18
141:18	100:6,10 101:13	117:20 118:4	break 10:19 13:14
biorepositories	102:5 103:2 104:7	119:11 121:15	46:8 140:17,19
200:13	113:21 118:10,17	122:4 127:9	204:11 218:6
biotech 58:13 67:7	119:13 121:17	246:15 269:22	295:16,18
200:4	122:2,4,7,13	270:3,4,12,20	breakfast 287:4
biotechs 184:5	176:8 195:14	271:9 274:15	breaking 347:11
bioterrorism	214:13 225:6	328:18 344:7,8	breakpoint 70:17
95:18 128:2	242:2 249:4,10,19	bone 119:10 242:1	breakthrough
biotherapeutics	249:21,22 252:1	254:8,20	308:22
297:8	255:12 270:9	bonomo 2:16 11:7	breath 121:6
bioweapons	272:13,15,17	11:13 26:19,19	225:17
112:14	273:12,14,15	151:2,5 152:9	breathes 269:6
bit 20:19 35:21	275:10,11,14	162:7 165:6	breathing 32:11
46:5 52:3 55:2	276:8,10,11,13,22	185:20 200:12,18	32:14 33:2 120:6
56:15 100:10	277:5,16,21	201:10 235:10	273:3
125:3,22 129:5	279:13 286:18	242:18 257:19	bret 280:1
135:15 137:14	315:13 323:13,15	262:16	bridge 92:2 98:8
159:11 160:7,12	324:3,4 325:7,11	book 36:5	bridging 83:8
173:6 176:4	325:12,16 327:1	boring 80:21	90:22
178:22 179:5	bloodstream	bottom 68:19 81:1	brief 176:21 296:7
189:21 204:10	40:12 68:3 71:17	82:9 101:16,19	briefly 51:14
207:8 213:6,8	75:15 76:20	106:6 117:19,21	140:2 293:22
214:9 218:6	146:14 154:9	177:22 223:8	350:7
223:10,17 232:13	167:15 169:19	230:7 254:18	brigham 8:4
235:17 236:11	171:2 196:20	261:16 263:20	189:19 191:5
253:6 276:15	197:10 200:22	botulism 297:13	brilliant 286:11
295:15 299:10	229:17 320:4	boucher 3:4,9	286:12 287:2
304:6 322:17	323:9 330:11	9:10 13:17 26:8,8	bring 42:9 51:3
332:11 343:1,1	343:20	28:2,4,5,7,10,18	56:1 189:15 236:6
354:8	blue 82:5 86:4	28:21 42:16 62:9	236:14 296:17
bits 55:19	88:13 153:17	67:17 76:17	341:13 342:20
black 102:17	275:1 277:18	295:21 296:3,4	bringing 203:9
104:18 243:21	278:9 279:5	301:18 334:18	299:9

brings 32:2 broad 46:10 68:20 69:6,9,19,21 71:12 123:11 226:4 293:4 309:12 321:16 broader 73:17 168:9 bronchial 174:8 bronchiectasis 50:20 bronchoalveolar 326:20 327:1,4,16 bronchopneumo... 114:18 115:22 bronchoscope 290:7 brought 125:11 155:4 248:22 337:4 brute 53:12 bsl 96:1 bubble 157:11,11 157:12 bubbles 157:15 bubonic 90:5 128:8 budget 200:8 buffalo 240:21 342:14 bug 35:5 175:22 196:2 197:12 235:8 236:19 257:4 bugs 44:7 186:10 193:16 237:3 239:21 249:17,18 262:2 337:18 344:6,13,16 345:8 351:18 354:19 build 37:18 195:18 196:9 building 96:9 199:18	built 77:7 bun 323:19 bunch 44:21 131:3 192:10 bunnies 264:10 280:4 buprenorphine 251:11 burden 50:21 178:4 206:21 207:17 209:22 210:3 230:15 245:16 287:14,22 289:13 327:7 burkholderia 301:14 burn 144:16 154:11 160:11 burns 146:19 business 58:1 336:3 busy 25:2 42:18 buy 244:10 c c 2:1 3:1 4:1 5:1 6:1 7:1 8:1 9:1 10:1 11:1 12:1 13:1 14:1 15:1 38:6 47:1,6,8 48:1 69:21 70:4,9 118:9 142:22 152:14 158:20 160:19 169:15 194:2 227:10 297:22 300:14 301:13 c3h 190:15 c57s 190:14 c5a 352:15,17 cafeteria 287:5 cage 101:17 261:19 cages 121:22	calculate 209:21 232:4 calculated 114:7 120:4 122:3 california 3:22 13:6 26:12 264:12 call 33:18 65:14 99:7 195:19 225:9 252:17 344:13 called 39:21 125:15 157:15 208:4 217:16 227:8 263:1 296:18 352:12 calling 16:13 campbell 7:19 202:8,11 campus 29:3 campylobacter 31:17 canal 146:10 cancer 32:8,10 34:12 cancerous 280:12 candidate 36:20 36:22 37:1,2 94:21 181:14 267:2 candidates 38:11 44:11 299:7 303:19,19 304:18 candlesticks 193:2 333:10 cannulated 273:13,17 337:21 capabilities 298:8 298:18 capability 233:3 capacity 155:10 184:9 251:17 298:8 305:20 capital 1:20 capsule 163:18,19	carb 7:6 9:15 27:7 30:18 43:1 297:19 carbapenem 49:8 51:7,21 142:11 156:10 182:11 carbapenemase 32:21 33:14 156:14,21 carbapenems 211:21 carbon 186:19 273:11 277:16,20 cardiac 273:22 315:8,9,10,12 cardiogenic 34:17 care 6:6 34:11 35:9 48:22 49:10 49:11,22,22 50:5 54:6,7,7 71:11,20 73:14 75:16 78:4 96:15 98:22 135:3 139:20,21 154:4 182:21 234:21 263:17 280:10,14 282:2 284:6 286:15,16 294:2,4 316:1 321:13 335:6 336:1,2 cared 243:9 careful 283:19 334:2,9,13 349:22 carefully 287:12 carl 7:21 350:4 carotid 273:13 337:21 carries 239:9 253:13 cartoon 141:14 147:18 149:2 cascade 164:18 165:8 case 2:21 11:13 17:21 26:19 32:7 33:6 34:14 50:15
---	---	---	--

51:2 55:4 56:1 61:19 72:4,9 84:12 88:14 91:16 92:9 93:3 98:19 121:20 123:13 124:3 151:2 169:13,17 171:2 173:2 175:5 178:2 178:8 199:9 201:7 206:11 209:2,19 210:13 211:2,5 212:1,17,21 213:5 213:9,12 217:9 218:2,18 219:1,6 220:7,12 226:9 231:12 236:19 247:20 273:18 277:1 278:4 284:12 287:20 323:15 cases 32:5 37:6 40:13 52:9,22 61:21,22 68:16,16 68:17 70:10 89:15 90:5,14,15,19 99:15 100:19 127:16 128:8 141:17 146:8 172:8 299:18 350:21 351:17 cat 36:12 catalog 54:13 categories 46:11 188:12 categorized 266:19 category 230:12 230:13 231:8 catheter 81:15 124:1,6 146:14 188:8 225:11,13 315:11 337:22,22 causality 45:18	cause 32:18 58:15 130:16 141:17,20 145:14 146:5,6,9 146:12,16 147:3,6 150:7 152:11 154:8,11 159:16 169:19 172:1 174:3,15 186:12 187:11 236:11 239:4 266:12 279:7 338:1,4 caused 1:4 15:7 20:18 21:4 111:19 150:12 193:9 289:7 309:10 causes 146:20 154:2,5 186:22 276:3 causing 187:10 225:17 347:3 caution 197:10 cautious 47:21,22 caveat 64:13 95:16 97:15 101:1 158:9 cavity 119:2 159:14 cbc 103:6 cbcs 101:12 cbrn 3:5 26:9 297:4 cdc 30:22 101:21 182:1,2 203:19 204:2 236:14 296:16 297:2 cder 2:8 3:16 4:6 27:3,5 124:21 cefazolin 36:7 ceftazidime 34:4 ceftobiprole 215:12 ceftolozane 34:4 cell 101:13 102:5 113:9 119:13	148:4 158:10 164:21 195:14 196:4,4 202:22 203:12,12 249:1 276:11,13 300:18 cells 118:10 145:3 158:10 163:20 249:20 255:13 center 2:20 5:17 6:11 8:9 9:10 10:10 15:10 26:20 27:15 28:5,11 65:15 94:14 155:21 157:20 168:20 200:20 205:8 222:16 226:5 centers 63:2 65:15 centimeters 273:8 central 162:13 237:10 centric 297:8 cents 169:1 century 24:10 cephalexin 36:7 cephalosporin 208:7 209:3 210:12 cephalosporins 188:22 211:20 212:13 certain 21:2 75:20 148:6,7 154:16 156:13 162:10 224:15 333:1 341:2 346:17 354:4 certainly 18:5,18 20:16 25:19 29:4 30:16 32:1 37:10 37:15 38:9 39:7 197:3 204:5 211:11 235:6 238:13 252:3	255:6 257:7 323:3 323:7 329:22 343:6 certara 184:4 certificate 356:1 357:1 certified 181:9 280:9 certify 356:3 357:2 cessation 108:8 cf 20:8,8 50:19 147:5,8 148:21 150:10,15 cftr 150:14 cfu 176:8 178:1,6 226:12 245:8,9,16 248:8,9 250:5 255:2,4 256:14,15 256:21 262:13 268:21 271:10,12 272:7 275:14,20 275:22 cfus 114:5,15,20 116:3,4,14 252:3 260:12 271:13 chagas 124:11,14 chain 29:20 chained 162:3 chains 162:7 chairs 11:6 12:7 challenge 39:7 63:4 85:2,6,18 86:5,7,9 87:7 88:7 88:9,14,17,19 93:22 114:7,12 116:3,14 117:21 118:1,16 120:3,19 272:2 283:17 284:2 289:17 291:3,6 299:14 313:13,13,14 318:13 319:1 348:19
---	--	---	--

challenged 114:14 268:20 272:6 290:6 292:8,9 challenges 9:4,12 15:2,19 16:6 17:5 17:20 25:4 39:4 42:20 43:13 62:6 66:4 71:4,4 119:18 130:6 132:14,20 140:3 154:15 282:5,7 challenging 38:1 63:3 64:17,19 78:11 129:14 130:1 133:11 154:18 158:22 199:13 change 18:19 149:15,18 153:19 153:21 157:21 177:16 186:22 189:2 193:14 197:3 231:19 266:3,9 286:5,6 287:21 340:5,6 341:16 349:18 changed 349:2 changes 102:2 103:5,6,6 118:8 149:2 153:14 156:16 240:6,8 242:11 266:4 changing 78:21,22 187:13 197:4 characteristic 187:5 349:5 characteristics 113:7 133:15 143:14 224:5 242:14 265:14 317:8 characterization 300:19	characterize 92:21 198:2 241:17 281:16 characterized 21:19 119:21 147:15 153:5 154:9 193:12 197:19 296:19 333:7 348:9 cheap 244:10 cheaper 193:17 339:14 check 200:20 224:2 checklist 228:7 229:2 checkpoint 228:20 checkpoints 198:6 348:13 chemical 21:6 162:9 chemistry 103:6 113:21 253:6 297:5 305:10 chemotherapy 32:9 145:18 188:1 cherry 219:9 chest 87:5,17 100:3 chew 242:21 chief 2:19 4:19 5:9 7:5,6 27:6,7,12 80:1 chimpanzee 266:7 chimpanzees 265:22 china 89:19 chip 121:13 202:17 chips 121:2,11,16 202:11,12 chloramphenicol 143:2	choice 191:8 choices 139:22 choose 132:6,7 177:16 291:11 320:15 chose 116:10 230:4 241:20,21 chosen 132:11 christian 164:21 christmas 49:6 chromosome 142:20 chronic 32:11 115:16 122:9 147:3,7 148:17,22 149:14,22 150:9 chronicity 115:5 chronology 274:10 324:9 chung 73:19 cipro 83:16 ciprofloxacin 22:17 36:16,17 82:14 83:12 circles 162:3,8 circuit 273:3 circular 142:20 circulating 101:22 102:8 104:6 167:15 circulation 105:4 circumstance 130:8 131:14 134:13 135:10 circumstances 129:14 140:8 clade 241:7,7 262:17 263:1,1 clades 241:11,12 242:11 clarifying 79:9 clarity 50:1 191:11 192:1,6	class 58:14 59:8 69:20,21 70:3,4,7 70:8,9,11 169:14 169:15 188:3 212:4 classes 187:19 211:22 215:21 classic 195:20 classical 183:16 188:21 195:18 198:22 classification 153:13 classifications 187:20 classified 325:1,2 classify 187:21 classifying 242:8 clean 50:17,18 cleaner 48:10,11 cleaning 121:22 clear 17:4,10 52:1 54:17 57:12 63:9 97:5 132:15 164:9 197:17 209:11 221:15 259:16 286:13 326:2 341:21 clearance 120:16 178:9 247:12 248:14 cleared 32:22 60:14 305:1 clearing 249:16 clearly 21:20 31:11 32:1 47:5 53:3 72:2 77:11 78:7 84:1 94:4 97:22 99:11 100:13 184:19 190:13 236:11 243:7 281:10,14 294:16 323:8 331:13
---	---	--	--

clears 249:18 255:10	159:5,6,7 169:7 170:11,17,20	252:9,14 253:2,3 254:21 256:20	collaborative 110:12
cleveland 2:19 26:20 167:12	174:8 175:7 178:21 187:8,9,17	289:13 295:3 300:1 321:11	collaborators 239:8
clever 56:13,17	188:17 193:11,17	322:6 348:10	colleague 89:13 90:7 340:14
clients 182:8	193:20 194:3	closed 228:13 261:20 270:15	colleagues 37:7 63:17 66:1 93:20 125:10 304:2
clinic 30:11 31:12 38:4 40:18 151:8 180:16 280:15 323:16,21 324:11 325:7 351:22	199:3 200:6 206:5 215:22 216:4,6 218:1,3,11 227:7 227:9 238:13 240:20 245:7,8 248:6 277:12	closely 104:10 207:1 265:17,19 285:3 295:2 298:22 305:22 306:4	collect 56:2 93:6 122:3 123:5
clinical 9:4,12 15:2,18 16:4 18:4 20:17 23:7 24:9 25:3 28:13 37:22 38:14,17 39:14,17 39:21 40:4,5,7,13 40:15,21 41:2,6,7 41:15,16,18 42:21 43:9,13 45:9,19 46:2,14,16,19 47:9,11,14 48:9 56:21 57:21 58:4 59:3 60:18 61:14 62:11 69:3 71:15 71:21 73:8 74:2 74:17,19 77:20 84:7,9,15,16,17 87:4 89:12,13,22 90:2,7 92:5,9 99:15 100:15,19 101:2,3 102:7 103:6,13,14 105:22 106:1 111:21 113:21 114:10,15,16,19 114:22 122:20 123:15 128:5,5,10 128:17 129:4 134:3,6,9,14,18 136:7,14 137:2,8 137:15,15,19,21 138:6,7 140:6,9 143:14 158:16	281:12 283:16 284:17 296:18 297:18 298:6 299:15,18 303:12 303:19,22 304:5 304:18 306:15,18 310:1 322:2 326:7 326:10 327:10,22 328:10 331:21 334:15 335:22 341:11 345:18 346:17 351:18	closer 91:16 189:5 246:12 closes 252:10 closest 246:7 closing 14:8 355:5 closure 253:17 322:19 clue 156:17,17 clues 155:17 276:8 278:6 cmax 208:22 209:9 cocktail 256:3 code 20:21 coefficient 211:13 cognizant 332:17 colesville 1:14 coli 235:5,6 colistin 19:6 29:18 30:5 33:3 49:10 49:15 50:4 60:12 155:3 163:7 335:14 colistin's 50:2 collaborated 101:19 collaborating 185:14 collaboration 65:6 180:4 222:13,21 280:1 306:1 321:14	collected 61:18 101:8,11 collection 44:18 104:9 122:7 201:2 203:20 collections 113:21 colonel 155:22 262:19 colonization 247:4 292:22 293:4,5,8 colonized 246:19 colonizes 246:18 colony 114:8 115:13,19 146:2 290:7 colored 178:1,6 274:9 colors 228:10 column 85:7 combat 30:15 96:13 205:11 combating 302:19 309:20 combination 33:3 69:12 70:18 106:3 106:12 107:4 109:11 155:5 233:4 248:9,11,12 318:8,9 combinations 30:10 combine 65:9 188:17 237:5

combined 64:5 come 15:13 24:7 31:19 42:12 83:5 84:18 125:8 135:19 166:8 172:6 197:20 205:15 209:6 249:1 295:16 298:13 336:22 352:11 354:20 comer 18:16 comers 76:4 comes 35:2 126:22 152:16,19 157:2 195:15,16 196:16 249:7 339:20 comfortable 195:3 coming 16:9 33:11 198:16 199:19 305:4 355:12 commensal 119:3 comment 30:12 57:15 127:22 189:13 196:11 197:13 202:2 204:8 318:11,16 319:2 320:10 321:6,21 322:11 323:12 330:22 337:5 338:16 339:15 352:7 353:13 355:1 commented 192:14 comments 25:18 62:6 125:1 183:5 186:2 202:15 206:14 253:18 265:3 315:22 316:19 319:3 330:20 342:3 346:12 353:12,15 commercial 95:10 111:16 296:22	commercially 178:16 commit 53:22 committed 180:13 committee 83:14 105:10,21 129:18 130:3 131:5 165:18 168:8 197:16 198:4 295:22 committees 296:1 common 48:21 53:11 72:12 74:11 75:14 112:1 146:6 146:20 147:6 169:6 172:16 173:9 174:4 175:10,18 224:14 commonly 61:10 68:2 213:17 296:17 communicated 83:3 communication 91:14 community 23:8 53:21 59:1 73:2 92:20 96:8 109:14 112:9 139:20,21 144:4 154:5,8 184:7 185:12 186:7 219:11 comorbidities 34:16 companies 73:6 95:13 151:16 184:6 205:22 company 1:20 58:13 59:5 62:7 67:8 184:4 242:22 341:10 comparative 76:22 77:8,10	comparator 19:6 76:12 207:6 comparators 248:6 252:6 compare 65:10 116:8 148:16 190:11 266:6,22 326:22 compared 19:9 23:15 64:6 78:3 81:5 84:17 103:11 105:16 106:7 121:10 186:6 210:17 214:10 263:17 265:6 275:7 330:16 comparison 60:7 75:16 90:12 217:11 223:17 283:21 comparisons 81:4 88:3 competent 183:8 353:19 competitive 298:13 complaining 261:3 complement 163:19 326:7 329:2 complementary 319:17 complemented 137:16 complete 144:10 149:16 276:10 301:5 completed 209:5 287:5 completely 240:4 262:4 287:21 320:20	complex 148:15 151:22 157:20 158:18 161:15 184:8 242:6,9 complexes 242:8 242:10,12 complexities 38:19 153:22 complexity 52:3 94:4 156:15 161:5 161:5 163:2 316:16 compliance 108:4 complicated 51:9 55:10,15 78:15 94:7 148:6 150:11 153:13,14 162:4 186:8 284:20 330:17 338:20 complication 35:18 complications 81:17 224:17 227:22 component 51:22 128:15 341:13,14 344:9 components 134:11 344:12 compound 60:1 66:14 133:4 139:14 173:20 175:3 177:18 203:8 233:20 247:16,17 248:1 252:18 320:15 341:8 344:4 354:18 compounds 43:8 141:19 177:1 179:7,21 200:11 203:5 233:15 comprehensive 63:13 78:9 87:18
---	--	---	---

272:15 compromise 145:16 compromised 71:10 262:18 concentration 182:22 247:11 248:1 292:11 319:1 concentrations 214:13,14 248:18 concept 93:12 247:7 248:16 307:6,19 concepts 305:2 conceptually 65:10 concern 31:4 169:8,12 170:16 285:21 concerned 257:14 299:6 323:6 concerns 20:9 79:12 83:8 171:8 conclude 24:4 25:15 concluded 56:11 64:17 108:20 conclusion 56:19 64:1 65:8 166:18 294:14 conclusions 63:21 conclusiveness 62:18 concomitant 18:22 136:17 137:11,13 277:15 concurrently 273:5 condition 283:15 285:3 conditions 21:4 119:22 120:1 128:14 246:9	319:11 conduct 18:5 62:13 81:19 94:3 128:17 206:6 309:8 conducted 21:8 61:15 82:14,18 91:20 105:5 107:18 134:6 conducting 17:5,8 17:17 20:4 93:21 confident 227:1 confidentiality 304:12 306:9 308:3 confirm 277:4,7 293:12 confirmation 103:19 confirmed 64:8 102:22 conflicts 95:11 111:17 281:4 confound 189:10 confounding 18:21 conjunction 69:20 connected 273:2 cons 312:5 consent 62:16 consequence 164:3 consequences 57:16 235:1 conservative 314:21 315:4 conserved 162:18 323:2 consider 18:21 150:21 151:10 194:18 213:15 216:15 227:10 287:12 339:11	considerable 128:21 134:4 consideration 62:22 205:12 263:3 316:17 considerations 9:19 10:12 12:10 25:9 79:16,20 111:5 131:4 138:7 considered 20:10 23:11 131:21 190:2 312:8 considering 96:14 140:8 322:4 335:6 consistency 153:21 195:6 consistent 47:12 78:2 88:6 99:15 102:6 116:19 117:9,17 123:2 134:4 178:12 189:7 191:1 192:11 244:19,22 271:16 278:3,12 279:6 294:1 336:14 consistently 119:15 121:21 consists 176:19 250:21 consortium 143:8 143:17 constant 91:14 constantly 157:21 301:8 constellation 161:18 constitutional 32:17 constraints 53:11 104:2 106:19 construction 144:22 147:15	constructive 63:17 constructs 145:2 consult 348:21 consulting 59:4 consuming 97:6 293:18 contact 146:8 204:6 308:9 311:7 contamination 124:6 225:6 contemporary 69:22 70:14 contending 29:22 content 142:22 context 20:2 43:10 50:8 103:20 312:21 315:5 335:3 continually 349:1 continuation 17:2 continue 73:7 122:12 180:7 185:3 204:12 291:22 355:16 continued 3:2 4:2 5:2 6:2 7:2 8:2 10:2 11:2 12:2 13:2 14:2 230:19 230:20 continuous 279:22 continuously 144:8 272:12 313:16,17,20 continuum 47:20 contract 95:9 181:2,8 298:21 311:3 contracted 234:3 contractile 253:19 253:21 contracts 298:22 303:17,21 305:17 306:4,5
---	--	---	--

contrast 16:4 151:6 186:4 contributed 318:5 contribution 310:16 control 37:3 50:3 81:11 231:20 245:11 268:17,18 268:19 269:10 271:5,15 272:3 273:1 274:5 275:12,21 276:3 276:12 277:13,19 279:9 299:22 349:7 controlled 23:5 47:16 331:6 controls 39:12 104:19 231:19 330:1 333:12,13 conventional 77:16 225:3 converging 151:10 conversation 46:8 192:7 291:21 336:4 conversations 46:6 convince 80:19 81:4 91:7 207:8 281:2 283:6 convinced 55:7 216:13 345:17 cooked 57:9 cool 254:7 265:9 cooling 118:5 coomassie 226:6 copd 147:5 core 113:18 116:17,21 117:2 117:20 118:4 121:15 222:17	corneal 148:9 corner 59:15 correct 63:19,20 63:20 236:10 313:5 correctly 324:21 correlate 102:20 203:13 324:10 correlated 104:7 116:21 119:12 271:8 correlates 40:10 103:9 133:3,10 207:1 324:15 correlating 85:11 correlation 85:10 91:13,15 158:12 203:14 259:6 correspond 103:3 corresponding 118:8 corroborate 327:17 corynebacterium 35:6 cost 193:17 283:12 289:18 293:17 304:11 306:8 321:7,10 338:21 339:8 costly 97:6 325:11 costs 296:19 cough 32:16 269:7 council 305:1,2 counsel 356:8,11 357:6 count 54:9 102:5 195:15 249:1,4,5 255:3 271:10,12 275:20,22 276:11 276:13 277:10 countermeasure 94:17 100:21 103:16 184:18	countermeasures 3:5 26:10 235:8 297:6,10,14 299:17 counting 76:6 countries 68:13 71:9 73:19,20 237:14 country 29:22 89:21 counts 101:13 119:13 182:16,18 276:10 couple 15:12 16:17 32:5 39:19 42:2 175:11 223:3 223:7 230:1,2 301:15 304:15 316:19 322:7 331:14 course 29:6 33:11 35:22 59:21 62:3 62:14 65:3 85:19 89:12 90:13 91:7 105:8 108:3 114:10 122:14 123:16 179:10 188:19 198:15 224:2,13 227:14 229:7 231:5 239:11 255:5 281:6,8,17 282:4 282:13 285:2,14 285:20 289:11,18 301:6 312:4 315:20,21 316:15 325:10 cover 60:20 69:6,7 69:9 70:3 302:12 303:10 coverage 52:5 64:12 65:4,18 69:20,21 71:12 105:7 108:10	covered 51:11 223:18 covering 70:2 covers 24:12 cox 3:14 10:17 27:2,2 124:20,22 189:15 194:8 201:18 202:4,6 204:4 319:3 320:10 336:8 338:8 341:18 343:14 346:8,11 349:6 350:10,13 crack 347:21 cracking 66:2 craig 8:7 184:1 cre 31:4,15 33:13 42:4 create 39:2 52:14 54:14 55:11 185:2 283:15 288:21 318:13 349:17 created 318:14 creating 332:2 creatinine 272:18 278:18 323:18 creative 30:6 creatively 30:11 credible 56:6 credit 354:8 crew 319:4 cringe 122:18 criteria 21:13 117:5 123:2 228:21 238:16 269:4 347:2 critical 6:5 31:10 42:4,5 110:4 120:1 142:13 155:11 162:10 209:15 280:9,14 282:2 286:15 316:1 322:2,12
---	--	--	--

critically 68:7 101:7 151:11 cro 100:13 crop 341:11 cross 95:22 305:19 cross 61:10 crp 101:15 102:5 crush 249:11 crystal 262:19 cuff 273:1 291:13 292:5 culture 49:7 52:10 53:1 54:16 87:22 100:4,6,10 102:16 102:21 103:2 118:17 203:12 320:5 327:5,15 cultures 33:1,12 36:15 104:7 275:11 culturing 90:17 cunning 168:3 curated 144:7 curbs 255:22 cured 32:10 34:12 cures 24:11 curiously 274:22 276:15 277:18 current 1:2 15:6 58:5 98:21 158:12 170:11 171:7 193:10 238:21 303:3 307:17 309:6 currently 23:21 68:8 94:17 106:16 111:2 112:4 144:10 curve 104:13 208:15 210:17 228:11 231:17 curves 269:9 custom 181:20	cut 192:21 300:6 cutoff 154:19 cyanotic 269:6 cyclopeptide 59:15 cyclophosphami... 160:13 227:12 245:2 248:18 258:13 259:14,20 cynomolgus 112:16 cynos 112:19,20 113:13 114:3 cystic 4:10 20:6 38:7 147:4 148:18 149:4 150:1,11 182:11 cytokine 160:3 cytokines 163:14 cytosol 157:1 cytotoxic 268:22	dan 165:20 200:6 342:7 dan's 199:18 201:7 dangerous 355:3 daniel 7:12 12:20 234:2 283:2 286:12 daptomycin 220:9 dark 178:6 darpa 258:5 darth 44:21 data 20:12,15,17 22:1 23:7 30:4 37:12,15 39:13,15 39:17,21 40:4,18 41:3,4,9,11,16,18 46:2,14,16,17,19 47:9,9,11,15,15 47:16 49:5 50:1 54:22 55:4,11,13 55:19 56:2,21 60:11,19 61:8,18 68:2,18 69:21 74:17 75:3,4 76:13,18 77:3,4,9 77:20 78:9,11 81:3 84:7,10 85:12 86:6,6,17 89:11 93:6,7 98:20 101:8 102:1 103:10 104:9,11 104:11,20 105:9 106:10 109:16 110:7,11 112:18 117:11 135:16 137:3,15,15,16 138:1 139:13 144:2,7 179:5,14 179:18 182:17,19 188:14,18,18 189:7,11 193:13 194:9 200:21 208:6 209:2	210:12 212:1,12 212:22 214:4,17 217:8,9,15 218:14 219:10,17 227:6 228:3 230:5,21 232:16 241:9 242:5 244:13 247:21 251:20 260:20 267:16 271:2,3,16 272:20 274:4 286:16 288:6 293:3 295:22 306:10 307:6,19 317:2 324:18 326:10,21 327:9,22 329:2,3 329:5 331:21 332:12 347:5 database 77:22 101:4 112:13 116:11 194:14 datasets 24:9 39:14 48:3 84:12 date 103:21 david 2:10 3:4 12:12 13:17 26:8 26:15 205:4 295:21 320:11 331:2 davis 322:16 day 16:18,21 17:4 17:14 29:6,12 30:13 33:11 42:18 50:13 75:17 88:6 88:12,15,16 114:6 114:6 118:12 127:8 133:15 182:20,20 195:15 195:16 204:7 234:16 235:11,16 236:16 238:9 245:9,20 246:14 248:18 249:1,2,6 252:8,9,14,16
--	---	---	---

255:20 256:8,14 257:6 260:3,17 287:2 308:16 312:4 328:9 335:12 346:12 355:7 days 29:4 42:2 49:10 81:12 100:5 114:15 115:13,20 116:20 117:18 118:1,16 122:2 174:17 196:18 197:11 230:19,20 231:2 248:21 253:2 289:2 291:16 293:18 327:12,13 344:17 344:17 dead 141:15 227:20 243:22 328:15 deadline 309:11 309:15 310:13,20 deadly 112:2 deal 160:22 341:15 dealing 127:19 130:11 dealt 151:7 194:2 death 48:15 58:15 85:4 88:6,8,18,20 89:2 114:6,11,18 114:21 115:22 116:6 117:4,15,17 120:7 174:3 229:1 229:7 232:3 245:5 245:20,20 246:21 269:7 270:11 271:1 274:11 275:13 276:3,14 279:7 296:18 324:10 deaths 236:15	debate 52:5 216:5 debated 56:11 deborah 357:2,13 decade 31:22 91:11 95:5 156:9 290:1 352:14 decade's 53:8 decades 282:20 december 24:11 309:2 decide 288:1,3 332:18 345:22 348:21 decided 82:3 235:14 291:7 deciding 197:16 decision 64:14 68:1 349:11 deck 254:4 declaration 281:9 281:9 decline 283:1,7 decrease 102:4 117:3 118:5 231:14 232:11 277:10 290:16 294:5 315:8,12 decreased 276:15 276:20 decreases 231:6 decrement 257:4 257:6 262:13 dedicated 279:21 deep 120:15,21 177:3 225:17 300:19 deeper 36:13 212:7 defense 163:19 184:10,11 deficit 278:9 define 99:8,20 161:2 172:7 209:16 211:8,16	216:14 346:4,4,5 defined 98:5 102:13 147:14 172:9 216:1 315:7 331:7 defines 157:21 209:13 defining 155:18 215:19 221:20 definitely 236:13 248:12 321:22 definitive 21:7 definitively 211:10 degree 76:11 98:12 128:12,15 128:21 129:1 131:21 132:7 134:20,22 135:2 135:11 137:4 138:10 139:6 198:13 199:12 213:17 degrees 142:2,2 228:19 delay 175:15,15 delayed 109:2,5 173:12 178:4 delays 175:21 deletions 186:17 deliberately 21:8 delightful 44:15 delivered 226:13 delivery 157:17 226:11 233:1 delve 166:20 demerits 312:5 demonstrate 19:12,22 32:6 46:17,18,19 63:11 98:2 103:17 105:6 106:17 137:7 182:15 183:14	demonstrated 21:15,18 55:6 demonstrates 155:1 demonstrating 19:18 63:8 demonstration 23:10 52:2 77:13 78:3 177:11 denominator 49:17 dense 164:11 dental 234:7 department 2:20 4:9 5:18 6:5 7:14 184:10 205:4 222:15 234:5,7,15 235:16 259:12 280:14 departments 2:11 depend 351:3 dependent 19:20 114:11 131:22 232:2 293:6,8 depending 104:10 115:5 173:16 190:4 depends 314:2 325:6 339:9 352:9 353:3,9 depicted 88:21 deposited 120:5 depositing 120:14 deposition 119:5 120:6,10 338:2 depth 120:7 deputy 4:5 27:4 derived 203:1 descends 224:21 describe 48:3 303:4 described 84:16 126:5 157:8 165:20 351:12
---	--	---	--

describes 57:3 122:5	develop 44:16 45:1,5 50:10,14	312:9,21 348:20 348:20	develops 146:10 282:3 293:10
describing 123:22 336:13 338:12	52:7 58:22 66:8 66:14 67:15 87:19	development 1:2 3:6 7:9 9:20 10:5	device 34:19 35:1 35:12,12,18,18,20
description 90:2 125:6	92:19 109:22 126:14 127:21	10:13 12:5,11 15:6 16:20 18:4	36:21 54:12,15
descriptions 89:14 89:22 90:3,8	129:10 150:22 155:8 170:22	18:13 24:1,2 25:9 25:14 26:5 28:16	devices 285:18
deserve 39:19 354:8	171:12,17 181:19 186:13,14,17	31:19 39:18,22 40:21 41:15 43:6	devise 51:6
design 9:12 42:21 43:13 55:3 56:7	188:10 265:1 275:12 282:5	43:9,9 46:11 53:4 58:5,6 59:2,4	dextrose 273:19
65:2,10 137:1 138:6 193:6	288:20 291:8 299:16 306:1,1,5	60:17 61:10 62:10 66:20 67:1 69:3	diabetes 34:16 159:12
207:11 208:5 209:6 310:1	309:3 310:6 314:12 345:7	71:15 72:1 73:9 74:12 79:17,21	diabetic 159:11 174:12,13 175:8
designed 132:4 222:21 345:6	346:8,13 354:7 developed 24:8	80:8,11 84:6 94:17 95:19 100:1	257:19
designing 53:10	58:13 97:17,18 111:10 113:6	101:21 109:20 111:6,9 112:6	diagnose 100:20 103:14
designs 17:19 56:17 107:8	132:5 144:5,13 164:22 166:6	125:7 127:17 129:8,14,19	diagnosing 100:2 104:3 106:6
desire 134:5	170:7 222:12 224:10 228:7	131:20 135:12 139:3 140:4	108:15 137:11
desired 21:21 178:5	263:10,14 267:17 288:17 290:2	142:14 150:3 184:8,18 186:5	diagnostic 18:17 38:22,22 52:13
desires 83:3	308:20 316:7 331:13 342:14	204:14 205:8,13 214:18 223:6	64:9 72:22 73:7
despite 30:8 36:19 96:14 216:21	345:8 348:1,22 developer 43:6	229:22 231:22 237:15 290:1,22	100:9 104:5
detail 51:15 105:11 133:1	developers 135:3 303:13 346:20	296:11,19 297:19 298:16 299:4,5,12	diagnostics 52:14 53:14 80:8 302:21
282:13 304:13	developing 15:20 16:22 20:20 25:4	301:1,21 302:7,8 302:13,21 303:11	306:8,20
details 101:6 136:12 177:9	29:8 30:14 40:6 57:21 66:17 94:20	303:14,16,20 304:1,5,11 305:6	dialogue 180:8 355:16
detect 121:11 123:8	96:2 99:1 100:8 104:5 111:1 112:9	305:10 307:3,7,9 308:1,12 309:14	diaphragm 121:4 diaphragmatic
detectable 231:13	126:5 139:1 157:9 165:16 170:6	309:21 310:5 316:21 318:7	121:7
detected 104:6	171:3 199:20 200:12 202:1,10	319:18 320:8 335:9,11,20,22	dictated 109:19
detection 231:11	202:12 223:20 232:7 300:3 304:3	338:15	die 81:11 124:4 236:16 238:3
determinants 155:11 156:6			244:1 269:11,14
169:11			269:14,15,21
determination 156:2 157:2			270:15,17 271:5
determine 91:2 207:21			274:6,6,16,20
			275:3 276:9
			277:17 279:10,15
			284:12 314:15
			354:21
			died 49:22 81:15 87:1 114:15 115:6

116:1 124:4 236:19 247:4 262:21 274:7 278:4 diehl 122:6,7 diep 3:18 13:6 26:11,11 264:11 264:19 313:4,17 314:16 315:18 323:12 337:5 338:16 339:8 352:7 dies 260:10 diff 38:6 194:2 difference 68:4 108:19 239:14 253:12 255:4 276:2 319:6 differences 122:19 123:15,16 201:19 213:19 215:8 221:4,11,13,13,14 223:14 229:21 231:18,21 283:22 317:3 different 40:2 49:16 60:2 63:5,6 64:18 82:17 85:1 94:1,6 122:20 131:20 144:12,17 150:13,18,19,20 151:8 161:17 166:17 167:4,13 167:15 172:19,21 172:22 175:2,12 177:14 190:12 192:9,10 193:8,13 193:22 195:5 197:15 198:10,12 198:13,19,20 199:4 201:11,12 201:14,15 203:21 208:12 212:6 214:11 217:1	219:12 223:5 224:12 226:16 232:14,15 233:13 239:5 241:11 242:6,14 243:5,7 245:14 251:1 252:3,21 255:11 262:2 263:15 264:21 265:2,18 266:18,20 267:18 268:7,9,11,17 271:14 274:9 279:13 284:2 297:10 299:11 303:12,15 304:10 305:19,19 306:18 307:22 308:7 309:6 312:3,19 314:7 320:5,6 324:13 325:2 328:20,21 331:9 331:21 344:7,8 347:18 349:20 351:13 differential 272:17 differentially 149:13 differentiate 231:17 differently 132:15 243:6 344:7 difficile 300:14 301:13 difficult 16:3 19:6 19:13,19 20:1 43:18 56:1,17 62:10 65:19 69:5 69:9 71:21 128:6 136:18 152:12 154:15 189:14 211:9 225:5 317:1 317:3,14 320:19 326:8 328:12	335:18 336:1 337:13,16 345:15 354:7,20 difficulties 15:20 17:8,17 168:12 328:4 354:16 difficulty 38:14 dig 238:12 dilution 315:11 dimension 47:3 52:19 331:21 diminished 160:3 dinner 287:5 dioxide 273:12 277:16,20 direct 270:12 direction 12:6 25:15 55:6,20 63:1 204:15 355:4 356:5 directions 303:3 directly 148:4 185:15 202:2 232:19 330:11 director 2:6 3:10 3:15 4:5 6:19 7:5 27:2,5 28:10 124:20 205:7 308:18 dirty 259:17 disabling 21:5,10 disagree 236:9 discerning 209:8 disclaimer 67:12 80:21 disclaimers 234:19 disclose 141:10 disclosure 95:7 111:14 disclosures 29:10 43:21 151:12 184:3 205:21 264:22	discontinuation 61:20 discovered 114:9 156:13 166:4 167:12 discoveries 308:22 discovery 8:6 180:20 181:1,13 205:8 discriminate 133:22 discuss 15:5 39:22 57:20 66:11 74:7 150:3 183:18 206:1 210:5,7,8 305:3 312:12 336:19 355:16 discussed 16:19 17:14,20 18:5 20:4 34:7 39:5,11 40:3 58:17 105:11 202:18 311:8 312:11 322:9 327:21 329:22 342:22 discussing 16:16 31:2 66:1,17 130:2 227:14 322:4 332:4 341:15 discussion 11:18 14:5 15:16 17:2 17:16,18 18:1 24:7 25:16 29:12 30:13 32:3 41:5 56:9 75:9 108:22 131:5 141:15 185:21,22 188:15 199:19 204:10,12 205:1 221:3 308:17 311:13,16 311:20 313:1 325:21 326:14 328:6 329:1,9
--	---	---	--

335:2 discussions 23:18 31:9 63:17 64:2 83:10 84:1 302:4 346:16 disease 22:16 28:11 47:19 66:21 73:2 80:9 81:6 82:11 84:16,17,17 85:11 86:3 87:4 87:11,14 89:12,15 90:4,6,8,12,13 91:14,15 92:18 95:17 96:4 97:22 98:1,12 99:9,20 100:3,4,5 102:13 103:19,21 105:8 105:15,17 108:9 108:10,11 114:10 114:21 115:8,11 116:6 117:1 120:2 121:5 122:9,15 123:16,21 124:11 126:17 127:12 128:16,20 132:10 141:20 145:15 150:12 154:9 179:12 186:13 187:17,18 198:1,5 198:12,19 228:8 245:4 280:12 281:15 287:22 293:21 297:17 317:18 318:2,22 319:7,9 321:1,3 322:13 338:11 341:19,20 342:2,7 343:15,17 344:1 344:18 347:3 348:10 353:7 diseased 89:8 diseases 2:13 3:10 3:20 4:16 7:14 16:5 22:22 26:7	80:4 94:20 111:2 128:15 129:11 141:17 187:10 205:6 284:13,21 301:22 302:11,15 318:17,18 dismutase 163:4 displaced 50:4 disrupt 196:4 disrupted 86:9 dissected 290:19 disseminate 147:1 147:10 150:6 disseminated 114:21 229:17 disseminates 260:10 disseminating 343:19 dissemination 115:4 119:9 231:20 245:18,19 246:14 250:10 257:17 323:8 dissimilarities 283:20 distill 350:16 distilled 319:15 distinct 103:13 113:6 265:7 distinction 86:16 96:21 distinctions 152:22 distress 288:22 316:6 318:12 distributed 115:14 226:9 distributes 59:16 distribution 59:17 226:4 346:7 diurnal 86:8,13 116:20 117:22 118:2	dive 212:7 diverse 152:9,10 187:2,3,4,7 189:6 189:9 193:8 242:3 243:5,8 diversity 187:6,18 188:11 242:15 243:2 divided 270:2 division 2:13 3:5 3:20 4:9 6:19 7:13 15:9 26:6,9 80:3,6 205:6 280:13 297:10 301:22 302:10,14 dna 240:9 242:21 243:3 doable 177:6 328:3,3 docs 254:22 doctors 254:11 263:13 document 303:2,4 documentation 110:6 301:7 305:15 documents 78:3 dog 286:7 324:7 doing 49:12 128:11 134:1 142:16 157:8 170:4 171:21 172:14 180:9 195:6 199:20 203:11,13 205:22 211:3 235:17 236:18 238:8 239:12 243:1 249:19 250:1,6 251:14,16 259:13 259:22 262:10 263:21 308:12 322:10 333:5 338:14 340:14	342:6 354:8 dollars 321:11 339:2 dominated 114:16 dominates 262:4 dopamine 285:8 dosage 71:14 74:11,15 321:16 dose 22:3 39:8 50:20 74:19 77:15 77:17 86:5 88:7,9 88:14,18 91:3 93:16 104:17 107:10,15,22,22 108:1,7,15,16 109:3 114:12,14 116:3,14 120:4,4 130:18 132:17 146:3 172:2 182:20 183:14 208:3,4,10,14 209:12 211:19 227:16 230:16 231:4 232:2,4 245:4 250:7,8,12 250:15 256:13 257:17 258:13 259:22 260:2,5 266:9 269:16 271:6,11 317:13 318:8 319:19 dosed 81:16 doses 85:3,19 88:19 114:4,20 171:19,21 178:19 178:21 208:9,11 208:16 226:16,21 228:10 231:6,15 232:5 247:7 268:17 322:3 dosing 60:15,19 65:7 106:22 107:20 108:14,15 109:5 116:5
---	---	---	---

123:17 171:19,22 173:18 208:12,13 208:17,19 260:7 306:21 320:15 dotted 231:11 double 65:18 314:22 doubletree 1:11 doubts 286:8 downselect 300:13 downselection 299:6 doxycycline 252:12 dozen 215:21 dpu 176:20 dr 15:4 17:22 23:4 26:2,3,8,11,13,15 26:17,19,21 27:1 27:2,4,6,9,11,13 27:14,16,18,21,22 28:2,2,4,7,7,10,13 28:18,21 37:13 38:1,13,18 39:3 39:14,22 40:20 41:19 42:16,16 43:4,7,12,15,15 43:20 57:18,18,19 57:21 58:2,8,9 66:12,12,15,16,19 66:22 67:4,5,17 69:5 76:13,17 78:10 79:7,7,18 79:22 80:5,10,14 94:12,12,13,14,17 95:1,2 110:20,20 110:21 111:2,7 124:18,18,20,22 140:15,21 141:5 143:22 151:1,2,5 152:9 155:21 162:7 165:6 168:11,19 169:1 176:14,14,16	180:17,17,19 183:22 184:1,2 185:19,20,20 186:1 189:15,18 191:4,7 193:5 194:8,21 197:13 198:21 199:17 200:12,17,18 201:3,10,16,18 202:4,6,8,14,19 203:7 204:4,9,16 205:3,14 217:10 221:18,18,19 222:7 234:1,1,2 234:11 235:10 242:18 257:19 259:20 262:16 264:9,11,19 280:3 280:6,7,8,8,19,21 280:22 291:18 292:1 295:11,13 295:14,20,21 296:3,4 301:18,18 301:20 302:2 308:15,15,17,20 311:14 312:14 313:3,4,6,10,17 314:11,16 315:16 315:18,21 316:19 318:10 319:3,14 320:2,10 321:5,21 322:15 323:12 325:18,20 326:15 327:20 329:10,21 330:7,20,21 331:1 333:3,12,13,15,18 333:19 334:1,4,6 334:8,9,12,13,15 334:18,18,20 335:1 336:6,8,14 336:18 337:4,5 338:8,16 339:7,8 339:15 341:18 342:10 343:11,14	343:17,18 344:20 345:20 346:8,11 347:1 348:6,15,19 349:6,10,14,16 350:1,2,4,10,13 351:15 352:1,7 353:12 354:10 355:6 drafts 90:9 drainage 35:7 36:2,11 draining 119:6,8 dramatic 87:2 122:19 277:9 dramatically 120:9 190:5 276:13 draw 81:22 282:15 294:3 drawing 122:13 253:7 draws 85:15 dreier 7:20 345:20 345:20 dressings 251:12 261:15 dressings 261:17 drill 78:16 drive 192:5 driveline 36:2 driven 75:11 76:2 driver 209:8,11,13 213:2 drivers 297:19 drop 271:13 344:4 droplet 224:20 droplets 246:2,2 344:14 dropped 276:13 drops 249:1 drug 9:13 15:10 16:20,22 17:11,12 19:4 20:2 22:15 24:19 25:6,7 26:4	42:21 43:5,14 45:6,15 47:21 48:7 50:5,9,9,11 50:11,14,21 54:1 59:21 60:8,10,14 61:9,14 62:10,11 63:11,14 65:9,15 66:18 69:4 76:19 77:22 82:21 83:1 84:6 88:2 91:5 129:2,8,19 132:15 133:6,22 134:16 137:19,21 181:13 184:8 192:10 194:9,13,18 195:9 203:4,16 205:8,11 205:22 206:10 208:11 209:16,21 210:3 211:22 212:3,8,21 213:4 213:4,10 214:10 214:21 215:2,15 215:21 216:10 217:2 218:17 220:1,4 238:21 259:4 286:16 288:11 300:15 301:21 302:13 308:1 309:20 310:5 314:13 316:21 319:17 328:14,15,16,19 329:14,16,17 335:4,5,8,15,20 338:7 340:8 349:19,20,21 drugs 15:20 17:14 18:2 24:2,6,14,14 30:3,6,14 37:10 38:4 40:6,17 43:7 44:2,6,8,17 45:10 48:8,18 57:5,8 69:9 82:13,17 83:11 84:3,9 91:1
--	--	---	--

91:10 93:18 112:4 125:19 126:20 127:2,5,14 129:21 133:17,19 139:1,8 139:11,17 140:6 168:2 193:1 194:5 197:22 201:13 202:1 213:8 215:21 216:10,11 219:12 220:5 230:6 236:21 281:19 283:4 285:6,7,7,8,10,13 286:20 291:2 309:22 312:21 315:17 316:7,12 327:10 330:2,4 331:4 334:16 335:11,21 336:1 337:11 339:16 345:11 drusano's 218:15 dry 161:7 dst 184:11 dual 52:4 64:12 167:5 dubious 152:21 due 15:22 17:6 18:15 19:14 20:5 29:9 49:22 81:15 83:17 142:7 157:22 160:3 188:7 220:7 224:17 263:19 277:6 309:7,16 310:21 312:9 duoderm 261:12 duration 107:10 108:16 314:9 durations 156:16 dvm 5:4 10:15 dye 226:6,8 dying 34:13 252:10	dynamic 211:9 dysfunction 278:5 278:6,7 e e 9:1 10:1 11:1 12:1 13:1 14:1 15:1,1 235:5,5,6 254:18 273:9 ear 146:9,10,11 169:20 273:17 340:13,18 earlier 36:3 37:14 38:8 40:20 72:6 76:13 83:9 84:8 88:8 91:17 97:20 197:5 206:14 214:1 216:3 221:3 235:10 237:22 240:7 245:15 257:16 262:17 320:15 342:5 346:16 early 43:8 61:18 71:14 74:11 81:22 86:9 89:21 91:12 91:19 98:18,19 99:9 107:21 148:18 171:21 197:5 203:2,5 240:2 302:12 303:11,16,22 307:22 338:9,13 347:22 easier 44:16 48:9 289:22 335:19 easiest 82:21 easily 177:7 186:13,14 337:18 easy 19:8 78:15 265:8 338:18 ebola 132:21 297:16 ec50s 230:6	ed 3:14 10:17 27:2 140:15 336:6 ed50 232:4 edema 89:9 edge 88:22 89:2 edged 314:22 edward 124:20 effect 19:5 21:15 21:17 50:22 99:3 132:5,12 133:6,8 133:10 172:1,2 206:12 256:15 effective 16:7 22:3 59:13 68:21 81:14 91:9 93:16 97:4 98:21 103:19 135:13 164:4,8 175:3 183:10 194:5 208:17 221:16 309:1 effectiveness 21:12 63:14 98:2 100:7 133:4 effects 276:5 efficacious 60:10 98:16 253:8 316:12 efficacy 19:9 20:12,14,15 21:3 21:7 22:14 23:10 39:21 40:4,11 47:14 50:2 61:18 62:4 63:8,11 65:11 70:22 74:17 74:18 75:7 76:4 76:19 77:4,5,12 78:3 82:14,18 83:22 91:4,8 93:18 94:1,21 98:9 105:6 108:17 109:4,18 110:9 116:9,13 117:9 123:10 126:19 127:15 131:10,12	133:10 134:1,16 134:22 137:7 139:11,18 160:18 171:17 172:7,9 174:6 176:9 181:6 182:9,21 183:9,14 188:18 193:21 194:3 206:5 207:10 208:15 209:17 214:19 216:19 218:19 219:4 220:19 224:9 229:6 239:18 254:1,2 267:10,16 291:2 298:16 301:3 314:19 331:5 344:3,19 350:15 350:19 351:8 efficient 226:11 efflux 142:9 163:10 171:10 effort 60:16 64:17 110:6,13 124:16 137:5 143:6 251:19 264:6 efforts 30:16,18 31:15 66:6 95:19 222:2 efl 215:13 eight 61:15 either 18:22 23:13 41:15 53:2 70:9 71:17 73:21 146:7 178:8 179:17 180:5 186:20 210:21 230:22 232:20 243:22 244:1 268:15 305:19 306:4 307:11 315:19 327:15 352:9 elected 34:11
---	--	---	--

elective 188:6	empirically 19:2	330:13 348:12	entities 95:10
electrolyte 272:18	109:8	349:4	entity 110:14
electron 142:4	employed 356:8	engaged 56:11	111:15
153:8,8	356:11 357:7	enhance 41:8	entry 118:21
elegans 158:20	employee 80:22	164:18	120:20 123:14
160:19	234:20 356:10	enhanced 208:15	enumeration
element 73:10,11	enable 192:17	245:18	245:8 250:5
342:17	enables 164:10	enhancement	environment
elements 155:15	encountered	21:22	29:20 71:3 141:12
157:22	129:9 140:4	enhances 271:17	141:21 148:17,20
elevated 90:14,19	encountering	enhancing 164:15	148:20 152:22
276:18	169:12	239:13	153:20 186:19,22
elf 174:5 214:13	encourage 25:18	enormous 54:2	187:15 189:3
214:20 215:2,6,9	168:7 171:15	55:16 353:17	193:10 320:5,6
218:18 221:14	185:13 304:22	enrich 72:4,14	environmental
eligibility 310:17	310:11 355:4	73:3	143:9 186:18
eligible 76:21	encouraging 66:5	enrichment 73:1	187:3
307:6,13,18	ended 34:12	enroll 16:3 19:10	environments
eliminated 60:14	230:21 299:18	19:13,16 52:10	161:7
elimination 59:18	endobronchially	53:7 72:16,19	enzyme 278:21
else's 291:20	268:20	74:13 75:19 76:3	enzymes 119:16
elucidate 281:15	endocarditis	79:1	163:9 272:19
ema 48:2	154:13 267:12	enrollable 77:10	epidemic 187:12
email 185:16	337:8,14 338:4	79:3	352:13
308:9	339:11	enrolled 76:9 77:1	epidemiology
emax 208:22	endothelial 270:8	enrolling 38:14	264:14
embarrassed	endotracheal	74:8 75:12	epithelial 196:5
346:21	174:7 272:7 273:1	enrollment 18:14	202:22 347:11
embraced 125:12	273:2 285:19	72:17 74:14	epithelialization
emerge 148:17	291:13 292:5	ensure 22:10	253:17,22
emerged 39:6	314:8	41:20,22	equal 70:20
emergency 33:16	endpoint 52:20	entasis 5:10 9:17	equals 53:1
emerging 38:12	75:17 76:5,8,20	25:6 27:12 43:3	equivalent 150:15
157:19 297:16	98:5 172:8 175:1	66:16 67:7,14	317:13 331:10
emory 4:11 11:10	176:6 206:22	136:22	333:19
26:17 141:2	207:5,16 214:7,10	enter 303:17	era 29:16 89:18
emphasis 63:6	218:5 299:16,20	enterobacter 35:8	336:5
83:6 97:2,9 99:1	endpoints 21:20	enterobacteriace...	eradicated 129:16
emphasize 93:15	87:16 93:7 122:17	49:8 51:8 65:5	error 108:18
93:20	174:1 176:6	enterococci 182:6	ertapenem 51:6
emphasizes 42:6	209:22 210:2	enthusiastically	51:16,19 64:5,21
empiric 64:12	223:21,21 228:3	125:12	64:22 65:9,12
empirical 36:5	245:7 250:5	entire 307:3	erythema 35:4
45:19	256:20 329:19	335:17	

esbl 30:6 212:14 212:18,19	etx2514 66:18 67:9,15 69:3,17 70:12,16 77:2	evaluations 62:22 171:20	148:8 179:9 188:21 190:12,14 208:6 212:9 215:11 255:14,16 256:18 266:1 285:4 288:5 303:7 307:2 326:4 338:21 339:13 341:8
esbls 51:9	eu 73:13	event 75:11 76:2	examples 22:15,21 25:5 45:5 50:9 53:5 57:11,12 182:10 219:9 230:2 286:10 306:22 329:13 330:2,3,4
escape 48:6	eu5 68:1	events 126:15 240:17 274:10 324:9	exceeding 91:5 excellence 205:9 excellent 89:22 125:5 138:9 169:4
eskape 67:20 340:16	eurofins 8:6 180:18,20 181:1 181:12	eventually 109:17 117:3 123:8 197:20 252:10	exception 209:7 exceptional 131:13 exceptionalness 131:22
eskapee 235:4 250:16	europe 63:6 181:4 335:16	everybody 43:16 63:18 125:16 135:2,4 137:6 152:17 234:13 255:5 307:13,15 355:7	exceptions 45:20 45:21
especially 19:4 38:15 146:21 197:1 200:2 202:14 233:5 276:14 307:22	european 63:7,21 66:1 71:9 242:7 335:5	everyone's 137:7	exchange 37:1 exchanged 35:19 exclusively 299:8 excreted 278:15 excretion 257:11 257:14
essence 127:20	euros 321:10 338:22	evidence 21:12 77:11 124:13 129:3 274:21 279:17 331:5,6 352:1	excursions 121:8 execution 298:22 executive 66:20 existence 349:21 existing 19:19 113:9 180:1 204:21 233:8 284:21 306:21
essential 73:5 161:21	euthanasia 87:12 117:4 122:18 123:2 269:5	evading 162:11	exists 337:14 exoenzymes 148:4
essentially 76:6 118:5,14 130:18 225:10,16	euthanize 123:1 274:14	evolution 67:14 240:15	
establish 74:18,19 75:7 78:12 85:9 93:9,13 113:12 123:1 173:6 177:14 196:6 197:6 223:11 227:5,15 228:2 303:21 305:18 306:5 317:21	euthanized 113:20 118:15 230:22 269:3,8	evolutionary 240:6	
established 174:18 195:4 196:19 227:12 228:2	evading 162:11	evolve 148:22	
establishing 75:1 305:17 350:19	evaluabale 52:22 53:1	evolved 186:11,12	
establishment 122:17	evaluate 101:21 103:20 106:4 116:8 126:19 129:10,21 131:12 131:14 139:14 176:22 179:21 181:5 183:9 242:13 244:12 255:6 309:5 311:1	evolves 187:13	
estimate 71:14 74:11,15	evaluating 96:18 139:8 170:3 171:13 182:9 306:20 322:2	exact 284:14 316:14 323:3	
et 73:19 235:22	evaluation 15:11 22:7 32:17 62:18 63:10 127:14 306:12	exactly 189:4 290:4 292:5 293:9 293:15	
etest 154:22		examine 123:9 211:17	
ethanol 161:9		examined 90:16 207:7 208:18	
ethical 22:9,12		examining 123:12	
etiology 173:16		example 17:19 18:8 25:7 30:4 37:17 49:4 57:9 68:20 70:5,10 74:15 115:9 123:22 145:22	

exopolysacchari... 149:6	explored 317:16 317:19	external 39:12 305:3 309:5	factor 74:3 109:9 127:1 190:19 255:18 268:1,3
exos 148:10	exponential 282:19 292:21	externally 307:12	factors 62:19 147:11,16,19 148:8 149:19 150:18 157:18 158:8 159:12 161:6,17,18 163:2 163:5,6,13 166:12 166:13 239:1 347:7
exou 148:9 268:22	export 292:20	extracellular 148:12	factory 250:22
expanding 251:19 256:10 305:7	expose 21:9	extraordinarily 68:6	facultative 142:2
expect 47:4 54:10 91:6 209:3 218:10	exposed 23:11 103:11 114:19 115:12,18 120:22	extrapolate 20:7 37:18	fail 339:17
expectation 92:7	exposure 21:5 98:14,16 99:17 101:18 102:20 107:19,21 113:13 115:6 116:20 117:20 118:21 127:6 128:9 132:16 206:11,12 210:16 212:2 217:4 218:3 219:2 219:4 220:9 333:7	extrapolating 128:22	failed 219:15 329:16,18 341:8,9
expected 21:16	exposures 45:15 208:18 217:21 218:9,22	extreme 131:1	fails 137:19,21
expensive 325:16 339:3,3	express 148:7,9,10 150:18 217:4	extremely 24:9 91:21,22 93:17,19 104:7 187:3 188:4 189:9 240:8 339:2 355:14	failure 33:9 34:16 36:22 52:20 81:15 156:11 218:11 246:21 270:11 274:20 277:17 279:11,11 290:17 316:4 329:20
experience 43:7,8 57:20 66:13,17,19 94:15 106:21 111:1 124:7,8 132:21 160:21 180:11 181:7 189:21 190:4 195:1 201:7 215:19,20 216:9 298:19 314:3 315:3,14	expressed 70:8,9 208:20	extremes 115:10	failures 220:2 341:4
experienced 17:8	expresses 161:7	extubate 313:14	fair 128:12 135:15
experiment 62:20 178:7,13,13 279:22 321:9,10	expressing 171:9 212:10	eye 147:7 169:20	fairly 25:2 102:6 115:14 116:19 119:15,16 131:1 133:5 135:20 190:8 228:22 333:19 342:14
experimental 76:15 235:22	expression 70:7 145:3	f	fall 103:5 188:12
experimentation 280:13 281:8,11	extend 297:1	f2g 7:5,6 9:15 27:7	falls 230:11,13
experiments 145:7 177:9 222:18,19 345:6	extended 212:10 309:11	fab 267:22	familiar 30:20 69:10 97:13 129:6 296:12 307:22
expertise 57:22 180:7 301:6	extensive 66:19 115:16,21 121:5 283:13 290:20 291:3 300:19	face 135:5 155:7 159:2	families 37:10 236:22
experts 286:9 307:21 348:21	extensively 59:21 268:6	faced 63:4 154:14	family 34:8
explain 123:15	extent 91:19 128:22 198:3 204:5	facilitate 16:19 57:8 80:7 260:15 308:21 309:21 310:4 335:10	fantastic 144:3 204:1
explained 294:16		facility 124:10 258:20,21	
exploit 348:4		fact 34:8 74:7,8 106:11 124:11 125:13 126:11 128:4 134:14,18 137:8 150:11 163:21 190:16 192:8 212:15 215:20 216:21 261:19 265:8 331:17 332:9 350:22 354:2	
exploratory 58:5 61:18			

far 31:21 45:9 88:13 155:20,20 162:15 205:16 220:7 233:12 240:15 241:7 246:10 257:14 281:20 319:16 322:19 323:5 341:16 343:7 344:2 fared 215:15 farkas 1:19 356:2 356:17 farley 4:4 27:4,4 168:11 176:14 180:17 183:22 185:19 farm 258:18 farms 353:8 fascinating 295:12 fashion 39:10 48:4 fast 80:20 176:5 faster 39:3 256:1 292:15 fatal 81:9 fatalities 299:19 favor 312:15 favorable 59:16 fc 268:3 fda 2:8 3:16 4:6 6:20 9:7 10:17 13:19 15:11 27:3 27:5 63:9,16,21 78:2 82:3,7,20 83:3,10,14 91:7 91:12,15,17 105:9 110:8 124:21 151:13 182:1,2 186:5 194:1 203:19 204:2 220:15 239:19 259:6,8 281:18 283:3 295:1 299:10 301:4	308:19,20 309:12 310:21 316:10,22 322:20 346:3 fda's 92:7 309:20 310:16 feasibility 22:13 56:5 62:21 feasible 18:10 20:14 21:11 22:9 41:1 53:4 56:3 79:3 128:13,17 134:9,14 136:7 137:3,20 138:8 328:13 336:15 feature 69:18 74:11 117:9 278:3 features 69:14 126:16 187:5 205:1 279:6 287:12 febrile 33:16 85:8 118:3 federal 20:21 80:21 feedback 355:15 feel 61:8 66:4 76:16 170:8 179:20 192:6 193:2 195:8 203:10,15,15 227:1 263:11 311:6 312:7 344:9 feels 191:8,19 332:15 fellowship 3:10 28:11 felt 107:6 195:3 354:7 female 114:3 fever 32:14,17 85:10 86:11 87:20 88:1 89:1 93:7 114:11 116:19 117:8,14,16	121:12,14 fiber 77:14 290:6 339:22 fibrin 338:2 fibrosis 4:10 20:6 38:7 147:4 148:18 149:4 150:1,12 182:11 field 21:10 43:5 47:17 144:5,20 152:12 197:20 213:11 222:9,10 241:8 284:5 294:19 316:11,18 337:6 352:10 fight 127:20 figure 42:11 102:15 161:22 168:4 figuring 42:7 file 82:6 files 84:5 fill 307:9 filling 307:2 filtered 278:15 final 76:8 94:9 110:2 182:17 183:22 finally 42:9 78:7 123:4 124:15 150:17 190:20 196:11 229:19 258:7 financial 95:11,12 111:17 financially 356:12 357:8 find 30:10 44:7 45:1 52:15,16 55:14 73:11 89:14 134:18 154:22 165:13 201:4 238:6 250:12 283:15 336:15	355:17 finding 44:9 102:11 133:2 155:18 185:13 250:15 319:19 findings 29:17 140:12 295:2 fine 51:16 296:9 fio2 273:6 277:11 277:14,20 290:16 324:21,21 325:3,5 327:14 fires 251:6 firm 98:6 first 16:18 28:8 32:7 43:4 45:14 50:9 58:10 59:7 79:22 80:16 82:8 82:10 84:22 85:5 85:13 92:17 93:5 105:12 107:17 113:12 116:16 122:3,21 125:4 126:2 134:5 141:1 142:17 155:20 159:16 169:5 180:2 186:4 188:22 205:3 206:1,6 207:22 209:10 210:11 224:10 234:18 238:1 241:12 243:10 248:21 265:3 268:12 269:2 288:15 290:13 295:20 297:21 300:6 316:20 321:12 339:13 343:22 346:3 350:11 353:15 firstly 185:5 fiscal 310:6
--	---	--	---

fish 56:1 254:4	131:18 136:10,21	formulate 25:20	francisella 111:19
fit 209:2 238:21	138:13,22 168:11	forth 143:6	352:5
fits 55:18	189:16,16 202:1	fortunate 93:4	frankly 29:21
five 207:3 208:11	217:20 241:2	95:5 97:12 112:12	38:16
269:11,14 272:16	253:10 346:13	156:1	fraught 153:15
290:10	351:12	fortunately 65:3	free 59:17 204:3
fix 39:1 52:13	folliculitis 146:17	forward 25:20	213:10 214:21
flagella 147:22	follow 113:14	29:5 30:19 38:9	215:2 218:17
149:11	168:14 229:16	40:4 42:7,13	251:11 300:7
flank 32:14	244:16 354:22	45:11 92:14	311:6 346:9
flexibility 177:15	followed 25:10	135:12 138:5	french 240:20
floating 227:21	119:5,7 207:18	139:5 200:10	frequency 18:19
floor 1:13	following 25:13	203:9 320:18	208:3 343:4
flow 54:14 273:7	67:13 96:16	336:20,21 337:2	frequent 52:4
fluid 90:18 270:9	103:18 106:20	355:17	58:17
273:18 286:17	123:2 146:18	fosfomycin 30:6	frequently 15:15
314:16,21,22	172:11	found 54:12	208:16
315:6	food 29:20 186:21	148:19 165:22	front 64:10 81:2
fluorescent 145:2	335:4,15	166:9 257:1	341:10
fluoroquinolones	foot 258:21	262:11 289:3,4,6	fruit 80:19
81:10 213:1,2,9	force 53:12	290:19 292:21	fruits 80:17
fly 258:14	forced 30:3 40:17	311:9	full 34:20 47:3
focus 28:15 41:5	forecast 216:19	foundation 37:17	139:12 204:5
44:1,8 76:20	220:19 221:16	41:14 96:3 109:16	309:16 310:19,21
78:16,19 112:5	forecasting	four 21:13 46:10	fully 39:20 40:7
141:15 235:14	207:10	79:21 84:19 88:4	47:3 180:14
246:12 282:3	foregoing 356:3	118:16 172:16,16	function 60:16
298:1 310:2 312:2	forever 193:3	208:11 241:12	188:13 323:7
326:16 327:21	forget 261:5	242:10,12 250:21	327:13,15 347:10
328:9	form 63:13 90:6	271:5 272:4,8	functionally
focused 16:21	112:1,1 298:12	276:3 311:17	331:10
43:7 44:12 61:17	formal 168:16	fourth 242:9	fund 184:15,22
94:19 157:3 222:2	formation 148:14	276:5	303:13,21 339:10
264:13 281:20	158:11 161:15	fraction 59:18	funded 94:19
311:22 326:2	162:17 175:6	331:18	111:13 258:4
focusing 75:14	285:12	fractionated	funding 82:6
97:15	formed 67:8	208:11	151:15 264:22
fold 211:22 266:12	former 264:4	fractionation	294:2,9 304:15,20
266:12 272:8	formerly 315:8	208:5,10 209:12	305:3 307:11,18
338:4 341:16	forming 114:8	fracture 239:8	310:5,14
folks 95:21 125:2	115:13,19 130:19	frames 142:21	funds 307:9
125:8,9,14,17	146:2 290:7	francisco 3:22	fungi 182:6
126:2,8 128:4	forms 84:13 92:10	13:7 26:12 264:13	funneling 236:4
129:7 130:22	111:22 157:10		

funnels 235:19 funny 156:5 further 1:2 15:6 23:22 34:10 42:6 60:11 67:11 105:19 150:11 157:13 257:9 267:10 300:13 326:11 356:10 furthermore 226:20 fusions 145:1 future 12:6 25:14 139:2 167:21 185:4 193:14 204:14 303:3 fy17 310:2	gene 149:12 150:14 156:21 157:13 general 74:6 97:4 112:8 129:21 132:4 141:8 282:22 316:2,4 generalized 115:1 generally 21:21 71:10,12 78:1 111:21 112:2 114:15,20 117:18 132:4 145:14,21 148:9,19 150:5 generate 46:13,16 47:11 55:4 75:2 326:10 generated 77:9 139:13 generates 162:19 generating 326:13 generation 119:22 184:15 188:22 generic 83:11 93:22 genes 156:3,14 157:14 161:9 163:8 166:5,9 167:5 168:5,6 238:7 239:3 genesis 162:21 genetic 144:21 155:11,15 156:2 157:22 186:16 187:13 265:9 genetically 166:1 167:13,14 238:22 genetics 153:13 157:21 genome 6:14 142:19 161:5 203:22 240:8,10 240:13 242:12	genomes 143:7,17 144:10,11 145:8 197:2 genomic 144:2,9 144:15 165:14 187:4 283:13 genotypes 143:13 gentleman 34:15 34:15 genus 44:9 141:11 geographic 74:2 geographically 113:5 geographies 60:4 geography 73:17 george 218:15 getting 51:12 138:7 140:7 174:19 188:7 193:15 194:1 197:9 207:12 231:20 234:13,22 237:21 238:15 245:10,11 246:13 249:11,20 254:11 259:5 276:22 320:6 328:4 346:12 gi 176:1 gianluigi 6:4 13:11 280:6 give 20:19 23:1 35:14 45:4 68:19 81:1 88:1 91:3 130:18,19 132:17 143:20 158:22 159:9 160:9 175:8 176:21 178:4 194:4 241:18 242:3 253:8 255:14 285:4 286:10,20 288:5 321:6 326:20	given 57:9 61:11 106:12 107:20 108:6 140:7 260:17 gives 45:17 81:18 91:3 172:2 177:15 giving 149:8 159:20 176:17 264:20 282:8 296:5 glad 50:1 125:15 glands 246:16 glandular 111:22 glass 242:22 glaxosmithklein 7:22 glaxosmithkline 176:15 glimpse 204:20 global 3:20 7:21 350:4 globally 31:16 globulin 96:20 glp 93:18,22 110:9 181:17 glucose 272:18 gmp 305:12 go 16:10 29:13 32:13 37:4 45:12 47:21,22 56:1 63:1 64:3 65:19 79:19 92:15 120:17 139:2 153:3 161:10,22 162:2 163:4,13 164:7 172:15 174:3,19 175:3 179:16 181:19 196:2 202:6 204:17 205:2 222:22 223:4,5 229:2 232:20 237:15,18 238:12 240:13 243:18
g	g 15:1 142:22 256:21 gabe 27:14 111:15 124:15 125:5 gabriel 6:9 10:9 gain 219:16 gained 132:21 gaining 224:4 gaithersburg 243:1 game 332:5 gap 99:16 307:2 316:11 gaps 32:1 307:10 garenoxacin 213:6 220:8 gas 272:17 325:12 gastric 176:1 gather 134:12 194:9 gc 31:17 gel 241:8 262:12 gelhaus 7:21 350:4,4 gemifloxacin 213:6		

250:9,11 253:6 260:6,9,11 265:15 266:8 280:17 282:13 292:15 294:1,8,15 296:7 296:8 299:2 300:21 301:1 304:13 307:6 308:2,6,7 314:5 325:19 335:12 336:6 344:2,3 346:15 349:19 350:10 355:4 goal 106:17 194:8 195:2 203:12 291:10 296:21 goals 180:1 335:15 god 151:22 goes 46:9 50:5 76:17 116:10 133:4,15 170:14 176:5 240:15 246:15,17 249:5 252:8 270:5 343:7 going 34:9 36:13 38:11 39:10 45:3 45:4,6,8 48:18,19 50:10 53:15,16 56:14,22 57:7,12 57:14 70:1 71:1 73:1 75:8 80:14 81:1 83:5 87:18 88:3 93:3 94:5,8 95:16 96:5 97:6 97:15 100:22 105:18 107:5,6,15 107:16 109:21,22 111:8 120:14,16 120:17 121:6,8,8 121:16,19 122:14 123:7,10 124:22 125:3 126:16 132:18 133:1 140:21 141:8	165:6,20 170:12 170:18 171:1 179:14 180:20 189:9,10,15,20 190:8 191:9,14,14 191:16,17 193:3,7 193:11,16 196:21 198:5 199:11,12 202:15 203:2 204:9,19 215:10 220:22 222:11 223:2,9 224:16 227:6 229:12 234:12,17 237:15 237:16 238:1,4 239:6 243:18 244:3 246:22 248:15 252:2 254:13,21 258:3,6 258:9,14 259:3,9 261:4,6 267:15 281:1 282:13 295:1 296:7,7 298:17,19 299:2,3 299:3,9,13,14 304:13 307:3 314:16,17 317:1 319:22 322:19 323:9 328:12,12 329:5,6,12 331:15 336:8 340:5,5,7 344:12 345:4,16 345:22 346:5,6,6 347:15,20 350:10 351:21 gold 84:22 144:8 288:16 289:11 337:6,10 goldberg 4:8 11:10 26:17,17 141:1,5 143:22 348:15 gonorrhea 38:6	good 15:4 27:2,11 28:4 38:17 39:3 40:1 41:17 42:13 49:1 63:15 85:9 90:3 96:3 122:21 122:22 123:21 125:11,16 155:17 160:4,6 161:1 172:12 175:9 179:6 189:7 195:9 198:9 203:10,15 222:13 226:18 234:11 236:8 244:13 253:1 257:5 279:13,16 280:19 295:4 302:3 307:19 321:15 327:14,17 330:6,13 339:7,20 340:11 343:22 351:1 353:8 gosh 319:22 government 94:19 95:10,21 96:9 100:14 110:17 111:16 184:14 200:7 234:20 294:2 governments 184:7 grab 301:15 graduate 279:19 gram 29:19 30:7 31:22 32:19 35:8 59:9 71:7 182:5,6 278:3 grams 219:2 270:1 270:2,3,5,6 274:17,18 grand 1:13 grant 310:18 grants 303:15 graph 49:13 81:10 101:6,10 106:7	226:11 graphic 88:17 graphs 101:14 177:20 212:16 grapples 135:2 grateful 182:1 gratified 42:11 gravity 293:7 great 20:5 38:12 66:12 115:9 170:18 176:7 182:2 190:13 192:7,12 205:14 205:15,18 222:9 242:16 246:10 280:8 318:16 322:7 344:5 greater 18:11 33:17 68:13 70:18 120:16 134:19,22 135:1,11 137:4 138:10 140:11 187:10,10 217:19 218:20 269:5 319:9,12 greatest 254:17 greek 152:18,18 152:19 green 23:5 81:8 82:12 84:20 90:13 104:16 105:3 124:2 149:7 153:9 275:1 grew 32:19 35:8 grey 228:14 gross 118:17 252:4 256:21 group 49:14,15 51:15 71:19 76:12 76:15 80:5 82:3 168:8 170:1 176:19 180:9 184:11 186:7 200:15 204:2
---	---	---	---

218:15 219:9 241:14 244:11 245:11 263:6 264:3 271:5 272:4 275:17 306:16 332:9 groups 49:14 65:7 81:11 104:17 225:22 240:20 242:7 245:12 266:20 grow 141:22 142:1 142:3 164:5,5,6,6 207:15 346:6 growing 246:5 340:17 grows 33:17 growth 119:22 141:16,22 166:11 177:21 199:15 206:18,20 207:15 285:6,10 327:3 gsk 176:20 180:9 guess 108:21 161:11 190:2,7 191:7 202:8 224:4 233:22 346:9 guidance 63:7 75:11 78:2 82:20 253:4 guide 225:11 guided 61:5 guidelines 122:6,7 guina 4:13 13:18 26:2,3,4 197:13 301:20 302:2 308:15 321:21 348:6 guy 34:20 guys 222:11 223:2 223:7 230:9 232:12 281:20 351:21	h haemophilus 260:3,4 half 59:18 71:16 251:15 256:16 hallmark 102:7 hamilton 225:14 hammering 301:7 hamper 100:7 hand 34:2 89:2 114:20 140:14 143:20 182:10 226:12 227:9 228:9,11 231:4 232:1 297:1 handle 122:22 160:22 265:8 handles 210:10 212:21 hands 232:16 233:9 hanging 80:17,19 hap 218:4 323:5 happen 37:9 48:19 215:10 329:12 354:3 happened 56:16 96:11 200:20 286:19 happening 166:22 167:1 324:15 343:21 happens 65:3 292:6 happy 179:17 191:10 258:8 264:7 283:2 301:16 hard 44:7 46:22 56:4,8 75:17 162:8 171:22 238:10 319:18 342:1 347:20 349:18	harder 50:6,7 harvard 8:5 189:19 191:5 harvest 229:20 harvested 226:7 hatch 48:6 hate 153:5 head 2:13 7:9 27:9 58:4,6 59:3 63:18 113:13 118:21 120:19 158:13,13 205:6 280:12 heads 167:6 heal 253:18,21 healing 253:19,21 256:1 322:19,21 323:1,4 heals 252:11 health 3:5 8:8 71:11 135:3 139:20,20 154:4 168:20 224:2 228:20 287:1 294:2,4 297:17 321:13 335:6 336:1,2 healthy 21:9 34:19 34:20 75:3 103:22 122:8,10 145:15 146:1 150:5 188:4 249:18 hear 16:14 17:21 23:3 25:5,6 26:3 38:11 45:6,8 57:10,12 133:14 138:12,14 181:11 188:16 189:16 205:17,18 280:20 283:2 301:11 312:18 322:13 heard 17:7 45:14 97:20 100:13 126:3 136:21 138:8 145:13	214:1 221:3 253:18 305:21 306:3 312:3,4 346:15 hearing 16:12 43:17 191:21 192:4 254:22 291:20 319:3 heart 34:15,18 35:13 86:14 90:18 113:17 116:18,22 121:21 124:13 228:6,15 246:19 286:18 heartmate 35:12 heavily 298:3,9 301:4 353:16 heavy 154:7 270:7 301:6 held 109:1 helen 3:9 9:10 28:4 45:7 54:22 54:22 helen's 135:7 hello 27:22 264:19 help 18:18 23:19 23:22 25:20 39:2 41:8,11,22 45:11 46:8 52:15 63:10 72:22 73:1 125:18 133:14,21 138:21 138:22 158:7 159:22 166:6 180:15 190:9 191:1 194:13 206:2 298:20 304:10 305:5,14 305:15 307:10 319:11 321:3 helped 99:4 123:13,14,17 264:4 helpful 32:4 46:6 47:6 56:9 73:5
---	--	---	--

129:13 133:17 200:1 201:9 312:18 319:4 326:7 355:10,15 helping 30:18 47:10 307:20 308:11 349:9 helps 76:18 126:9 126:10 127:13 163:20 164:8 helsinki 281:9 hematocrit 122:13 hematocrits 122:11 hematogenous 119:9 hematologically 176:2 hematology 113:21 hemodynamic 282:8 285:14 hemorrhage 89:10 herella 152:5 hereto 356:11 heterogeneous 289:16 heteroresistance 155:2 hewitt 4:18 10:8 27:13,13 79:22 80:10,14 94:12 hewitt's 23:4 80:5 202:12 hey 253:4 hi 26:8,11 27:4 180:19 hierarchy 193:19 high 41:3 60:2 65:16 68:6 77:18 107:6 142:22 147:2 152:9 159:1 166:3 169:17 173:21 180:13	220:5,15 236:12 250:14 260:10,12 267:3 275:15,18 276:17 279:14 284:11 285:1 288:9 289:18 292:10 293:4,17 296:19,19 317:9 342:16 351:21 354:12,16,21 higher 20:5 88:19 120:14 164:10 178:4 213:6,8 214:13 231:6,15 232:5 245:16 250:10 266:20 275:22 285:11,13 339:4 highest 88:7,14 114:14 232:4 271:11 293:8 highlight 223:3,9 224:7 227:13 233:14 316:10 highlighted 37:13 38:2,7,13,18 40:20 41:6 287:13 highlights 337:1 highly 48:20 59:13 68:21 112:15 114:11 126:12 142:5 178:11 186:11 188:1 226:11 286:1,11 291:1 hilton 1:11 hinge 268:3 histology 178:22 277:7 293:12 histopathology 123:6 245:21 253:16 256:22 327:5	historical 109:16 112:12,18 113:12 116:11 historically 297:11 history 82:11,16 84:20 85:13 88:4 89:6 113:15 118:13 228:8 hit 93:4 132:18 223:4 227:19 248:13 318:15,18 340:7 hits 51:8 hitting 56:3 hiv 3:20 hoard 171:16 hoffman 58:3 hold 244:17 259:9 holder 83:17 holding 348:17 holds 237:9,11 holes 247:18 hollow 77:14 220:2 339:22 home 32:10 36:1 167:20 honestly 44:16 honor 95:4 honored 264:8 hoover 7:22 176:14,16 hope 23:17,18 37:13 40:9 41:9 46:18 50:5 55:5 126:1 207:8 216:13 255:15 355:16 hoped 109:10 186:7 hopeful 42:12 hopefully 80:18 168:13 197:20 204:18	hoping 17:1 131:18 311:18 hopping 155:15 157:22 hospice 34:11 37:4 hospital 8:4 18:8 32:12 73:16,22 146:21 154:4 156:15 169:18 186:20 187:14,15 189:19 191:5 218:8 219:11,13 220:22 280:15 hospitalized 71:7 71:10 hospitals 287:17 host 148:4 158:8 162:11,12 164:8 164:11 169:14 170:2 197:4 210:9 210:9 212:20,20 221:21 229:21 233:18 276:6 281:17 304:4 305:7 322:18 345:14 346:14 351:4 353:10 hosts 141:13 hot 73:12 146:17 hotel 1:11 hour 86:22 87:7 87:10 101:17 213:2,13 251:15 268:16 269:13 271:4 279:21 hourly 101:11 hours 59:19 64:13 72:14,15 85:17 86:10,22 87:4,19 87:19,21,21 89:4 100:6 101:18 102:20 103:1 107:21 117:14,15 118:2,4 119:14
--	--	---	--

173:15,15 178:3,8 178:10 182:17 207:14,17 208:14 219:2 230:17,19 240:9 244:4 245:6 246:13 247:10 251:15 262:21 268:15 269:1,2,2 269:4,15 272:2,6 272:13,14 274:6,7 274:8,14 275:19 286:2 290:3,12 292:10,10,14 313:15,18,20 314:1 327:11,11 house 307:21 housing 124:9 hr 315:4 huge 130:18 132:9 165:21 187:18 258:22 262:6 274:17,19 288:12 290:1 293:18 316:11 333:4 341:13 human 16:5 21:7 40:10 47:19 81:6 89:14 90:4,8,12 90:15 91:1,2,8,14 91:15 92:17 100:19 103:22 111:9,11 115:8 121:18 127:3,7,12 129:3 130:17 132:16 133:4,10 136:4,8 141:20 150:14 154:2 158:10 179:2 186:21 189:3,5,8 189:9 192:16 201:10,11,15,20 202:13,17 203:1 203:11 221:4 238:20 247:1	249:18 254:21 258:3 259:2 261:9 266:6 303:6 318:2 319:13 322:6,12 328:17 329:1,2,5 331:18 334:20 348:10 349:13 350:6,7,8,14,18 350:21 351:9,10 351:17,20 352:3,4 352:4,8,16 353:2 353:20 humane 269:4 humanize 257:11 humanized 106:22 108:7,16 109:3 171:21 172:5 257:21 258:2 333:7 humans 20:14 21:17,21 22:3,4 91:6,10 93:3 98:4 98:9 108:2 111:18 111:21 116:12,15 126:18 128:20,22 129:3,17 130:15 145:20 159:17 161:11 178:20 188:18 213:18 253:19 254:10 257:13 265:22 283:21 284:3,12 292:6 293:9 295:2 295:4 317:7,8,17 323:2 330:3,4,14 341:6 343:6 350:20 351:8 352:3,18 humbling 133:2 humoral 113:9 162:19 hundreds 321:17 hung 192:13	hurdles 107:7 220:21 hutt 5:4 10:15 27:16,16 110:21 111:2,7 124:18 hypocapnia 277:22 278:1,2,2 hypoperfusion 278:12 hypothetical 17:19,21 49:4 50:12 hypoxemia 277:12 i icpd 217:20 icu 156:15 282:4 284:10,12,19,20 285:9,18,19 286:1 286:14 287:6 290:4 316:4,8,9 316:14 335:12 343:21 idea 23:1 46:4,6,9 48:5 54:2 125:11 131:8,11 201:21 226:18 244:15 252:22 259:13 320:11 321:15,16 330:6 337:2 355:2 ideal 30:4 291:1 293:19 328:1 ideally 93:12 ideas 39:6 45:12 56:17 57:3 138:9 253:8 307:19 identification 72:2 73:10,11 identified 15:15 17:16 19:1 32:20 117:7 347:7,9 identify 18:18 19:13 23:22 39:3 64:10 71:5 72:13 92:20 93:6 123:13	123:17 152:13 158:7,8 166:7 191:3 194:13 205:10 211:4 identifying 74:3 163:1 idiosyncrasies 172:13 idsa 31:20 idsc 296:2 ied 234:22 iffy 317:11 igg 277:19 279:9 ignorance 53:13 ii 35:12 iii 148:3 illness 285:1 illustrate 61:1 102:17 104:21 illustrated 103:4 illustration 129:12 image 153:9,10 207:12 images 153:7,16 226:2 imaginary 50:18 50:19 54:11,11 imagine 302:15 imipenem 68:20 imit 225:10 226:3 226:10 227:4 232:21 immediately 173:13 226:7 imminent 269:7 immunatory 284:1 immune 96:20 124:5 145:17 162:11,19 183:8,9 221:21 227:20 249:14,16,21,22 250:2 252:2 258:3
--	--	---	--

258:7 259:15 303:6 342:18 immunity 113:9 immunize 97:3 immunocompet... 178:14 223:14 227:5,10,18 immunocompro... 28:14 145:17 160:9,12 223:15 223:16 227:6 immunologic 113:6 163:13 immunology 2:12 5:18 205:5 256:22 immunomodulat... 233:19 immunosuppres... 187:22 immunosuppres... 188:13 immunotherapy 168:1 impact 88:17 121:19 123:21 132:9 179:11 190:13 206:3 210:6 211:17 212:7,22 214:3 impacting 122:14 impairment 71:13 imperative 91:1 imperfect 45:21 impermeability 142:8 implanted 35:13 113:17 116:17 121:3 implanting 121:13 implants 85:21 importance 32:6 42:7 60:13 216:4 281:7,10 287:14 294:16 349:7	important 10:12 17:11 18:20 19:17 23:5 30:17 31:16 39:8 41:3,4 42:10 44:4 58:21 66:8 72:3 74:3,9 75:2 78:19 79:2 84:14 91:21,22 92:6,11 92:20 93:17,19 101:7 111:5 127:4 137:5 139:12,16 139:19,21 149:22 150:19,21 151:11 155:18 158:7,8 162:14,20 163:15 163:17 164:16,20 165:1,19 170:8 174:21 190:11 195:1 197:14 198:5,16,19 213:15,16 214:2 215:5 216:7,15 237:13 239:16,17 282:9 283:13,14 291:17 292:2 293:3 295:5 302:7 307:10 312:12 316:9 323:8,11 332:3 336:4 347:8 347:9,9 348:7 importantly 31:9 34:2 42:2 52:13 141:19 142:5 145:11 146:18 207:7 233:2 impose 22:10 impossible 62:12 321:18 impractical 104:3 impress 101:8 198:18 impression 325:21 impressive 319:16	improve 98:17 138:21 206:7 233:7 improvement 106:14 107:3 109:8 327:11,12 327:12 335:9 inadequacies 38:19 inadequate 48:14 inaudible 34:6 41:7 54:16 59:7 190:15 199:2 288:17,19 292:18 292:19 316:15 326:18 inbred 123:20 146:1 incidence 65:16 73:2 187:10 inciting 318:6 inclined 220:10 include 22:11 24:18 28:13 62:15 95:21 101:12 103:6 182:3 192:22 206:15 225:15 265:12,13 305:8 333:22 included 83:4 100:19 343:2 includes 43:8 144:10 177:10 181:15 267:4,11 including 23:8 31:4,22 59:14 67:2 92:18 128:7 143:9,12,15 144:18,21 147:22 148:12 158:10 176:12,19 181:22 182:5 215:22 265:7 300:19 302:7 303:6 337:3	inclusion 41:10 297:2 inconsistencies 155:3 incorporate 211:7 240:10 incorporated 196:10 increase 54:19 73:1 102:3,5,8,19 103:3 109:7,11 116:22 118:10 119:15 136:13 137:1 139:7 182:15,18 217:17 220:3 231:4 232:2 247:10 257:16 266:4 277:15 278:10 282:19 286:3 290:14 292:21 increased 36:11 58:20 59:1 79:1 94:8 102:7 105:16 118:11 119:13 154:3 278:17,18 278:22 increases 87:2 94:4 increasing 121:15 208:9 308:11 335:7 incredible 355:3 incredibly 157:19 166:22 354:6 incremental 320:9 ind 82:6 83:13 296:16 305:15 independent 45:18 87:8,13 independently 102:11 indicate 60:19 70:1
---	---	---	--

indicated 24:20 51:9,10,10 81:13 83:21 indicates 60:13 231:11 278:11 indicating 208:15 indication 88:1 96:22 109:19 171:4 172:3 296:22 322:20 333:20 indications 23:7 40:16 55:5,6 129:3 169:7 170:12 306:2 indicator 101:15 122:22 228:18 individual 81:3 85:12 92:10 103:15 118:8 147:16 215:20 298:15 304:3 individualized 102:6 individually 298:14 individuals 103:22 145:15,18 229:2 induce 177:2 266:3 315:1 induced 272:10 278:5 318:15 industry 66:6 125:17 180:11 265:1 294:2,4,9 321:13 335:6 336:2 indwelling 124:1,6 ineffective 48:16 164:9 inexpensive 265:8 infeasible 140:9	infected 58:19 124:14 167:13 254:10 256:7 270:1 275:7 infection 12:14,19 15:16 16:3 18:2,7 19:14,17 20:13 23:20 24:15 30:16 32:18 33:10 34:13 35:5 36:10,12 37:3 38:16 40:13 41:10 52:15 61:7 69:8 71:6,18 76:22 90:5 92:19 98:14 103:9 124:1 127:18,21 132:22 133:3,20 134:20 135:1 136:3 137:17 138:1,2,13 138:16,22 139:4 140:10 141:1 145:5,15,21,22 146:5,9 147:9,17 148:18,22 149:21 149:22 150:7,9,20 150:20 155:13,14 158:6,18 159:1,4 159:8,10,18,21 160:8,10 167:11 170:13,21 171:2 171:12 172:11 173:7,10 174:15 174:16,18 175:15 175:16,19,21 176:3,18 177:15 178:3 179:10,12 180:22 181:8 182:2,3,7,13 183:3,11 190:1,5 190:14,19,21 195:4,18,20 196:7 196:17,19 197:6 199:5,21 200:22 200:22 205:20	206:2,6,15,16,22 207:13,14,19 208:2,8 209:18 210:13 213:22 214:2,3,3,4,14,17 215:7 216:16 217:1,22 218:5,18 219:18 220:21,22 221:2,5,8 222:6 223:11,12,12 224:3,11 226:15 227:5,15 228:12 229:10,14 230:17 231:1,2 232:7 234:10,15 235:2 237:4,18,19 238:3 238:20 239:5 241:6 249:6,12 250:14 252:8 255:5 256:11,17 257:3 259:12 260:7,12 265:2 267:7,13 268:16 268:16 269:2,4,13 269:15 271:4 272:11,13 274:7,8 274:9,14 275:19 281:3 290:13 309:4,10 312:9 313:18,21 314:1 316:2,3,5 317:21 318:6 319:7 320:12 324:19 337:3 338:5 343:7 343:15 346:19 infections 1:3 7:14 10:14 15:7,22 16:5 17:6 18:15 18:19 19:2 20:5 20:18 23:8 25:12 28:14,15 29:9 30:7,8 37:8,16,17 38:6,10 40:9 42:8 48:15 49:9 52:17	58:16,18 61:13 67:22 68:1 71:8 71:17 72:3,11 75:14,14 76:1,21 111:6 119:2 123:18,20 127:3,8 135:14 137:12 143:9 144:18 146:12,13,14,15 146:16,18,22 147:4,5,7,8,9,14 148:7,9,16,19,21 150:6,6,8,18 152:11 154:3,10 154:11,12 163:21 167:10 169:7,10 169:18,20,21 170:4 175:18 190:9,17 194:20 224:16 234:4 237:4,8 239:4 242:1,2 260:4 282:12 302:20 336:11 infectious 2:13 3:10,20 4:15 22:16,22 26:7 28:10 66:21 80:3 80:9 94:20 111:2 163:22 205:6 228:10 280:11 297:17 301:22 302:11,14 318:8 infective 6:19 15:10 28:16 46:11 67:2 105:10 181:12 214:18 infects 68:2 inferiority 18:6,12 18:20 38:20 40:22 52:21 55:12 64:7 75:15 78:4,5,8,13 infiltrates 89:10 90:19
---	--	---	--

infiltration 175:22	inhibitor 69:12,18	inoculation 173:8	institutes 287:1
inflammation	inhibitors 69:19	173:9 174:14	institutional
101:15 105:13,16	151:17	227:2 230:18	335:21
119:4,6,7,17	initial 52:4 62:21	244:18	instrument 251:5
164:14 326:17,21	82:20 98:13	inoculations	251:5,6,8
326:21,22	101:20 119:4	318:21	insults 249:9
inflammatory	123:17 148:21	inoculum 132:6	integrate 165:12
89:10 105:14	150:7 172:6 182:9	159:1 164:1	integrated 163:17
122:9 149:18	182:16 184:22	173:14 182:16	integrating 60:18
162:12 165:8	256:12 267:2	195:17,22 196:9	integrity 110:7
327:1	initially 35:6,10	224:20 226:5,17	186:16 188:3,13
influences 120:9	119:4 121:3	227:1 261:14	intended 24:14
influx 270:9	initiate 207:13	272:11 287:14	226:13 307:8
information 22:1	311:4	318:21 337:20,21	intensive 71:11,20
22:12 37:21 89:17	initiated 96:11	342:15,15,16	73:14 222:19
91:2 96:3 105:22	initiation 100:1	354:5,17	284:6 286:16
106:15 127:4	113:10	input 309:5	293:17
134:12 138:15	initiative 30:18	311:18	intention 184:22
167:8 302:6 309:3	31:20	inquiries 183:19	303:4
309:4 310:9,11	inject 159:13	insects 141:16	interact 141:13
311:7,8 319:4,17	248:17 251:10	insert 225:12	interacting 163:12
320:7 328:18	injected 266:2	inside 167:2	interaction 281:16
351:5,7	injecting 289:1	insights 132:22	interactions
informative 20:14	330:11	inspectors 110:8	221:20 345:15
134:2 136:14	injection 232:18	inspiratory 273:7	interacts 351:4
186:3	338:7,20	installation	interest 95:11
informed 62:16	injects 148:4	223:10	96:12 111:17
infrastructure	injury 146:7 249:9	instance 286:11	126:1 137:7 148:3
142:17	249:11,12 270:13	288:2,6 289:20	281:4 301:9
infrequent 16:1	271:1 272:10,19	318:13 321:6	311:19
infrequently 16:2	275:9 277:4	instances 351:10	interested 177:19
17:16	278:16,17,20	instant 53:14,14	180:5 185:13,14
infusion 273:18	279:3 315:1	instill 225:13	221:20 238:6
inhalation 113:13	317:17,20 318:9	317:10	259:5 301:13
inhalational 10:6	318:15,19 323:18	instillation 225:9	356:12 357:8
22:19 80:12 95:17	326:18 327:7	226:1,8,15	interesting 33:3
96:14 97:18 98:11	innate 145:17	instilled 225:18	44:13 53:20
98:15 103:9 104:3	249:16 259:15	226:6 230:16	135:18 141:7
111:10,11 128:9	342:18	232:19	157:5 160:15
inhaled 30:5 33:4	innovation 309:15	instilling 226:18	285:5 318:11
inhibit 173:21	innovative 309:1	317:12	319:2
inhibiting 164:13	inocula 354:21	institute 4:15 5:6	interestingly
inhibition 164:17	inoculating 245:4	7:15 10:16 12:21	147:7 149:19
165:3,9	251:9	27:17 111:3 234:5	

interests 28:13,15 interfere 165:8 interferes 54:3 interfering 165:8 interim 7:9 58:6 intermediate 230:13 231:8 233:6 internally 16:17 international 143:6,7 181:3 interpret 19:8 136:18 interpretable 136:20 137:3,20 329:6 interpretation 65:18 interrupt 291:18 interruption 143:21 165:5 intersection 331:2 interstitial 280:11 interval 132:17 208:13 intervals 208:12 intervene 103:15 116:8 132:10 intervention 93:13 98:19 100:22 106:5 107:11 intra 40:12 51:10 52:12 55:10,15 146:12 intranasal 145:22 173:8,9,11 224:14 224:20 232:20 244:18 intraperitoneal 159:14 intratracheal 225:3	intravenous 23:13 36:14 338:19 intravenously 266:2 intriguing 102:2 intrinsic 69:13,15 127:18 132:7 142:7 intrinsically 126:8 160:3 intro 236:7 introduce 27:21 43:4 224:12 225:1 introduced 46:7 206:14 introducing 209:19 227:3,14 introduction 9:6 15:3 58:10 62:9 124:20 280:20 introductions 26:1 introductory 9:6 15:3 intubate 225:10 intubated 33:1 225:9 272:22 291:15 292:7 313:12 intubation 177:4 188:5 286:4 289:15 invasion 158:11 invasive 266:18 268:8 273:14 invented 50:11 54:11 invest 340:3 investigate 326:1 investigated 60:8 105:19 investigation 284:6 316:11	investigator 7:13 94:18 investigators 293:19 303:13,18 304:8 305:12 306:17 307:14,16 308:12 investment 184:6 investments 95:13 invitation 28:22 58:11 205:15 222:8 invite 168:19 inviting 67:6 111:8 302:2 involve 171:19 203:6 involved 66:22 129:7 141:18 149:12 162:16 163:6,7,8 166:13 166:14 167:5 185:8,15 196:5 197:5 299:18 300:13 323:1 353:16 involvement 224:17 278:19 323:22 involves 131:2 involving 345:14 ip 175:21 232:17 306:10 iraq 235:7 iron 161:12 166:4 166:4 irrelevant 268:18 irrespective 262:7 283:6 295:4 irritant 159:21 irritation 35:3 isaacs 5:8 9:17 27:11,11 43:2 66:16,16,19,22	67:4,5 79:7 island 113:4 isoflurane 273:6 isolate 171:4 196:18,21 197:1 197:11 210:18 227:8,9 238:19 isolated 113:5 143:3 144:15 241:22 263:6 isolates 68:12,14 70:19 76:6,7 143:8,17 149:4,14 155:22 156:1 170:20 175:7,17 177:14,16 178:17 178:18 193:11 197:5,8 199:3 200:6 209:19,20 211:11 216:1,1,4 216:6 238:14 240:20 241:4,20 299:15 300:5,6,7 300:12,12 isotype 268:18 issue 16:2 38:13 52:8 64:11 65:4 68:14 130:1 169:22 174:21 236:13 298:12 339:8 issued 309:2 issues 32:11,14 37:14 38:2 129:9 150:2 189:14 items 223:5 iterations 110:1 iv 33:4
j			
j 257:20 jacket 261:17 jane 5:12 12:8 27:1			

jared 339:19	k	317:13	knew 98:11
jennifer 7:22	kaplan 88:5	killed 244:5,5	109:20,21 228:17
176:14	104:13 269:9	262:18,22	333:2
jid 57:3	keep 19:18 54:9	kill 164:19	knisely 5:12 12:8
joanna 4:8 11:10	123:7 137:18	210:2 250:14	27:1,1 204:16
26:17 141:1 169:3	155:9 234:12	343:20	221:18 234:1
job 251:14 264:5,6	240:14 251:11	kills 238:9	264:9 280:3,8,21
joe 202:11	258:2 261:13	kilo 258:16,16	291:18 295:11,14
johanson 288:18	278:8 286:4 292:2	331:17	336:6,18 350:2
294:18	296:6 306:10	kilograms 268:14	knock 239:3
john 4:4 7:4 9:15	313:15 314:17	kind 23:1 28:22	knocked 50:21
27:4,6 43:1 62:9	351:15	34:5 35:4,22 36:5	knocking 173:14
64:4,11 194:22	keeping 256:11	40:15 45:1 49:3	know 37:22 38:9
195:7 297:21	keeps 256:17	58:11 77:16 78:17	42:17 55:1 56:6
349:16	261:20	79:4 95:15,15	73:6 91:9 127:2
johnson 82:22,22	ken 280:1	96:6 97:12 98:5	129:15 136:3,8
join 28:8 125:8	kept 108:15	102:11 105:11	138:6 151:18
joining 27:19	keratitis 146:7	108:3 196:13	153:1 155:16
355:14	key 23:22 45:11	204:19 228:8,14	156:5,7,10 171:21
joint 64:17,21	73:10 76:16	237:21 241:1,2	176:6 186:16
66:6 267:12	155:19 195:5	242:9,20 247:4	187:11 189:1
jon 222:14	199:22 250:15	250:2 253:9 254:7	190:18 191:11
jones 262:20	337:1 339:8	255:10 256:10,11	192:7 193:8 194:1
joseph 7:19	347:14	259:13,17 261:12	199:9 200:12
journal 177:9	kg 247:11,21	261:16 283:8	201:4,7 202:9
jove 179:15	248:19,19 259:22	286:14 287:22	204:5 215:15
judith 4:18 10:8	260:1 266:2,6,8	291:5,14 294:6	228:18 247:1,2,2
79:22	266:10,11 269:16	298:1,2 299:2	249:13,16 253:7
judy 27:13 125:5	269:18,21 270:14	301:7 303:18	259:8 263:22
202:12	270:19 271:6,7	304:16,17 318:22	268:10 283:11
julie 5:4 10:15	272:6 315:4	321:7,15 332:15	287:20 300:22
27:16 110:21	kick 250:8	336:2,19,22 343:3	302:11 314:22
125:5	kidding 346:11	352:11	315:15 316:14
july 39:5 40:20	kidney 174:15	kinds 93:21 283:8	320:12 321:12
134:6	175:1,4 246:17	322:21 328:19	323:5,10,17
jump 129:13	278:15,16,16,20	330:1 340:10	328:11 330:1
junctions 347:11	323:17	kinetics 22:2	331:4 333:7,14
june 309:16	kidneys 257:12	59:19	339:9 341:2 347:3
310:21,22	276:1	kingdom 155:20	347:5,7,17 348:2
justifiable 65:9	kill 199:3,6 210:2	kitchen 236:2	348:2 351:20
justification 331:8	211:6 214:8 215:3	klebsiella 32:21	knowing 99:4
justify 55:13 78:8	217:19 220:13	33:13,18 240:12	knowingly 48:16
justifying 332:13	221:2 239:11,21	266:17 337:15	knowledge 53:14
	247:9 250:11	340:15	72:17 356:7

known 29:14 30:8 43:5 152:11 188:19 204:1 265:21 knows 152:17 kolobow 287:1 kpc 182:5 kraft 155:22 kylie 340:14	lactamases 69:20 70:3,8,11 169:14 212:11 lactate 272:18 278:10,10 279:16 lady 32:8 34:12 lagomorphs 265:11,16 laid 84:2 242:10 347:2 language 48:1,2 large 53:3 70:5 84:5 91:19 111:1 124:16 142:16,19 142:19,21 143:5 143:11 144:1 145:8 163:22 185:9 207:6 211:19 212:11 215:18 216:9 218:9 219:3 223:22 225:22 227:18 239:14 269:22 281:2 282:17,22 283:5 286:7 288:17 304:19 312:14 313:10 321:2,7 325:22 326:13 larger 120:13 312:15,16,21 319:15,21 320:19 322:5 329:11 331:9 larvae 144:19 160:19 laryngeal 32:8 laser 251:6 lasers 251:7 lasr 149:12 lastly 22:1,11 109:2 110:12 163:16 175:20	late 140:16 204:11 274:16 297:18 311:17 346:12 lately 308:11 lateral 54:14 laugh 119:19 laughter 152:8 162:6 259:19 339:6 346:10 349:15 350:12 launch 66:20 lavage 174:8 318:14 326:20 327:2,4,16 law 24:11 lawrenz 5:16 12:15 26:13,13 221:19 222:7 234:1 351:15 lay 191:19 layer 107:15,16 261:12 layout 260:22 261:1 ld50 113:13 114:2 114:7,9 116:2 120:10,17 ld90s 190:5 lead 65:10 67:8 88:19 94:8 135:1 161:2 176:18 194:10 203:3 267:2 leader 6:10 leadership 58:4 200:15 306:16 leading 58:15 71:13 95:19 105:5 248:14 274:10 324:9,10 leads 48:15 52:18 95:15 245:17 246:21 299:8 304:18	lean 46:3 learn 30:4 91:11 177:5 320:12 learned 9:19 10:5 25:8 79:16,20 80:11 81:7 119:18 121:2 127:10 220:17,18 281:6 320:16 learning 29:5 130:5 235:13 258:14 leave 78:14 127:22 232:12 233:22 leaves 252:16 led 41:22 left 34:18 35:12 88:22 101:10,16 115:11 117:19 149:5 182:10 207:12 208:15 210:15,17 212:14 214:7 217:15 219:19 220:8 222:16 227:9,11 228:11 231:4 232:3 235:19 246:16 252:7 255:11,13 256:6 290:14 342:22 legislation 289:20 length 285:22 286:3 288:4 lens 146:8 les 182:12 lesho's 262:19 lesion 318:3 lesions 115:3,4,6 115:10,14,15,17 115:20 123:7,20 lessons 9:19 10:5 25:8 79:16,19 80:11 81:7 119:18
l			
l 70:17,20 la 58:3 lab 154:17 157:21 160:21 162:18 180:16 203:11 266:14 279:20 281:10 287:10 294:6 label 39:13 55:21 77:1 83:19 labeled 297:4 labeling 22:11 24:17 47:21 labor 222:19 293:17 339:4 laboratories 96:1 181:10 laboratory 33:22 93:11 113:1 234:4 labs 152:13 181:2 181:3 214:11 283:8 294:11 305:20 lack 50:2 57:15 99:16 108:10 135:14 lacked 158:11 lacking 83:8 147:16 lacks 51:7 lactam 68:21 69:11,13,17 70:2 lactamase 69:12 69:18,19 151:17			

lethal 21:5,9 126:10 130:17 146:2,3,17 223:11 227:5 229:9 230:16 266:9	335:1 336:14 339:7 349:10 350:1	250:22 263:20 280:6	157:11,14 159:11 160:7,12 162:2 172:13 173:6 176:4 177:5 178:22 179:5 189:21 204:10 223:9,17 225:4,17 230:12 232:12 234:14 236:7 242:11 243:15 250:13 253:6 256:1,17 257:13 262:20 276:15 295:15 296:6 299:10 304:6 332:11 354:8
lethality 130:20 266:13	libraries 144:13 licensure 296:21 299:9	lined 55:18 lines 101:6 105:1 169:10 link 98:5 156:22 167:18 168:6 308:6 linked 166:19 links 99:13 304:16 lipid 149:18 157:14 lipopolysacchari... 149:15 liquid 300:21 list 30:20,22 31:7 67:20 123:11 135:8 142:13 239:4 241:3 263:18 283:3 305:1 listed 22:21 31:3,5 34:1 84:12 142:12 201:1 308:5 listen 45:12 listening 54:21 literally 234:16 240:9,18 250:22 341:15 literature 55:14 89:14 113:12 115:7 123:22 209:12 240:2,19 248:20 259:10 278:2 liters 273:7 litran 8:4 189:18 191:4 little 20:19 35:3 43:18 45:4,16 54:14 55:2 56:15 92:14 100:10 125:3,22 129:5 137:14 151:8,21	live 116:13 141:15 186:19 259:16 liver 114:22 115:17,20 119:10 119:15,17 246:19 272:19 276:2 278:21 323:21 living 199:14 load 229:13 231:6 loads 231:13,15 lobe 290:9 292:19 293:7,7 lobes 246:7,12 290:10,20 293:11 293:13 local 35:2,5,9 119:3 326:21 localized 147:8 150:8 256:12 261:14 location 120:5 log 182:18 207:15 210:2 211:6 214:8 215:3 217:18 220:13 221:2 244:20 248:10 250:10 256:15,16 344:4
letter 152:6 310:19 letters 82:3 152:18 310:20 leukocyte 352:12 352:22 leukopenic 227:11 233:16 level 68:6 75:20 109:1 132:19 149:6 162:9 192:6 208:3 213:11 262:6 278:10,14 284:9,11 314:14 352:17 levels 101:22 102:9 105:4 164:11 213:4,10 228:6 236:12 245:14 276:18 317:10 leveraged 185:1 levofloxacin 22:17 22:19 23:2,6,13 23:14 33:12 82:18 82:22 83:7,15 106:7,8 If 101:22 102:8 103:4 li 6:4 13:11 27:21 27:22 280:6,7,8 280:19,22 292:1 295:13 312:14 313:3,6,10 314:11 315:16,21 318:10 321:5 325:18 326:15 333:3	life 21:4 24:15 49:4 59:18 146:18 184:6 light 88:13 153:17 lighter 178:1 likelihood 20:5 136:13 137:2 139:7 220:3,5,15 319:12 350:19 limit 18:14 231:11 limitation 179:13 285:17,20 limitations 17:20 30:9 57:13 104:9 139:13 283:18 284:4,5 289:10 293:17 294:12 limited 19:20 24:5 24:12,16,18,20 40:3,17 41:21 48:3 50:16 55:22 56:14,21 61:9 62:13 68:15 75:2 85:14 99:15 101:3 135:10 139:18 193:20 194:14 196:13 256:17 283:12 307:16 326:1 limiting 159:10 limits 56:7 line 27:22 31:11 31:15,19 36:9 81:1 86:3,4 103:5 104:16,17,18 105:3 107:13 126:15 165:11 193:2 231:11	list 30:20,22 31:7 67:20 123:11 135:8 142:13 239:4 241:3 263:18 283:3 305:1 listed 22:21 31:3,5 34:1 84:12 142:12 201:1 308:5 listen 45:12 listening 54:21 literally 234:16 240:9,18 250:22 341:15 literature 55:14 89:14 113:12 115:7 123:22 209:12 240:2,19 248:20 259:10 278:2 liters 273:7 litran 8:4 189:18 191:4 little 20:19 35:3 43:18 45:4,16 54:14 55:2 56:15 92:14 100:10 125:3,22 129:5 137:14 151:8,21	

logic 332:16	257:10 258:7	257:18,21 260:4	229:4 236:17,17
logistic 66:4	266:9 269:19	262:2,14 294:11	237:10,14 240:16
logistically 320:19	275:4,5,6,20	298:8,8,9 299:5,7	247:2 249:22
logistics 62:15	276:8,19 278:1,14	299:8,16,20,21	258:14 259:17
logs 248:12	279:13,13 282:21	300:1,5 301:2,4	261:9,22 263:20
long 30:2 78:20	283:16 297:12	304:16,20 306:18	264:6 275:5 288:2
91:12 107:16	298:18 301:5	319:22 322:18	296:4 298:2,3
109:5 116:7 128:6	304:22 305:5	336:20 339:21	301:10 302:3
155:19,19 185:8	314:6 319:6 322:5	340:8 343:16	316:4,15 317:22
188:19 191:20,22	322:21 323:11,16	344:1 345:5	319:19 330:12,15
199:20 217:1	323:18,18,19	347:17	330:18 331:8,19
221:12 223:20	324:8 325:11	looks 44:13 51:3	336:9 338:21
265:11 282:9	326:17 327:6,10	51:16 52:6 133:5	339:13,22 340:1
284:7 307:4	327:12,13 329:19	153:7,9 179:6	344:21 346:2
313:21 340:9	331:12 346:1	213:3 243:3	348:2,2 351:16
343:7 355:7	348:16 351:15,21	255:12 260:22	354:9,17
longer 36:21	352:19	261:9,9 262:9	lots 191:17 198:6
98:21 139:2	looked 36:12	279:15,16 296:8	200:8,8 252:19,21
156:15 314:6,18	82:11 101:12	loosely 299:4	260:15,15 302:16
340:3	102:1 104:22	lose 121:9 149:10	302:16 304:7
longitudinal 149:3	105:11,13 108:14	154:21 186:16	307:21 308:1
look 40:6 41:2	109:4 124:12	244:20 249:21	louie 218:15
44:17 71:18 75:10	157:5 218:2 232:1	losing 224:4	louis 2:19
77:6 84:4 88:11	232:18 241:4	loss 114:22 118:2	louisville 5:19
126:13 130:22	246:19 247:3,16	149:19,21 183:5	12:16 26:14
135:17 136:8	257:14 278:21	188:3,13 249:10	222:12
152:2 153:7 162:4	289:5 300:14	lost 116:20	love 134:2 161:22
165:13,15 166:15	333:2 340:21	lot 16:12,14 17:16	180:11 244:9
176:8 179:9,9,16	351:14	23:3 29:5 30:5	lovelace 5:6 10:15
187:8 192:21	looking 29:5 31:18	31:3,14 37:13	27:16 111:3
197:14 212:7	40:19 47:11 69:22	38:2 46:13 78:11	loves 152:22
214:2,16 217:21	71:19 92:14	84:9 89:19 96:12	low 52:9 61:19
217:22 219:17,17	102:10 107:12,12	97:7 100:8 104:4	80:19 149:6 190:3
219:19 222:22	107:18 123:6	110:5 126:4,9,10	195:17 236:9
229:5,8,13,15,20	136:3 138:18	126:17 132:19	245:3 246:9 250:7
229:21 230:15	145:3,4 157:13	136:11 152:15	260:11 272:5
231:16 232:14,22	162:22 165:16	155:2 156:8	273:10 337:20,21
237:9 238:11	175:4,4,5,14,14	159:16 161:6	342:14 343:4
239:1 241:9,19	197:8 199:7	171:20 172:8	348:8
242:3,14,22	206:12 221:1	174:2 177:15	lower 34:2 61:13
245:21 248:8	223:12 229:18	185:8 189:6 191:1	85:18 86:4,5
252:1,4 254:2,5	240:20,22 241:1	202:9 203:21	195:22 196:8
254:12 255:16	242:13 247:13	204:9 223:13	207:2 215:14
256:6,8 257:5,7,7	255:17 256:4	224:14 227:3	218:9 224:22

227:16 267:8 270:19 271:9 272:11 293:7 303:14 319:1 lowering 258:12 318:8 lowest 80:17 114:19 211:12 232:4 269:16 271:6 lpad 41:19 48:1 139:15 194:12 lps 148:1 149:16 161:21,22 162:4 162:10 163:3,20 227:21 266:1,2,12 317:7,13 330:14 lpxc 164:13,17 165:3,9 luck 44:9 54:10 luckily 157:7 lucky 197:7 luminescent 145:1 luna's 290:1 lunch 11:21 25:13 168:13 204:11,13 204:16 234:13 lung 50:21,22 51:11 59:17 68:3 75:15 76:20 89:7 89:10 90:18,20 115:9,15 120:15 120:21 147:7 148:22 149:1 159:20 173:2,3,13 173:21 174:1,4 177:3 182:7,13 183:11 187:16 190:1 191:16 196:1 206:15 214:1,5,11,19 218:14 220:13 223:11 224:11 226:13 227:8	230:15,15,21 238:2 245:14,21 245:22 246:5,7,15 248:15 257:2 269:20,22 270:4,5 270:11,13,19 271:1,9,10 272:5 272:10,11 274:15 274:17,18 275:4,9 277:4 315:1 317:17,20 318:14 318:15 323:7 327:13,14 341:21 342:7,10 343:10 343:15 344:11 353:18 lungs 40:12 115:3 118:21 178:2,7 224:13 226:5,7,9 226:14,19 227:19 229:14,20 231:13 232:11,19 233:1 244:22 269:19,22 270:2,18 271:13 274:17,19 275:1,3 275:4,5,6,7,20 277:2 290:19 292:8,18,20 323:9 326:16,18 327:3 343:19 lymph 119:8,10 lymphatic 119:6 lymphocyte 101:13 lynn 8:6 180:17,19	macaque 112:16 macaques 112:22 116:12 machine 33:2 macrophage 119:9 macrophages 163:14 magnesium 163:15 main 169:8 281:1 282:5 290:21 295:7 311:11 312:2 326:19 327:21 mainland 113:2 maintain 186:11 maira 8:4 189:18 189:19 191:4,4 major 21:22 79:12 193:9 241:12 242:12 268:11 285:21 majority 68:16 88:16 89:9 289:6 294:10 making 16:3 149:15,16 159:9 186:2 230:11 236:21 256:2 340:18 malaise 115:1 male 114:2 mammalian 144:17,18 160:14 160:16 man 37:3 manage 234:4 managed 35:9 42:1 62:19 64:12 290:4 management 58:1 110:4 280:11 314:21	manager 308:10 manipulation 283:14 manipulations 331:11 manner 24:19 77:16 manually 144:7 manufacture 305:12 manuscript 156:4 177:10 mapping 242:20 242:21 243:3 march 1:7 234:17 309:11,16 310:14 357:13 margin 18:12 52:21 78:8,13 108:18,18 marginal 106:20 133:22 marginally 133:18 margins 55:13,16 331:9 mark 151:13 167:17 marked 117:21 marker 156:21 277:12 278:16 290:16 327:14 markers 239:3 272:19 279:14 322:21 323:4,10 323:13,20 325:7 327:1 333:17 market 71:1 209:6 marks 91:8 marra 199:17,17 200:17 201:3,16 married 34:21 marrow 119:10 maryland 234:7 356:19
	m		
	m.d. 2:10,16 3:9 3:14 4:4 5:8 6:4 6:13,18 7:4 9:7,10 9:15,17 10:17 11:6,7,13 12:7,12 13:11 m.p.h. 3:14 4:4 6:18 9:7 10:17		

massive 53:12 196:20 249:10 270:9 278:10	89:1,2 131:1,8 132:10 135:10,22 137:21 139:10 190:18 194:1 202:19 203:1,8 211:12 216:17 219:3 220:12 229:7 232:3 240:14 244:11 315:12 320:11,17 322:17 323:7 328:15 331:10 332:7 336:8 341:7 343:18,20 347:2,4 347:22 354:12	mechanically 146:22 272:4 290:3 291:15 292:6	5:19 6:6,14 8:7 28:6,12,13 58:1 61:5,6 65:11 184:1,4 205:5 222:16 280:10,15 284:6 316:1
master 92:22 300:18	match 132:16 228:10	mechanism 21:14 41:19 59:10,11 61:11 99:4 267:11 270:21 293:16 339:12	medicines 58:22
matched 268:18 289:22	material 119:21 187:14 299:14	mechanisms 97:12 161:12 176:12 203:22 212:8 216:2 284:15 291:11 295:8 303:13 304:15	medimmune 267:17,20 280:1
materials 25:1	math 49:21	medi3902 267:20 268:10,17 269:16 270:21 271:11 272:3 274:13 275:6,8,16 276:1 276:4,16 279:12	medium 186:17
mathematical 52:8	mathematician 209:1	media 199:15	medtronic 296:1
matrix 193:15 322:22	means 49:21 120:15 121:7 145:14 152:20 236:15,18	medial 293:7	meet 72:8 108:13 300:4 310:17
matt 26:13 239:18	meant 156:8,17 192:15 221:5	median 211:12	meeting 16:13 23:18 67:6 83:2 105:10 129:19 141:7 168:15,18 185:20 236:18 355:21
matter 81:11 191:13 257:3 332:22	measure 113:17 116:17 118:9 172:7 174:5,5 175:2 229:5 248:9 251:4,7,7 256:14 257:2 270:12 272:17 273:16 285:5 315:10,14 327:2	mediated 98:12 113:9 225:9	megabases 142:20
matthew 5:16 12:15 221:19	measured 86:18 87:16 245:1 315:9 324:1 333:11	medical 2:11,19 2:20 5:9 7:5 8:5 9:10 26:20 27:6 27:12 28:5,11 65:9 67:18 72:9 75:11 94:16 96:15 96:17 100:21 103:15 155:21 162:1 184:18 189:20 191:5 200:20 205:5 294:3 302:8	megabytes 84:5
mature 297:13	measurement 155:3 250:5 273:22	medically 63:20	meier 88:5 104:13 269:9
mauritus 113:4	measures 293:20	medication 62:5 62:17	meisel 8:6
max 195:15	measuring 121:20	medications 316:5	meister 6:9 10:9 27:14,14 94:13,14 94:17 95:1,2 110:20
maximal 172:2 218:19	mechanical 156:12 284:7 285:22 288:4 289:2 293:2 295:6 314:9	medicine 2:11,17 3:11,12,21 5:17	melbourne 143:4
mbio 167:17			melinta 199:17
mcg 70:16 230:11 230:14 266:8,10			member 58:3 251:9 296:13
mcm 109:14			members 25:22 27:18 264:4 311:18 312:19 330:21 355:8
mcmi 110:15			membership 298:10
mcr 29:17 182:6			membrane 59:9 142:8,8 157:10,15 161:13 167:7
md 1:15			memorize 162:2
mdr 53:17 58:20 61:7 65:16,21 182:4 183:1,15 222:5 238:21			meninges 105:14
mdrs 61:21			
mean 33:20 62:7 76:3 85:3 88:22			

meningitis 154:12	269:16,18,21	microbiological	204:9 316:19
mental 46:5,9 47:7	270:14,19 271:6,7	44:5	319:14 320:2
191:7	miami 322:17	microbiologist	330:7 333:12,15
mention 30:9	mic 60:20 70:20	196:12 287:17	333:19 334:4,8,12
112:3,7 222:20	154:17 177:17	microbiology 2:12	334:15,20 337:4
261:22 268:5	206:11 208:21,22	2:18 5:18 6:14	343:12 344:20
297:22 306:11	208:22 209:3,9,9	26:7 72:13 77:11	348:19 352:1
mentioned 15:21	209:9,20 210:16	80:3 113:22	milliliter 290:8,9
39:15 41:19 77:21	211:5,18,21 212:2	152:12 158:16	milliliters 290:11
84:8 124:15	212:6 213:3,12,13	205:5 222:15	292:9,10
130:14 142:11	214:7 215:2 217:5	301:22 302:10	millimeter 260:17
163:3 169:16	217:18,19 218:18	microbiome 61:12	260:19,19
210:5 240:7	218:19,19 230:10	191:2 251:22	million 184:16,17
242:18 257:19	247:8	257:8 262:1	185:1 265:6 310:7
262:17 313:11	mic90 70:15,16	microliters 225:14	mima 152:4
338:22 344:14	mice 131:7 158:21	225:15 324:5	mimic 47:19
mentors 286:22	159:3 160:2,5,12	microns 114:5	100:15,22 108:3
merck 66:22	164:13,19 172:21	120:12,13	110:1 192:15
merit 310:16	172:22 173:3	microorganisms	206:16 329:17
merits 312:5	174:11,12 177:12	189:2	mimicked 100:18
meropenem 36:18	179:9 190:15	microphone	mind 16:11,14
64:6 218:15,22	213:17 214:22	189:16 200:17	19:18 123:7
230:4,12 231:7,9	215:8,13 216:21	microscopic	137:18 151:18
232:2,6 233:5,9	216:22 221:2,6,12	118:18	155:5,9 161:10
message 17:10	227:18 244:8	microscopically	172:15 286:11,13
46:1 63:9	251:15,16,18	90:16	287:16 326:2
messy 133:5	253:18,21 257:12	microscopy 153:8	335:17 351:15
met 21:14	257:19,20,22	153:8	mine 222:14
metabolism 166:4	258:2 259:15	mics 45:15 218:2	mini 132:17
166:5	260:1,1 265:9,13	230:6	258:17
metadata 143:11	266:7,10,22 268:6	middle 101:14	minimal 141:22
201:1	282:1,20 283:10	246:4	172:2
metallo 32:21	283:20 285:2	miesel 180:17,19	minimize 139:6
metalloproteina...	316:8,13 321:15	180:19	minimized 129:1
322:22	321:19,19 329:16	migraines 48:14	minimizing 73:4
method 223:10	331:14 335:20	mild 76:11 87:10	minimum 173:15
225:2,8,9,21	340:21 342:19	325:5	182:19
226:1,10 292:17	343:5	milestone 294:18	minocycline 33:5
methods 91:18	michael 1:19	military 241:4,9	minor 241:13
255:7	356:2,17	miller 6:13 11:6	242:11
mg 70:17,20	microbe 51:18	26:21,21 140:21	minus 117:14
247:11,21 248:19	141:12 144:9	151:1 185:20	minute 28:19
248:19 259:22	microbial 234:8	186:1 193:5	225:21 269:6
260:1 266:11		198:21 202:19	273:8 295:16

minutes 77:21	125:7 126:11	264:15,18 267:4,5	18:2 20:12 23:3
79:8 140:16 169:1	127:11,13,21	267:6,12,13,14,18	23:20 24:1 39:9
176:13 226:14	128:19 130:17	267:19 268:12,13	39:10 40:2,2
230:1 281:1	131:11 132:9	270:22 271:8,19	41:17,17 47:8,18
311:16,17	133:2,21 138:1	271:21 272:1,9	60:10 77:12,14
miracle 54:9	150:22 155:8	273:20 281:21	80:7,12 85:2
mirrored 90:10	160:5,6,8 161:16	282:5,14 284:9	89:13 90:20 94:2
misconception	170:6,22 171:5	285:16 286:5,6,14	94:20 96:4 98:3
152:16	172:3,14 173:2,3	288:15,20,22	99:11 109:17
misconceptions	173:13 174:2,4,13	289:8,10,22 290:2	110:1 111:1 126:5
153:15	175:8 176:18,22	290:2,21 291:8	126:7,9,13,14,19
missing 240:16	177:10,13,17	293:6,8,15 294:18	127:11,18 129:11
mission 296:14	178:10,11 179:1	294:20,21 295:7	129:15,20 132:2,3
310:16	179:14,20 180:3,5	298:16 299:11,17	132:4,22 133:8,15
mitigate 139:16	182:10,13 183:4	299:21 301:1	133:20 134:12,15
mitt 64:7	183:15 186:5	309:9 310:4 312:6	134:20 135:1
mix 248:1	188:18 190:17	312:6 313:4,7,10	136:3 137:16
mixed 137:12	191:7 192:15	315:2,8,11 316:13	138:2,12,15,22
175:17 273:22	194:6 199:1,5	317:2,11,11,15	139:3 140:10
ml 70:16 230:11	204:14 205:12	318:19 319:8,9	144:18 145:4,20
230:14 272:6	206:7 208:8,22	321:3 322:5,6,10	147:17 149:20
275:14 290:7	210:13 211:2	322:15 325:8	150:4 155:18
315:4	213:1,5,20 214:4	326:13,15,19	158:6,12,17,18,21
mls 122:4	217:16 218:14,16	330:16 333:6	160:7,10,11,14
mlst 241:17	219:18 220:13	337:7,7,8,10,11	161:2 166:2 169:2
mmhg 273:12	221:2 222:3,6,11	337:12,13,19,20	170:3,7,10,15,16
mobile 155:15	222:20 223:2,5,16	337:21 338:12,17	171:3,17 172:16
157:22	223:21 224:3,9,10	338:17,18 339:1,2	172:16,17 175:19
modality 315:20	224:11,15 225:1,3	339:11,13,20	180:1,6,8,10,14
model 9:20 10:13	225:4 227:3,4,10	340:13 342:7,11	180:15,22 181:8
12:5,10,14 13:5	227:11,12 228:2	342:13 343:3,14	181:18,20,21
21:19 25:9,14	229:5 230:3	343:15,17 344:10	182:3,7,8,14
46:10 47:9 60:9	232:13 233:2,12	344:11 345:9,14	183:1,4,6,7,11,13
79:17,20 80:15	233:16 237:15,17	346:19,20 348:13	186:14 188:9
81:5,6,8 82:5 84:2	237:20,20 238:2,5	350:7,9,22 352:9	189:5,6,22 190:1
84:21,22 88:20	239:7,8,16 240:1	352:22 353:3,8	190:21 192:9,20
89:4 91:13 92:18	240:22 243:11,14	354:14 355:2	192:22 193:4,16
92:19 93:10,10,10	243:21 244:7,9,14	modeled 51:13,14	195:5,6,7,14
95:20 99:1 100:1	244:16,17 246:11	51:15 65:7	196:1,1,8 197:15
100:18 101:20	248:5,15,16	modeling 60:18	197:16,19,21,22
104:8 106:16	250:16 255:16,21	74:19 77:19 99:6	198:2,4,10,12
108:13 110:2	256:19,20 257:3,9	326:5	199:11,21 200:9
111:6,9,11,11	258:8,11 259:6,11	models 1:3 10:6	202:9,16,17,22,22
112:5,7 120:2	262:8 263:14	12:18 13:9 15:6	203:3,5 204:21

205:1,20 206:2,4 206:13,16,20 207:7,9,16 208:2 209:12,18 211:8 211:15 214:4,15 214:17 215:18 216:14,19 217:12 218:13 220:19,21 221:5,15,22 234:9 236:5 237:18,19 239:6,9,20,22 243:17 248:20 258:12 263:5,10 263:16,21 264:21 265:2 266:19,21 267:2,8,18 268:8 280:18 281:2,3,14 281:14,22 282:12 282:17,18,22 283:5,8,10,18 284:7 285:2 287:9 287:11 288:16 289:21 294:13,17 294:17 301:2 302:8,16 304:10 305:9 306:1,5,6 309:3,6,9 310:6 312:3,8,10,15,16 312:17,20,21 316:22 317:6,6,12 318:11 319:6,7,15 319:20,21 320:2,7 320:11,14,14,15 320:18 321:1,7,20 322:1 324:1,15,17 325:17,22 326:4 326:16 327:19 328:7,20,21 329:11 330:8,9,10 330:15,17,19 338:10,11,20 339:21 340:1,4,19 340:21 341:19,20 342:8,8 343:9	344:18,22 345:4,7 346:1,8,13 348:11 348:20,21 350:14 350:17 351:13 354:7 moderate 325:4 moderated 11:18 14:5 185:22 311:13 modern 89:18 modification 162:10 modifying 163:9 modulating 164:14 modulatory 183:10 module 84:11,15 molecular 2:17 molecule 44:13 59:6,13 61:1 147:20 162:4 235:21 253:6 267:20 268:5 molecules 147:21 175:10 232:18 molten 177:3 moment 301:15 304:6 money 53:18,20 54:2 193:20 201:6 336:4 339:10 monitor 73:7 85:22 122:11 224:8 228:5,6 229:3 230:20 monitored 85:13 118:1 269:1 272:12 286:19 monitoring 145:2 349:8 monkey 81:8 84:20 120:8	monkeypox 131:7 197:21 monkeys 23:5 82:12 90:13 113:8 116:15 117:17 118:15 122:1 123:19 131:7 352:19,19 353:2 monoclonal 22:20 54:12 96:20 97:16 97:17 99:5 104:22 105:7 106:1,12 236:1 255:17 264:16 267:17 monoclonals 238:8 monocyte 277:10 monocytes 277:9 monoinfected 261:20 monotherapies 233:3 monotherapy 63:12 65:12 104:16 month 35:7 63:2 78:18 83:16 months 34:22 36:1 94:3 304:21 morbidities 74:9 morbidity 22:1 147:6 228:18 229:3 268:11 moribund 122:18 122:19 morning 15:4 17:22 25:3 27:2 27:11 28:4 71:21 74:22 186:2 306:3 morphine 249:11 249:20,20 morphological 265:14	morphology 153:14 mortality 23:14 49:15,16 58:21 61:19 68:6,8 75:17 76:12,14 85:4,11 96:15 147:2,6 154:3,6 236:12 268:10 288:8,9 299:15,20 300:2 moth 144:19 160:15,21 mother 127:20 motility 161:7 242:18,19 243:4 mouse 12:14,18 60:9 146:1,3 158:19 159:9,11 174:2,13 190:10 190:21 199:2 201:5,8,10,11,13 201:17,21 205:19 207:12 213:1,7 215:9 216:14,18 217:3,6,16 218:14 220:18 221:4 222:3,6 225:21 228:7 232:13 234:9 237:19 249:4 251:3 257:18,20 258:9 268:8 271:16 312:5 316:22 317:2 320:7 322:1 324:3 338:19 342:10 343:8 344:3,11 345:13 353:1,18,19 mousepox 131:7 move 42:19 45:11 79:10 101:5 135:12 138:5 151:1 186:20
--	---	--	--

200:10 201:20 212:20 220:3 248:16 258:10 264:2,10 308:16 311:21 336:18 337:2 338:10,11 342:2 351:17,19 moved 42:5 moves 153:18,18 153:19,20 moving 25:20 43:8 97:11 107:5 130:2 203:11 211:5 232:3 317:5 320:17 336:20 344:5 moxifloxacin 22:17 83:21 mri 7:21 350:4 mrsa 214:4 337:11 352:13 mssa 36:4 mucin 159:15 176:1 mucociliary 120:16 mucoïd 149:9 mucosal 120:21 145:19 multi 264:5 292:11 335:21 multidisciplinary 205:10 multidrug 17:7 19:15 29:19 30:8 32:20 33:19 68:14 68:17 70:14 72:6 72:9,11,14,20 75:12 76:1,5,7 135:8 169:21 184:19 230:9 288:8 336:5 multifocal 115:12	multifunctional 267:21 multiple 39:16 40:2 41:10 46:13 55:19 94:18 98:3 118:20 123:14 173:18,19 181:6 195:8 202:16 224:1,8 226:21 260:14 268:7 278:5,6,7 murepavadin 59:7 60:5,12 61:4 64:4 64:21 65:11 murine 166:2 206:15 237:17 263:10 muscle 254:8,14 254:19 mutant 143:2 144:13 340:9 mutants 144:22 147:15 354:4,19 mutate 149:11 mutation 171:10 mutations 150:13 150:14 mute 43:17 291:19 muted 313:9 muting 16:11,14 myriad 144:21 mystery 152:15 n n 2:1 3:1 4:1 5:1 6:1 7:1 8:1 9:1,1 10:1,1 11:1,1 12:1 12:1 13:1,1 14:1,1 15:1 244:11 naïve 103:22 nambiar 6:18 9:7 12:7 15:4,9 27:18 28:2,7 37:13 38:1 38:13,18 39:15 40:20 41:19 42:16	43:15,20 57:18 66:12 79:7,18 94:12 110:20 124:18 140:15 295:20 301:18 308:15 311:14 327:20 329:21 330:20 353:12 355:6 name 26:3 152:4,5 308:9 naming 161:5 narrow 38:3 40:16 44:1,3,3,5,8,22 57:5,5,7 303:7 narrowed 36:6 nasal 90:18 119:2 nasty 32:16 252:8 255:9 256:7,8 national 4:15 286:22 297:2 302:19 natural 82:11,15 84:19 85:13 88:4 89:6 113:15 118:13 228:8 353:6,7 naturally 128:16 nature 127:20 128:1 187:6 nda 77:6 83:17 219:22 220:6 ndm 171:9 182:5 near 108:17 109:5 109:9 218:19 219:4 neat 102:11 nebulizers 232:22 necessarily 41:4 113:7 119:20 176:7 241:16 312:16 321:2 344:18	necessary 104:12 315:5 necrosis 275:5,7 necrotic 256:10 274:19 necrotizing 115:3 119:17 need 16:7,21 18:14 19:10 21:13 22:7 24:16 33:1 38:9 44:6,18,21 44:22 45:8,18 52:4,5,22 53:1 63:2 64:11 67:19 70:3 71:13 72:9 75:11 76:17 77:18 78:7 79:12 84:21 85:1 90:4 91:12 91:18 93:2,6,9 96:17 100:18 122:10 127:20 133:8 134:19 150:3,4 156:11,12 167:3,6 170:11 171:7,14,16,19 172:7 192:8 193:12 201:16 205:2 209:1,17 211:7 213:12,13 221:10 266:8,11 267:3 281:2 283:7 285:2 287:12 288:10,12 293:18 300:4 307:18 312:8,13 314:13 318:18,20 321:12 328:9 330:18 336:12,17,20 337:1 340:8 344:5 349:1 350:8 354:16,18 355:17 355:18 needed 22:9 31:8 41:21 105:19
--	---	---	--

173:5 212:2 213:5 214:7,9 235:7,8 314:6,17 needing 33:17 needle 225:13 needs 48:22 58:22 64:9,14 74:16 78:20 96:7,9 124:19 172:5 213:19 311:22 326:1 328:8 332:12 336:10 345:3,10 346:18 negative 29:19 30:7 32:20 35:8 59:9 71:7 278:3 negatives 32:1 182:5 neighborhood 130:21 neither 85:8 356:7 357:6 neonatal 154:10 neosporin 262:12 network 181:3 298:6,6,10,13 305:18 306:17 networks 41:8 neurologic 34:9 neutral 316:20 neutropenia 190:19 192:14,14 192:16 195:12,13 206:20 227:15 245:3 248:17,21 249:9 250:1 263:11 276:20,21 276:21 277:5 342:17 neutropenic 60:9 146:3 159:3,7,9 173:1,2,5 183:11 188:1 190:17 206:18 221:9	227:11 353:18 neutrophil 101:13 276:22 neutrophils 118:11 195:15 221:10 249:19 276:19,19 277:3,6 352:16,17 never 48:16 85:19 91:9 238:3 265:10 341:11 348:14 353:22 nevertheless 61:17 new 19:21 21:2 28:16 30:14 31:7 34:3 44:9 48:7,18 49:6 58:22 67:7 67:19 72:8 84:10 99:21 101:9 103:12 104:1,15 106:15 107:13 112:4,9 135:12 142:14 170:3,6,19 171:13 175:9 186:14 216:10 222:22 236:21 247:17 252:18 265:10 268:13 281:18,19 283:4 291:2 302:21 303:1,4 306:5,14 306:20,21 309:21 327:10 335:11,22 336:12 337:11 news 125:12 ng 266:2,6 nhp 298:16 ni 56:17 331:9 niaid 4:16,20 5:14 7:19 10:8 13:18 26:7 27:1,13 80:4 82:6 83:11,18 104:4 111:13	125:10,13 222:21 296:16 302:1,11 302:18 304:22 305:1,2 307:11 308:4 nice 86:8 192:3 218:17 225:17 229:11 232:2 242:3 250:13 255:4 280:20 319:17 329:13,15 340:22 341:22 342:8 nicely 217:21 niche 338:3 niches 141:12 159:20 nih 4:15,20 5:14 13:18 27:1 82:3 200:14 205:8 265:1 295:22 296:16 302:1,11 307:17 nitrate 142:4 257:10 nitrogen 186:19 300:21 nl 102:5 nodes 119:8,11 noise 16:12,15 86:11 non 18:6,12,20 20:8 22:21 38:20 40:22 43:10 50:19 52:20 55:12 60:6 64:6 69:17 75:15 78:4,5,8,12 81:17 86:17 111:9,11 130:17 144:17 146:17 160:9,14 160:16 173:2 181:16 221:9 259:2 298:5 303:5 324:14 350:6,7,8	350:17,21 351:9 351:10,20 352:3,8 353:2 nonmotile 149:10 152:20 153:16 nonprofit 95:8 nonspecific 101:15 124:5 nonsubjective 223:20 nonsurgical 177:4 norepinephrine 285:8 288:11,13 norm 72:6 normal 86:20 87:9 115:15 117:22 118:2 173:3 174:11 196:3 228:14 249:4,5,17 273:11,11 275:2,6 277:19 321:18 normalize 213:10 normally 221:7 255:21 north 8:8 168:20 170:2 nose 169:20 244:20 nosocomial 23:9 52:11 53:6 55:10 55:14 58:15,16 123:22 146:13 notary 356:1,18 note 23:6 109:8,9 249:8 noted 149:3 noteworthy 126:6 notice 49:17 125:10 226:3 noticed 138:13 notify 310:17 notion 29:15 68:19
--	---	---	--

notorious 354:18	oags 310:18,20	139:21 186:8	248:15 249:15
novel 58:13 59:7	oap 2:7 3:15 4:5	190:4 234:21	255:2 258:22
60:13 66:8 69:17	311:10	241:17 253:11	264:9 280:4,16,22
141:19 165:10,16	obesity 34:17	255:2 256:21	291:22 314:11
167:18 170:19	objective 104:10	259:12 348:8	315:21 326:15
222:4 233:13,14	281:1	occasional 221:8	336:6 350:1,3
264:16 267:16	objectives 300:4	occur 16:2 18:19	old 32:7 34:15
nuance 201:12	oblique 292:3	101:1 127:8,8	37:3 48:8 197:11
nuclear 21:6	observation 44:2	170:13 353:7	240:3,16 278:1
297:5	105:16 155:17	occurred 114:6	older 251:5
number 52:16	158:14	156:4	oleic 289:1
68:16 73:5,21,22	observational	occurs 99:17	ompa 162:13,18
76:7 82:4,12,15	156:18	128:16 145:15	163:3
85:1,15,22 127:7	observations	318:4 338:6	once 19:21 46:21
142:21 144:17	29:16 99:14	offer 180:7 181:4	78:5 112:7 123:1
150:2 152:6 153:4	101:17 102:7	182:8 183:7 265:7	160:21 177:6
164:22 185:6,9	105:12	offered 203:19	208:13 228:19
207:2,4,6 210:18	observe 53:5	offering 204:2	244:14 261:15
211:19 237:11	102:12 108:12,19	offerors 298:18	328:10 349:1
256:3 260:16	109:7,10 324:11	offers 179:20	ones 147:13
277:19 282:16,20	observed 31:12	194:12	176:12 195:8
283:1,7 303:12,15	99:12 100:18	office 2:7 3:15 4:5	200:18 228:13
308:12 326:1	102:4 103:7,22	26:5 27:3,5 80:2	241:12,13 270:17
331:15 335:7	104:14,19 105:2,4	124:21 308:18	297:21 330:1
341:2 351:12	107:2,3 108:8	309:18 310:18	342:11
354:4	163:22 218:11	311:9	ongoing 180:8
numbers 56:4	219:7 324:16	officer 4:14 5:9,13	309:12
137:9 164:5	326:3	7:5,6 26:4,9 27:6	online 189:17
227:19 235:3	observer 316:20	27:7,12 202:11	291:20 296:9
236:14 260:8	observing 98:8	301:21 356:2	onset 102:6
300:3 328:4	obtain 41:9	oftentimes 127:2	116:19 117:8,14
numerically	327:18	132:15 196:16	117:16 118:3
220:10 331:7	obtained 20:12,15	197:1 235:1	121:12,14 175:21
numerous 95:10	175:8 181:22	339:17	onsite 42:18
141:12 142:9	219:15 272:13	oh 36:17 204:2	onslaught 29:18
147:11 197:9	280:10 292:18	262:1 269:12	96:12
nut 347:21	obvious 119:19	336:6 344:4	open 39:12 55:21
o	120:18 121:12	353:13	64:20 77:1 142:21
o 9:1 10:1 11:1	149:21 192:2	okay 16:10 35:6	228:12 270:16
12:1 13:1 14:1	obviously 61:11	65:8 140:16,21	307:13,15 309:17
15:1	61:22 63:12 64:22	143:22 144:1	312:22 348:5
o's 162:8	65:20 94:7 96:11	151:1 181:11	opened 82:6
o52 353:15	96:17 110:18	202:4,6 204:8	operative 35:21
	131:18 132:8	244:14 246:9	

opgen 243:1 opinion 322:14 opinions 332:21 opk 268:4 271:17 opportunistic 140:22 145:12 338:6 opportunities 128:4 305:4 opportunity 19:19 25:16,21 43:20 130:4 176:17 183:20 184:3,12 185:17,21 264:20 opposed 120:15 137:19 233:18 opsono 164:18 optic 290:7 optical 242:20,21 243:3 optimal 107:22,22 optimization 183:16 257:9 299:7 optimize 96:7 optimized 40:10 97:10 106:5 183:13 optimizing 109:17 option 18:5 20:3 20:10,13 40:1 options 17:20 18:3 39:5,16 42:13 53:10 55:22 130:7 135:12,13 140:7 194:17 336:12,16 oral 35:9 orange 105:3 ordeal 264:7 order 40:18 41:11 62:19 91:1 127:20 130:20 131:10,12 132:5,11 133:20 136:19 139:13	202:6 229:3 299:1 318:21 337:2 ordered 144:12 orders 298:12,15 organ 118:17 246:21 278:5,6,7 organism 17:7 33:19 34:3 35:8 36:4 50:21 120:19 126:11 151:9,20 152:3,10,22 153:6 154:1,22 155:1,10 157:20 158:17 163:11 164:4 165:14 166:9 167:1 187:12 188:11 192:17 199:2 206:21 210:8,11 217:4 221:6 232:8 263:12 organisms 20:18 29:19 31:1,4 127:19 128:2 141:1 153:3 169:6 170:9 178:10 182:5 186:18 187:5,11 188:2,20 197:2 199:9,13 200:2 203:21 206:19 207:14 210:1,4,14 211:20 212:12,15 215:22 216:22 218:2 221:9 233:9 312:22 organization 95:8 110:14 296:12 297:12 307:12 organizations 305:18 307:14 organized 281:18 organizers 58:10 67:6 95:3 111:8	141:6 176:17 183:20 185:17 222:8 296:5 organizing 141:6 organs 115:4 118:18 202:10,12 202:17 246:15,18 246:20 247:3 277:6 orient 102:14 105:1 orientation 292:4 original 143:2 254:4 originally 242:7 oro 291:15 oropharynx 289:15 292:9 osteomyelitis 154:12 otoscope 225:12 outbreak 53:18 124:11 165:20,21 outbreaks 89:17 89:18,19,21 187:12 193:9 263:7 353:7,7 outbred 265:10 268:14 outcome 58:19 98:4 106:20 108:7 108:8 190:13 206:8 207:20 356:12 357:8 outcomes 123:21 156:7 207:8 outer 59:9 142:7,8 146:10 157:9,10 157:15 167:7 outline 141:9 output 208:6 273:22 315:8,10 315:10,12	outside 167:1 246:5 overall 39:18 115:6 134:15 269:17 338:15 overcome 60:12 107:7 overemphasize 110:3 overlap 94:6 overlooked 56:12 overlooking 56:20 overproduced 149:8 overspecify 349:22 overtop 251:12 261:15 overview 111:18 176:21 ox 228:7 oxa 163:7 169:15 171:9 oxazolidinone 214:5,6 oxazolidinones 214:14 oxygen 32:10 33:17 228:6,16 246:9 274:1
p			
p 2:1,1 3:1,1 4:1,1 5:1,1 6:1,1 7:1,1 8:1,1 15:1 109:9,9 142:12 145:10,22 146:5,20 147:12 148:5,22 150:4,8 p.m. 355:21 pa 104:6 105:4 pa14 144:14,15 package 77:6,11 83:4,12,18 135:17 135:19			

packages 83:13	parameters 77:13	278:19 279:4,8,18	132:1,8 135:7
page 9:2 10:3 11:3	86:1 102:15	281:13 283:19	142:13 145:12
12:3 13:3 14:3	121:20 192:21,21	284:5,18 291:8	151:7,11 154:20
114:1 311:10	208:21 224:8	293:15 318:3	155:4 168:3 190:3
pain 32:14 36:11	314:7 315:13	351:3 352:11,15	198:22 236:8,9
251:11	parenteral 30:5	352:20	262:15 281:16
painful 48:12	part 30:14 41:6	particularly 58:19	283:17 289:14
pancreas 279:2,3	45:4 92:7 104:15	69:8 118:11	292:13 299:16
panel 9:6 11:18	112:14 116:3,16	126:21 129:7,22	300:13 338:6
14:5 15:3 25:16	118:13 137:5	147:1 156:7	345:15 353:4
25:22 27:18 70:5	147:14 157:10	169:15 170:8	pathogen's 60:1
101:16 177:22,22	180:7 184:14	174:12 199:12	pathogenesis 11:5
185:21,22 190:11	201:1,1 272:16	202:20,21 216:16	11:9,12 25:10
198:17 205:1	282:18 290:14,15	281:21 282:6,15	94:16 130:17
215:22 298:17	317:4,10 318:6	285:17,21 293:20	140:20,22 141:2,4
300:16 308:17	332:4 344:7,8	294:4,6,20 297:15	141:9 145:10
311:13,16,18	347:14 348:19	301:12 315:22	149:22 151:3,4
312:19 330:21	349:6	316:9 318:12	157:16 169:4
348:17 355:8	participant 191:3	320:3 330:13	196:3,6 197:6
panelists 2:3	191:6 202:3,5	333:5 336:5	199:8 221:6 222:1
105:21	203:18 313:8	particulate 38:16	234:8 235:11,18
panels 69:22	353:14 354:15	parties 64:18	263:12 264:14
70:15	participants 7:17	356:9,11 357:7	281:15 291:4
panlabs 180:18	participate 25:17	partner 64:21	341:14 344:6
181:10,12	25:18 42:17 95:5	222:14 236:3	348:1,3
panton 352:12,22	277:3	296:15	pathogenic 126:12
pao 143:2	participated	partnered 247:15	186:13 284:15
pao1 142:18 143:1	110:18	partners 63:7	291:11 293:16
144:14	participating	253:4 265:1 298:7	295:7 352:2
paper 57:1 84:15	25:22	partnership 27:8	pathogenicity
161:19 164:16	participation	185:2	97:21 199:4
166:6 167:17	355:9,12	parts 66:5 68:5	216:22
260:3 310:13	particle 114:5	154:7 237:16	pathogens 19:1
papers 43:18	120:9,11	passage 348:8	31:7,14 37:9,11
162:22 223:7	particles 120:13	passed 34:11 37:4	42:4 58:18 59:9
309:15 310:12,15	particular 39:1,9	186:17 196:17	59:11 65:13 67:20
324:13	87:12 91:16 101:6	passes 251:3	67:21 72:10 75:12
paradigm 320:17	102:14 109:15	passive 96:19	94:22 130:10
paradoxically	123:19 126:7,7	patent 83:1	142:13 152:1
48:11	132:1,8 139:14	path 38:9 40:4	184:19 186:8,11
parallel 48:2	148:3,8 150:17	48:13	186:15 206:19
335:9	156:13 160:13	pathogen 30:22	221:7,21 235:4
parameter 102:10	169:20 173:4	68:15 69:4 73:22	250:17 281:19
	177:17,18 215:18	126:8 129:16	289:6,7 291:12

299:19 309:10 335:7 340:16 352:4 353:6 pathological 99:14 pathologist 5:5 89:5 110:22 123:5 pathology 89:7 90:20 96:4 97:13 99:4,11,12 118:15 118:18 126:16 179:1,9 198:2 229:20 232:11 246:10 252:4 256:22 344:17 pathophysiologic 21:14 pathophysiology 319:16 paths 139:5 pathway 24:5,13 24:14,18,21 83:11 84:2 109:20 139:19 144:6 165:2 194:6 pathways 57:8 131:20 140:3 161:13 165:13 336:15 patient 32:5 34:8 53:8 63:2 78:17 108:3 144:16 167:11,12 187:15 196:21 197:11 198:13 217:3,14 240:9 286:15 316:8 327:12 335:13 patients 16:6,20 17:6 18:14,18 19:3,10,14,16 20:4,6,17 22:12 24:3,16,21 28:14 29:21 35:22 37:11	37:19 38:15 39:2 40:18 42:1,10 52:14,16,17 53:2 53:7 55:22 58:19 58:22 61:6 62:14 62:15 64:8,10 65:4,18,21 66:9 68:7,8,9 71:5,9,13 71:16,19 72:2,16 73:12 74:3,8,13 75:3,13,19,21,21 75:22 76:7,21,22 77:8 78:2 135:4 135:13 136:6 137:10,12 146:22 147:4,5,8 148:21 149:4 150:10 159:2,7 187:19,22 189:10 194:15,19 196:16 206:5,9 207:10 213:21 214:15 215:8,11 215:14 216:12,18 216:19 217:7,22 220:19 221:12,16 236:12,16 238:15 241:5 247:1,1,4 254:9,22 262:21 282:3,6 284:10,20 286:1,17 287:7 291:5 309:22 316:14,16 327:17 329:12,17 336:11 336:16 343:21 355:18 pattern 72:18 86:8 86:13 117:22 patterns 78:22 167:9 243:7 paul 51:14 65:6 paused 296:9 pay 50:4 92:3 332:8	payers 135:4 pcr 166:6 pcrv 268:1 pd 12:10 39:7 40:10 41:14 45:14 45:17,20 46:3 47:10 60:16 77:13 136:2 174:4 179:5 182:9 192:21 205:12,20,22 206:1,3,4,6 207:9 207:22 209:13 212:21 213:2,20 216:14 218:10 219:18,20 220:18 221:5 257:13 319:20 322:2 326:4 331:13 340:1,6 peak 132:19 273:7 275:13 pediatric 273:1 pediatrics 4:9 pedigreed 346:19 peep 273:9 pel 148:13 peleg 243:12 penetration 74:10 215:13 penetrative 343:6 penicillin 161:14 penicillins 211:21 people 16:11,13 49:21 50:13 53:19 56:10,10 79:9 110:15 121:22 122:20 150:5 157:13 165:2 171:15 173:8,10 185:6 188:4,16 193:19,21 196:14 199:4 200:5,7 202:10 224:1,4 225:20 235:13	236:8,18 250:21 257:15 261:2 262:1,16,18 263:19 301:11,15 322:9,10 329:13 332:7,16 342:11 355:13 people's 236:21 pep 107:19 perceived 100:7 percent 49:15,16 52:20,21,21 54:17 54:17 55:14,15 60:20,21 68:9,10 68:11,13 69:1 70:7,9,19 71:7 72:19 73:15 76:10 76:11,14 84:10 96:15 108:17 109:6 122:14 154:6,17 162:19 208:21 210:19,20 211:5,6 218:21 226:17 237:8 244:4,5 247:22 248:2 257:4 259:6 259:8 263:2 269:17 273:6,7,19 283:3 288:8 294:22 300:1 315:7 percentage 169:18 173:21 347:16 perfect 53:13 280:22 343:22 perfectly 53:17 perform 160:20 177:6,11 182:14 183:3 226:19 293:19 294:11 306:15 performed 111:12 133:18 181:9 183:7 216:11
---	--	---	---

292:14 performing 96:1 performs 111:15 181:12 328:19 period 78:18,20 111:13 282:9 340:22 peripheral 276:22 277:5 periplasmic 157:1 perish 245:10 peritoneal 183:4 peritonitis 159:17 159:19 permanently 21:5 21:9 permit 331:20 persist 161:6 164:10 persistent 268:2 276:6 279:14 337:9 person 28:9 29:2 188:4,7 219:19 251:1,2,3,14 264:5,6 308:9 personal 95:11 personally 203:10 297:6 perspective 9:9 28:20 29:8 38:17 40:5,16 62:7 65:20 95:18 98:9 98:10 100:13 123:4 180:12 326:9 pestis 23:12 90:15 pfge 241:15,16,21 242:5 ph 340:14 ph.d. 2:5 3:4,18 4:8,13,18 5:4,12 5:16 6:4,9 7:8,12 9:16 10:8,9,15	11:10 12:8,15,20 13:6,11,17,18,19 196:13 280:10 phage 236:1 252:20 phagocytic 164:19 phagocytosis 164:15 pharma 8:6 180:20 181:1 236:3 pharmaceutical 58:1 66:20 151:16 184:5 pharmaco 211:8 pharmacodynamic 74:20 208:21 209:8,16 210:6,7 210:21 211:4,16 212:4,9,17 215:19 217:6 pharmacodynam... 208:19 217:5 pharmacodynam... 22:2 pharmacokinetic 74:20 92:2 98:7 104:22 108:1 221:11 pharmacokinetics 17:12 59:16 91:21 105:2 207:19 214:20,21 215:6,7 215:10 216:17 218:1 pharmacologist 57:22 pharmacology 2:17 50:17 phase 46:13,21 47:2,3,4 50:18,19 52:20 53:2 74:13 74:20 75:1,5,9 77:7,17,17 78:4	92:5,8 118:10 119:14 207:15 296:16,17 299:5 302:13,14 303:22 304:1 306:12,13 344:15 phases 43:9 94:6 phemce 296:13 phenomenon 102:4 phenotype 19:15 149:9 177:18 phenotypes 18:16 143:13 212:6 phil 151:13 philosophic 151:21 phone 16:11 27:20 28:3,9 31:15,19 36:9 42:17 43:17 185:7 313:8 phones 16:12,14 photo 35:11 36:3 153:19 photograph 35:4 phrase 153:5 physician 41:22 43:5 174:19 280:14 282:2 286:15 287:16 316:9 324:12 physicians 66:9 76:18 287:17 physiologic 121:19 319:11 320:18 physiological 85:22 266:3 physiologist 286:12 287:2 physiology 283:21 321:4 322:7 pick 154:20,21 199:11 240:9,11	240:12 296:14 298:19 348:7,11 picked 152:6 picking 219:9 346:16 355:2 picks 240:10 pictorial 158:19 picture 63:13 87:18 252:15 292:16 piece 127:4 344:6 pig 12:18 13:9 234:9 258:10,11 258:15,15,16,17 258:17,17,19 259:6,7 260:10,13 260:22 261:4,5,8 261:17 280:18 294:20,21 312:6 317:6 318:11 324:7,16 331:17 339:1 pigs 259:2,3,17 260:2,2,4 264:10 280:4 282:22 286:7 288:3 290:2 291:14 313:22 321:20 322:16 323:2 331:16 333:2 338:22 339:3 340:21 343:5 352:3 pili 148:1 149:11 pillar 107:1 pilus 161:14 pink 103:4 248:9 pinnacle 1:13 pip 273:8 pivotal 92:4 104:16 pk 12:10 39:7 40:10 41:14 45:14 45:17,20 46:3 47:10 51:13 60:16
--	---	--	--

61:17 74:18 77:13 82:12 83:5,6,7 91:2,3 93:16 98:6 98:10 103:20,21 136:2,4,5 172:5,5 174:4 178:20 179:5 182:9 205:12,20,22 206:1,3,4,6 207:9 207:22 209:13 212:21 213:2,20 214:3 216:14 217:2 218:10 219:18,20 220:18 221:5 257:13 310:4 319:20 322:2 326:4 329:17 331:13 340:1,6 353:20 place 229:14 240:11 256:1 306:6 314:8 placebo 23:4,13 23:15 104:19 105:17 255:10 262:10 placed 337:22 placement 34:18 35:1 places 197:9 246:18 placing 177:2 plague 10:7 22:18 23:3 80:12,15 81:9,17 87:1 89:16 90:5 117:7 127:7,11,22 128:3 128:8 145:13 186:6,10 191:11 192:1 222:2 224:15 351:16 plan 74:6 305:5 308:21 326:2	planktonic 344:16 planktonics 246:4 planned 65:7 planning 329:7,8 plans 39:18 40:21 plant 141:16 144:18 planted 121:4 plants 141:15,17 143:10 plaque 130:19 plasma 59:18 174:5 214:21 215:3,13 plasmid 240:12,13 240:14 plasmids 240:11 plastic 187:15 197:3 240:8 plasticity 165:14 199:14 plate 87:22 189:1 252:3 320:5 plateau 102:8 219:4 plated 153:22 platelet 276:18 platelets 276:14 276:15 338:2 plates 186:12,16 199:15 243:6 play 24:1 54:5 56:1 126:22 134:15 139:21 155:11 161:12 191:2 250:12 328:21 player 235:7 playing 213:11 237:3 260:5 332:5 plays 249:13 plazomicin 17:9 49:7,14,19 50:3,6	please 16:13 29:13 30:22 41:12 43:17 284:19 287:8 288:10 289:5 291:19,22 294:1 311:6 plethysmography 120:5 pleuritis 115:2 121:5 plotted 81:10 plural 47:9 plus 54:6 106:8 117:14 240:3 322:18 pmrb 163:7 pna 254:4 pneumococcus 213:13 pneumonia 13:5 13:10 18:9,10 23:9 33:7 51:17 52:12 53:6 55:10 55:15 58:15 74:10 115:12 146:21 154:4,5 160:8,9 169:9,19 170:14 176:22 177:2 179:3 188:5 200:22 206:17 215:15 218:7,8 219:11,13 221:1 229:22 231:22 240:22 264:15,18 264:21 267:5,14 267:18,19 268:12 271:20 272:9 273:20 277:2 280:18 281:14,22 282:3,12 283:11 284:14 287:9 288:21 289:4,7 290:20,22 291:1,4 293:10,12 294:17	309:7 323:5,14 326:17 342:13 344:10 353:20,21 pneumoniae 33:13 266:17 pneumonias 73:16 74:1 pneumonic 10:7 80:12,15 81:8 87:1 89:16 90:4 112:1 po2 277:11,14,20 290:16 324:21 325:3,5 327:14 pocket 35:14 225:16 podium 168:21 point 49:20 52:6 74:5 76:17 78:14 83:20 84:21 85:5 87:10,20 90:4 92:4 99:9 132:9 154:19 167:20 169:5 182:17 185:10 188:15 195:21 198:8,21 199:18 201:3 203:18 231:9 236:6 245:12 247:14 249:6 312:12 324:19 325:13 329:21 339:7 345:9 351:1 pointed 67:17 69:5 71:20 72:5 78:10 235:10 pointing 55:19 246:1 points 63:12 72:21 74:21 92:14 113:20 126:1 212:1 216:3 224:2 252:4 253:13 272:16 325:15
---	--	--	--

<p>pokes 247:18</p> <p>pol7080 57:21</p> <p>polarized 202:21</p> <p>pole 191:9,12</p> <p>poles 191:8</p> <p>police 152:7</p> <p>policy 43:6</p> <p>polymicrobial 19:1</p> <p>polymyxin 60:10 230:4,8,10 231:3 231:5,16,18 262:11,12</p> <p>polyphor 7:10 9:16 25:5 27:10 43:2 58:6,12,12 59:4 136:21</p> <p>polys 163:14</p> <p>polysaccharide 149:8 161:13 255:12</p> <p>polysaccharides 148:12</p> <p>pool 300:6</p> <p>pooling 39:15</p> <p>poor 186:19</p> <p>popped 157:11</p> <p>pops 341:2</p> <p>population 17:12 18:16 20:8,8 24:5 24:13,16,18,20 41:21 61:16 75:5 77:4,5,17 97:4 150:14 349:13</p> <p>populations 64:7 73:3 198:14 306:15</p> <p>porcine 159:15 237:20 263:14</p> <p>port 273:14</p> <p>portal 120:19</p> <p>portals 118:20 123:14</p>	<p>portfolio 297:12</p> <p>portion 108:11 267:22 268:2,3 297:7</p> <p>pose 16:5</p> <p>position 292:2,3</p> <p>positions 43:11</p> <p>positive 54:16 100:3,6 102:16,21 103:2 104:7 206:8 268:22 289:6</p> <p>positives 182:6</p> <p>possess 347:12</p> <p>possibility 284:16 295:5</p> <p>possible 42:1 46:2 46:21,22 47:15 51:2 57:10 65:13 79:4 91:19 134:8 138:8 140:17,18 171:2 211:13 348:10</p> <p>possibly 55:13 101:9 320:13</p> <p>post 23:14 35:21 86:7 101:18 102:20 107:19,21 114:7 116:20 118:16 127:6 178:3 226:14 230:17 231:2 252:8 268:16 269:2,4,13,15 271:4 272:13 274:7,8,8,14 275:19 313:18,20 314:1</p> <p>postdoc's 262:19</p> <p>postdocs 279:19</p> <p>postmarket 22:7</p> <p>potassium 278:14 278:15,17 323:19</p> <p>potency 60:2 206:11</p>	<p>potent 61:2 70:12</p> <p>potential 15:17 17:18 18:1,21 20:11,13 44:4 61:4 73:8 107:18 108:21 123:18 125:19 221:13,14 224:19 225:6 229:6 233:7 281:4 283:13 300:6 305:3 306:7 310:11 321:13 328:16 350:16</p> <p>potentially 18:10 100:2 105:18 106:13 135:5 233:18 306:20</p> <p>potentiates 247:17</p> <p>power 52:21 76:10</p> <p>powered 40:7 47:3 128:11</p> <p>pox 131:6</p> <p>practical 17:17 136:7 328:2,4 329:4</p> <p>practically 128:13 128:17</p> <p>practices 110:6</p> <p>pre 24:22 29:16 43:8 82:6 83:2,13 113:8</p> <p>precision 61:4</p> <p>preclinical 60:18 70:21 74:17,20 77:19 136:1 151:15 170:1 181:2 222:4 264:16 302:13 303:20 304:5 308:1</p> <p>preclinically 59:22 179:22</p> <p>predatory 252:19 258:5</p>	<p>predetermined 113:20</p> <p>predict 40:11 98:3 131:10 206:4 214:19 215:10 218:13 239:18 329:11 351:8</p> <p>predictable 34:9 164:3 330:14</p> <p>predicted 219:5</p> <p>predictions 219:18</p> <p>predictive 5:17 21:17 74:18 222:16 257:1 319:13 329:18 350:14,19 351:2</p> <p>predictors 103:8 324:13</p> <p>predisposes 272:10</p> <p>predominant 141:11</p> <p>predominantly 97:19 149:5</p> <p>preexisting 75:10</p> <p>preferably 209:20</p> <p>prepare 97:7</p> <p>prepared 75:19 357:3</p> <p>prescreened 113:8</p> <p>prescribing 139:22</p> <p>presence 142:3</p> <p>present 24:5 37:20 53:15 67:7 90:15 183:21 185:18 234:3 235:16 241:10 262:5</p> <p>presentation 17:22 23:4 99:18 100:20 101:1 111:21 114:10 123:16 138:14</p>
--	--	---	--

180:2 183:22 281:5 312:14 313:11,14 presentations 11:16 45:13 126:3 168:17,22 169:4 191:21 197:18 287:21 322:8,8 325:21 341:22 355:9 presented 33:9 67:13 114:4 120:4 217:10 282:11 295:7 324:19 342:4,7 presenter 94:13 presenters 79:10 presenting 280:5 president 184:4 press 57:2 pressure 61:12 97:7 273:14 286:18 315:13 prestudy 136:17 137:10 presumably 119:3 272:9 presume 53:13 pretty 45:15 47:4 95:18 96:3 112:12 117:16 121:21 145:16 161:1 176:5 199:8 235:22 244:4,19 244:21 279:16 342:16 347:7 prevalence 349:12 prevent 268:11 preventing 21:3 275:9 prevention 21:22 30:16 280:11 preventive 293:20	prevents 257:12 previous 281:7 282:11 283:9 287:13,21 293:6 294:14,15 previously 72:22 124:14 142:11 166:1 350:5 price 50:3 primarily 65:14 65:19 112:19 114:21,22 124:4 189:22 205:21 264:13 282:3 325:22 primary 76:4,19 77:5 163:19 206:22 228:17 229:14 primate 111:9,11 112:17 350:7,9,22 351:9,11,20 352:8 primates 130:17 259:2 265:13,16 289:18 350:7,18 352:3 353:3 principal 7:13 94:18 prior 72:15,17 73:4 74:17 87:12 113:9 118:1 332:1 prioritize 104:11 122:1,11 prioritized 337:4 priority 31:7,11 42:4 135:7 142:12 142:13 pristine 123:19 private 27:8 185:2 298:6 proactive 184:13 probability 77:18 206:8 219:20,21 220:11	probably 39:1 63:1 97:3 127:17 129:13 135:20 148:20 152:21 153:2 158:1,3 160:4 186:18 188:11 203:2 211:13 221:1 223:4 234:18 243:18 246:4 250:9 264:2 301:10,10 317:16 317:17,18 318:1 340:15 344:15 345:5 probe 254:5 probes 121:3,4 problem 39:1 52:13,18 66:2,7 109:15 186:9 189:12 215:12 236:11 238:21 249:18 324:2 325:10 346:5 problems 125:21 130:13 227:18 315:22 procedure 35:22 188:6 225:7 proceed 67:11 130:9 proceeding 356:3 proceedings 356:4 356:6 process 81:20 98:1 112:6,6 129:21 130:12 226:8 298:13 307:5 310:13 335:17 procurement 297:1 produce 141:18 221:8 288:2,12 300:18 337:8	produced 116:5 212:18 279:2 produces 175:22 producing 33:13 212:10,14 product 17:13 20:20 22:2,11,13 49:6 67:8 69:12 96:2,8 97:22 98:2 100:7,14 103:21 104:5,21 109:19 110:18 135:17 194:13 303:14 305:6 production 212:19 298:17 300:15 products 2:7 3:15 4:5 6:19 15:10,13 15:18 18:4 21:2 22:6 24:3,8,17,21 25:4 27:3,5 66:21 67:2,3 95:14 96:2 99:3 109:20,21 124:21 131:13 140:1 184:18 296:21,22 304:4 305:13 308:19 309:1,18 311:9 350:5 355:17 professor 2:11,17 3:11,19 4:9 5:17 6:14 28:12 62:8 205:4 234:6 264:12 proficient 336:3 profile 33:21 59:20 60:22 70:21 91:4,5 98:7 102:18 103:13,14 104:22 108:2 143:15 297:4 profiles 353:21
--	---	---	--

profound 277:5 279:10	promotional 25:1	protein 118:9	51:8,22 52:1,9,11
program 3:10 4:14 5:13 26:4 28:11 50:18 54:3 59:5 60:17 72:2 73:9 75:6,9 91:12 91:17 92:15 101:21 112:14 137:22 139:7 195:2,20 202:11 235:21 236:1 301:14,21 302:18 303:2 308:10 338:15	prompted 238:12	162:21 166:5 212:22 213:7,15 213:17 215:5 216:16 221:14 265:18	53:15,17 54:8,20 57:6 58:14,16,18 59:14 60:2,6 63:11 64:8,22 65:12 68:5 69:7 125:20 133:13 134:17 135:9 139:4,9 141:3,4,9 141:11,14 142:15 142:18 143:7,8 144:4,20 151:6 158:2 169:2,17 170:12 171:1 172:18 173:4 174:13 175:6,18 176:11 177:1,21 179:21 180:21 181:21 182:11,12 183:2 188:5 191:10 192:1,9 194:16 202:20 203:20 204:22 209:14 210:13,15 210:18 213:22 218:16 222:5,6,9 223:1 227:8 230:10 249:15 264:17,18,21 266:16 267:22 268:21 271:22 280:18 281:3,21 283:10 285:6 287:9,18,19 288:6 288:16 289:3,8,9 290:6,8 291:9 292:11 293:5 301:12 309:8 312:10 314:3,4 315:3,9,15,19 316:2 327:2 335:13 337:14 338:6 341:20 342:12 343:9
programs 18:13 46:11 94:19 96:18 184:9 205:9 296:15 297:13 302:16	proof 45:18 93:12 247:6 256:4 292:22 307:5,19	proteins 59:8 157:1,16 161:14 162:14	
progress 31:20,21 48:20 57:13 245:5	proper 171:17,19 288:4	protocol 62:22 261:2	
progressed 33:6 35:15 117:1 254:11	properly 255:13	prove 62:4 71:1 307:6 331:16	
progresses 121:6	properties 346:17	proved 69:8	
progressing 254:14	prophylactic 107:19 256:13	proven 49:8 53:1 75:13 78:6	
progression 99:20 102:13 108:11 179:12 198:1	prophylactically 255:20	provide 22:7 23:19 41:14 75:22 77:3 80:6 95:9 106:14 107:15,17 130:4 135:13 137:3 139:16 144:6 176:3 285:14 303:10 305:16 306:13 307:5 308:1 314:13 319:17	
progressive 119:5 119:7 184:13	prophylaxis 127:6 268:15 271:2 272:2	provided 176:12 304:14	
project 26:9 258:5	proposals 140:5 298:11,11,12 304:19 305:5 309:16 310:19,21 311:1	providers 135:3 305:18 306:6	
projected 135:22	proposed 50:20 60:19	provides 139:15 253:3	
projects 145:9	pros 312:4	providing 184:7 308:6 338:1	
prolong 286:5 314:17	prospective 128:8	pseudomonal 25:6 61:2	
prolonged 295:6 340:22	prosthetic 267:12	pseudomonas 1:5 11:9 12:14 13:5,9 15:8,22 19:11 20:3,6 25:11 29:9 31:2,10 36:15,16 38:7,10 42:3 44:6 44:12,20 50:17	
prominent 24:19	proteases 147:19 149:14		
promising 296:15	protect 97:4 164:19 232:10		
promote 141:16	protected 65:12		
	protecting 232:6 271:1		
	protection 96:20 232:6		
	protective 162:20 267:16 268:7 270:22 272:5 314:18		
	protects 164:13 275:8		

344:20 347:22 353:5 pseudomonas.c... 144:4 psl 148:12 268:3 public 1:1 7:17 11:16 27:7 168:17 168:22 185:2 206:14 297:17 341:22 356:1,18 publication 90:3 122:5 158:16 223:19 243:12 282:21 publications 99:10 282:16,20 283:1,7 publish 177:8 255:15 published 70:6 78:2 164:21 167:17 200:21 209:11 223:6 253:14 255:15 303:1 347:6 pudding 256:4 pull 28:18 261:10 pulled 102:12 219:10 230:21 pulling 40:14 196:18 261:11 pulmonary 4:10 6:5 71:16 74:10 90:19 223:12 224:11 237:17 244:14,17 279:11 280:12,14 289:17 290:17 291:3 pulsed 241:8 pump 34:18 35:19 37:1 pumps 142:9 163:10	punch 165:10 251:21 255:2,3,8 260:17 261:10,11 340:13 punches 260:18 260:19 262:9 purchased 124:10 pure 289:8 purpose 283:5 309:4,13 328:22 329:8 purposes 129:12 221:5 pursue 85:1 pursued 20:16 pursuing 258:2 purulent 35:5 push 248:2 299:21 pushed 56:7 pushing 125:18 301:2 put 33:1 36:14 47:6 51:6,19,20 53:10 61:12 63:6 67:12 83:12 97:2 97:9 99:1 100:8 104:20 110:5 143:6 154:22 158:1,5 161:16 163:16 169:1 171:5,16 175:8 177:17 200:8 206:7,10 211:14 227:18 239:3 241:10 242:21 243:4 247:6 251:12 261:15,16 271:12 299:3 300:20 304:19 305:15 315:4 333:9 334:1 335:2 338:11 346:6 puts 87:15	putting 54:21 55:7 83:18 167:6 173:15 320:4 pyelonephritis 174:11 pyocyanin 54:13 147:20 pyogranulomato... 115:3 pyoverdin 147:21 q q&a 11:19 14:6 185:22 311:13 qualification 112:6 qualified 112:8 quality 41:3,8 46:14 91:20 93:17 110:3 133:14 180:13 198:6 298:9 301:4,7 348:12 quantitative 113:22 118:17 quantum 153:6 quest 106:15 question 20:7 53:20 62:2 64:20 70:22 91:8 164:16 193:6 207:22 209:10,15 211:10 311:20 312:2 313:4,6,11 314:8 320:7 327:20 338:8 342:21 345:21 346:9 348:5 349:10 350:15 351:12 353:16 questioned 98:18 questions 25:19 79:9,12 183:18 205:20 206:1 243:19,20 258:9	264:1 276:7 311:6 311:17,21 326:1 326:12 330:8,21 336:19,20 337:1 345:21 350:2 quick 60:22 111:14 quicker 84:3 176:4 quickly 81:11 83:12 115:5 138:21 177:7 199:16 325:17 quirks 191:17 quite 30:10 31:15 32:22 36:5 44:16 47:2 49:16 78:11 86:16 98:17 126:17 133:11 138:4 142:6 176:2 184:12 185:8,8 213:6,8 214:9 235:17 236:11 251:19 263:21 264:7 266:7 271:11,13 275:15 322:17 342:22 343:1 quorum 149:12,13 164:6 quote 97:8 99:18 r r 2:1 3:1 4:1 5:1 6:1 7:1 8:1 15:1 r&d 27:8 58:3 rabbit 13:5 99:21 100:3 264:15,18 264:21 265:2 266:21 267:4,5,5 267:18 268:12 270:1 272:15,21 273:17 274:7 276:5 312:6 313:4 313:7 324:7
---	---	--	---

325:15 337:7,13 338:17 339:1 340:13 343:1 352:17,22 353:8 rabbitpox 131:8 rabbits 101:9 103:12 104:1,15 107:13 131:8 265:4,5,7,10,12 265:15,22 266:2 266:10,15,19,21 267:1,9 268:9,13 268:14,20,22 272:1,4,4,12,22 273:5 274:4,6 276:4 282:1,21 313:17 317:6 330:14 331:14 352:18 353:6 radiation 32:9 radiograph 87:5 87:11 radiographs 87:9 87:17 radiologic 21:6 radiological 297:5 radiologist 87:8 87:13 raetz 164:21 raise 20:7 180:3 raised 42:3 64:11 183:5 189:14 raises 20:9 131:3 300:2 ramble 125:22 randomization 64:15 75:21 randomize 48:16 261:2,6 randomized 49:9 55:16 92:9 268:15 272:1 335:21 range 77:15 88:7 131:20 172:2	190:6 197:8 211:21 228:14 233:6 278:11 324:22,22 ranged 114:4 233:14 ranges 89:4 94:1 114:14 173:18,19 182:22 ranging 211:19 rank 311:2 rapid 18:17 38:22 72:22 73:7 87:1 100:8 183:5 290:22 rapidly 81:9 164:8 197:3 rare 16:1,4 38:16 250:20 rarely 159:18 rarity 72:7 rat 158:19 160:8,9 160:10 239:7,8 240:22 263:5 340:18 342:13,22 343:2,8,14 344:4 344:10 353:1,19 353:20,21 rate 52:9 54:16,19 68:8 86:14,18,20 87:2 90:18 96:15 113:17,18 116:18 116:18,22,22 120:6 121:21 147:2 228:6,15 259:8 269:5 273:8 286:18 288:9 311:2 rated 87:9,13 rates 52:11 98:17 rating 87:10 ratio 101:13 102:5 215:13 269:22 270:4,12,20 271:9	273:9 290:16 327:14 rational 320:21 rationale 116:3 281:13 ratios 274:15 rats 160:7 177:12 179:1 265:13 266:11 282:1,20 342:18 343:1 rattle 43:18 raxibacumab 104:15 106:8 ray 100:3 rayner 8:7 184:1,2 rct 55:9 reach 185:15 228:19 284:10 314:14 345:4 reached 63:20 react 21:16 reactive 118:9 read 152:18 readily 112:21 181:19 240:10 247:19 readiness 75:1 reading 90:10 142:21 324:12 326:14 ready 181:19 280:16 reagents 91:18 real 49:4 52:8 86:1 122:11 128:5 159:5,6 195:5 245:3 256:8 284:2 291:4 326:10 realistic 182:21 reality 135:5 152:14 realize 16:9 121:18 213:16 328:2	realized 108:5 really 16:21 29:1 29:14 33:19 38:3 38:4,19 40:20 41:7 42:13 44:5,7 44:12,21 45:1 47:18 49:1,16 50:15 51:3 56:6,7 58:21 61:2 62:4 63:10,16,16 64:2 64:8 66:3 73:3 75:8 76:18 77:15 83:7 84:7 86:22 87:22 89:15 91:9 92:1,6,8,11,13 96:5 101:3 106:10 120:1,1 121:16 122:21 124:16 125:5 126:4,17,19 128:10,11,13,16 128:21 129:16 130:14,22 131:13 134:4,10 135:10 135:20,22 136:15 137:5,6 138:4,8 152:3,12,19 153:12 157:9 159:2,16,22 160:15 161:20 172:13 173:4,14 174:14 179:3 180:10 185:11 190:17 194:8,22 196:9,21 197:14 198:18 227:20 234:18 236:20 238:6,10,12 239:15 242:2,16 244:12,17 247:2 249:7 251:18 255:9,11 256:7 258:1 259:3 260:5 265:9 273:10 278:11 279:17
---	---	---	---

307:8,9 312:3 319:16,17 322:1 328:1 329:5 330:4 330:17 332:22 333:6,6,11,13 336:13 338:18 339:19 341:14 343:7,20 348:7 350:13 351:1,11 352:4 354:8,19 355:3,17 rearrange 155:11 reason 15:16 116:10 136:8 137:13 214:12 270:22 285:10 316:14 333:4 337:10,16,20 351:2 353:9 reasonable 40:9 75:18 130:9 135:11 140:7 194:17 317:6,7 320:20 331:18 reasonably 21:14 160:18 332:13 reasons 22:13 65:17 284:18,19 334:17 341:9 rebound 229:11 recap 18:3 recapitulate 341:3 341:5 354:2 recapitulated 325:8 recapitulates 92:13 343:4 receive 71:12 264:22 294:9 295:1 310:9 received 23:13 294:1 receiving 294:9	receptor 352:16 352:18 recognize 15:17 15:19 158:6 215:6 217:2 recognized 147:12 150:13 recognizes 137:6 recognizing 137:8 138:10 194:15 336:10,17 recombinant 162:18 recommendations 81:7 recompete 298:7 reconvene 140:17 record 356:6 recorded 356:4 recover 226:17 231:13 recovered 159:18 226:14 recovering 159:21 recovery 221:10 recreated 353:20 recruit 63:2 red 86:2 104:17 105:1 153:9 255:12 reduce 211:3 268:10 reduced 356:5 reduces 45:18 300:3 reduction 172:10 248:10 271:12 reed 7:15 12:20 155:21 200:19 234:5 254:12 255:1 258:20 263:13 283:3 refer 122:5 179:15	reference 192:22 253:15 references 84:12 90:1 refined 96:6 refinements 106:16 138:20 reflect 261:4 322:12 reflected 67:19 reflecting 91:9 197:21 reflects 60:1 263:12 regard 30:19 38:21 332:21 regarding 96:3 105:22 180:8 293:4 regardless 135:18 212:18 regards 139:3 140:6 regenerate 122:9 regimen 51:20 60:20 65:7 75:16 116:5 156:16 171:22 regimens 19:6 171:20 208:19 221:16 306:21 region 121:14 293:6 registration 51:4 regrettably 157:3 regular 172:17,18 regulated 111:15 149:13 349:11 regulations 20:21 regulators 42:18 63:21 64:18 66:7 135:3 regulatory 29:2 63:5 67:1 71:2	81:20 95:22 96:8 100:15 110:5 112:4 219:15 305:14 308:21 309:14 rehab 32:14 33:11 rehabilitation 32:13 reimburse 332:14 reinfection 61:20 reinforce 72:21 74:7,21 reintubate 232:21 reiterating 62:8 relate 265:19 related 21:20 30:7 81:17 114:16,22 120:3 146:14 166:1 210:8,9 265:17 281:5 356:8 357:6 relationship 47:10 88:19 206:12 207:18 218:17 219:20 relationships 95:12 212:13 relative 50:2 69:18 210:2,3 214:13 217:5 298:18 356:10 relatively 67:7 68:15 72:11 75:3 78:19 115:15 138:21 186:14 212:5 275:6 relatives 62:16 released 31:8 relevance 170:20 relevant 23:20 24:8 77:12 92:21 93:3,6 159:2,12 170:17 171:13 173:22 174:9
---	---	--	--

178:19,20 190:18 202:2,14 238:18 240:4 247:9 250:3 250:8 263:9 300:11,17 338:5 reliable 277:11 285:16 reliably 98:3 209:13 reliance 140:11 relies 134:22 reluctance 79:1 rely 21:12 37:20 134:19 215:9 263:11 298:3 348:16 remain 32:1 remained 276:14 remains 146:10 remarkable 69:14 155:10 remarks 9:6 14:8 15:3 355:5 remember 55:18 150:4 217:2 271:12 324:20 remembering 342:9 remind 43:16 72:5 230:9 remotely 280:5 355:14 renal 34:9 36:22 60:15 71:13,14 74:11,15 272:19 renally 60:14 rendering 149:17 renewed 97:9 repeatedly 45:7 replace 92:5 329:1 replacement 249:22 replicate 284:14 321:4	report 84:13 92:9 94:9 reported 1:19 115:7 reporting 1:20 reports 62:2 84:11 repository 143:8 200:2 201:8,22 represent 67:13 67:14 68:17 71:6 104:17 105:2,3 178:1,6 198:12 214:6 264:8 representation 158:19 representative 113:7 170:11 177:21 179:16 representing 104:14 184:10 219:22 220:2 represents 21:18 101:10 104:18 107:14 149:2,7 211:18 212:2 294:18 reproduce 189:4 291:11 293:15 316:13 345:15,17 348:9 reproduced 285:2 reproducibility 81:5 93:9 120:2 182:20 344:22 reproducible 116:5,6,6 175:9 178:11 226:20 330:10 reproduction 295:7 318:18 request 106:21 138:15 181:20 298:11 309:3 310:10	requested 168:17 requests 106:19 108:13 require 75:18 137:12 required 34:18 46:3 52:16 56:22 110:2 166:10,12 209:21 210:3 238:7 268:4 272:8 requirement 24:22 351:20 requirements 22:5 71:2 99:8 141:22 288:14 rescue 137:22 research 2:6 3:6 4:19 5:6 6:10,11 7:15 10:10,16 12:21 13:16 15:11 26:5,6 27:15,17 58:4 80:1,2,3,6 94:14,15 95:9 96:12 111:3,16 138:16 142:14 181:2,8 196:16 205:9 221:22 234:5 264:13 265:5 295:19 296:11 301:19 302:7,12,12 303:12,16 308:18 309:13,18,19 310:2,5 311:4,9 335:9 337:1 researcher 6:5 196:13 198:9 researchers 144:5 198:17 resemble 285:3 reserve 2:21 11:13 26:20 151:2 resistance 18:15 29:18 30:15 33:22	59:1 60:12 61:9 61:10 65:15 68:21 72:6,12,15,18 78:22 132:7 142:7 142:10 151:9 155:5 156:3,6,10 157:4,12,14,20 162:17 163:6,7 164:13 166:14,18 167:5,18 168:5 169:11,22 176:11 177:18 200:14 203:22 205:11 212:8 216:2 231:8 238:22 300:15 302:18 303:2 306:16,19 309:21 335:14 336:5 339:17,20 341:2,4 341:9,11 353:22 354:3,6,14 resistant 17:7 19:11,15 29:19 30:8 32:20 33:19 34:3,13 36:16 37:9 48:20 49:8 59:14 60:6,7 61:3 63:8 68:14,17 69:2 70:14 72:9 72:20 75:12 76:1 76:5,7 135:8 142:6,6,11 143:2 143:15 145:21 150:5 164:14 171:8 178:17 182:11 184:19 189:1 203:19 230:9,13 302:20 335:8 352:20 resistome 155:7 163:12 resolve 52:5 resolved 61:22
---	---	---	---

resource 143:11 144:3 182:2 204:1 308:8 resources 4:19 13:16 26:6 68:2 80:1,2,6 200:8 201:6 295:19 302:7 307:1,8 308:5,8 respect 121:2 145:20 150:15 respectively 206:17 respiratory 5:6 10:16 23:8 27:16 33:9,15 86:18,20 87:2 90:18 111:3 113:17 114:17 116:18,22 120:14 121:21 147:3 150:9 224:18,21 224:22 269:5 270:10 273:8 274:20 277:17 279:11 283:22 288:22 316:6 318:12 response 21:17 28:1 55:7 79:15 105:14 118:3,10 119:14 125:13 136:4,9 162:12,12 162:20 208:14 210:17 229:21 249:14,16,21,22 250:2 258:8 283:16 284:1,2 289:13 297:15 317:7 319:13 327:17 342:19 responses 160:4 165:15 310:10 responsible 80:5	responsive 182:20 183:14 rest 157:7 restores 70:13 restrict 74:14 restrictions 22:10 300:8 result 52:10 90:5 281:11 resulted 88:8 117:17 270:10 resulting 119:8 results 104:14 117:13 175:9 191:1 210:18 232:10 284:17 287:3 292:20 316:13 321:15 resurrect 70:1 resuscitate 286:20 resuscitated 286:17 resuscitation 314:16 retrospect 118:22 retrospectively 102:22 returned 29:15 returns 86:13 reveal 166:21 review 73:18 75:4 78:9 89:5 110:5 112:5 295:22 310:11,15 reviewed 87:8 reviews 158:16 255:16 rex 7:4 9:15 17:22 27:6,6 39:3,22 43:1,4,12,15 57:18 62:9 69:5 76:14 78:10 191:7 297:21 330:21 331:1 333:13,18	334:1,6,9,13,18 349:14,16,16 rex's 43:7 202:14 rhesus 112:19,22 ribotype 300:15 rich 119:9 186:17 rid 164:5 rif 248:11 rifampicin 354:17 rifampin 247:6,7 247:21 252:11 253:1,5 341:1 right 28:2,7 34:2 35:20 42:9 47:7 48:10 51:2 59:15 65:1 79:13,18 82:2 88:13 89:2 101:14,19 106:7 115:18 118:7 140:17 149:7 193:5 196:14 200:12 202:7 205:17,18 208:9 212:15 214:8 220:7 222:7 226:12 228:9 230:5 232:3 234:11 242:7 245:9 246:1,17 250:21 259:10 277:8 287:4 288:1 289:16 290:15 293:6,7 296:4 311:7,15 314:20 334:18 336:18 338:7 340:11,16 343:11 345:8,19 347:4,14 350:10 355:6 rise 260:9 risen 31:10 risk 58:20 61:6,9 61:13 62:4 75:20 139:17 159:12	190:19 194:17 303:14 risks 336:10 rnaseq 145:8 road 1:14 139:10 251:8 roaring 249:7 robert 2:16 11:7 11:13 26:19 151:2 169:3,16 172:21 175:22 robin 5:8 9:17 27:11 43:2 45:3 66:16 robust 74:19 77:13,19 112:22 180:14 235:22 259:15 robustly 211:8 roche 58:3 rocky 35:21 rod 152:20 rodentia 265:12 rodents 265:6,6 265:20 role 24:1 58:5 131:6 134:14 137:14 139:22 148:13 149:22 155:12 161:21 162:11,13 163:17 165:17 167:7 191:2 237:3 249:14 309:20 312:20 319:9 328:21 roles 18:1 167:6 roll 251:14 rolling 156:19 room 33:16 37:8 56:10 110:8 118:6 121:19,22 185:6 318:7
---	---	---	--

rooms 190:22	s	350:7 352:13	scores 245:7,8
rotate 224:3	s 2:1 3:1 4:1 5:1	353:22	scrape 261:18
rough 149:16	6:1 7:1 8:1 9:1	saying 44:6 101:2	screen 52:16
roughly 101:18	10:1 11:1 12:1	195:12 259:9	60:22 165:3
102:19 103:1	13:1 14:1 15:1	331:12,22 334:9	168:13 233:3
206:16 207:11	s4 112:15 113:14	334:12	screening 54:12
266:19	sacrificed 81:16	says 192:4,8	80:7 172:6 222:4
route 84:3 92:19	safe 22:10 135:13	332:10 349:16	scrutiny 301:4
98:15 128:9	309:1 355:19	scale 82:1 107:12	se 190:19 345:21
135:18 138:5	safeguards 41:21	scan 36:12	sec 202:7
173:10,11	safely 287:6	scanning 153:8	second 16:21
routes 89:20	safety 21:3 22:8	scarce 289:19	17:14 29:10 46:4
232:15	30:8 41:4 46:17	scary 29:21	68:11 107:15
routine 50:4 72:13	47:15 53:3 59:19	scatter 182:19	113:19 180:4
188:5 281:8	61:17 75:3,4 77:4	scenario 41:15,16	185:12 192:14
routinely 48:17	77:22 84:10 110:9	100:16 101:3	194:21 195:11,12
221:22 238:15	123:9 139:11,18	105:22 106:1	209:15 295:6
341:2	181:5,16 220:7	194:17 332:5	318:15
rubric 46:9	291:2	scfv 268:2	secondary 61:13
rule 20:11,21 21:1	saline 318:14	schedule 295:15	102:8 119:1
22:6,15,18 39:10	saliva 288:3	scheduled 62:11	141:19
39:20 41:13,16	salmonella 31:17	school 3:12 5:19	secondly 309:8
46:15 80:18 81:21	188:21 199:1	8:5 28:6,12 162:1	secrete 149:14
84:6 92:5,12	240:12	189:20 191:5	secreted 147:19
97:20 100:17	sample 325:11	234:7	147:19
112:10 128:18	samples 122:2	schu 112:15	secretion 148:2,3
131:21 297:22	272:13 275:10	113:14	157:17 166:5
298:3 317:4	292:19 324:8	science 130:2	255:19 292:22
349:18 350:6	sampling 122:1,12	138:12 164:21	section 4:19 24:12
rules 328:20	147:18	184:6,11 235:18	26:5 80:1 202:12
run 65:14 66:4	samuel 6:13 11:6	286:8 308:21	280:5 301:21
71:21 78:20 106:4	26:21	309:14 310:1,3	310:3
110:9 132:13	san 3:22 13:7	sciences 6:15 8:9	sections 245:22
170:7,12 174:10	26:12 264:13	168:20	sedation 291:16
230:3 235:21	satisfies 71:2	scientific 9:4 15:2	321:8
255:20 333:6	saturation 274:1	25:4 62:17,20	see 31:12 33:21
334:7	savings 94:5	112:9 351:11	34:22 35:4,11
running 79:11	saw 35:21 36:3	scientifically	36:8 40:19 41:9
140:16 170:10,16	98:19 105:15	63:19	49:1,13,20 54:22
204:10 295:15	116:19 119:3	scientist 3:5 7:13	57:13 59:15,22
311:16 342:12	123:15 223:22	scientists 176:19	60:9 68:22 73:19
runs 170:2 222:17	231:19 232:5	180:5 284:15	75:5 79:8 85:2,7
russo 240:21	254:9,9,16 329:13	scope 184:21	85:17 86:8,10,15
342:13 343:18	341:10 343:9		86:19 88:9,12,18

89:8 91:6,17 94:2 102:2,2,3 105:21 106:6 108:2 115:21 117:13,19 117:22 122:18 123:7 126:4,18 128:14 130:10,11 131:9 133:4,7,9,9 134:2 136:10 140:5 149:5 153:9 153:10,16 154:19 163:5 168:13 177:21 178:9 179:8 180:4 182:18 190:13 195:19 208:8,9,12 208:14 209:1 210:16 211:3 212:3,13,16 213:3 213:7 214:9 215:1 217:17,18,18 218:3,17 220:4,11 220:14 226:8,15 226:22 230:8 231:3,5,7,10,14 232:2 235:4,18 242:9,15 243:4,12 244:2,16 245:4,5 245:15,18 246:2 246:14,18 247:5,8 247:11,22 248:2 248:10,22 249:10 250:4,10,13 252:9 252:13,14 253:11 253:14 254:13 255:9,21 256:9,10 256:14 257:4,6 261:8 262:13,13 263:12 266:7,8 269:10,16 270:17 271:3,11 274:18 275:11 276:11 277:12 278:22 279:21 282:18	285:9 290:14 297:10 299:11 304:14 313:1 324:14 329:13,15 332:13 339:18 340:19 341:3,4 343:6 344:4,16 348:17 seeing 79:18 98:9 195:5 232:6 237:8 237:13 246:11 254:1,17,19,20 323:8 343:5 seek 46:2 187:9 seen 15:12 37:8 90:20 133:7 135:21 169:18 179:2 190:3,6,6,8 190:10,20 206:13 217:10 229:10 235:5 259:7 260:7 326:9 341:4,6 sees 219:2 select 22:3 93:2 147:13 selected 112:15,16 116:2 selection 39:8 91:13 93:15 237:17,21 267:3 selections 181:14 self 185:2 sem 251:22 sems 255:8 send 310:19,20 senior 7:13 sense 35:14 53:12 81:18 97:3 168:9 220:20 332:19 352:6 sensing 149:12,13 164:6 sensitive 149:17 230:11	sensitivity 352:17 sent 155:22 separate 55:9 156:4 sepsis 150:7 154:11 164:7,18 196:20 206:17 250:15 257:17 260:10 267:5 279:17 323:6,10 323:14 338:18 september 311:5 septic 250:11 262:22 278:3,5,12 279:7,8,17 288:12 314:12,13 315:5 316:6 323:14 324:9 septicemia 175:20 septicemic 232:7 sequence 126:15 143:6 144:15 203:22 sequenced 75:9 142:17,19 347:17 sequences 265:18 sequencing 145:7 300:20 sequential 326:20 sequestration 163:15 serial 118:14 275:10,11 324:8 series 87:6 113:19 serious 1:3 15:7 21:4 24:15 31:3 37:9 42:5 48:15 135:14 194:19 196:17 203:21 309:9 336:11 serratia 124:1 serum 103:6 149:17 162:16	served 129:22 serves 94:18 295:22 service 2:19 181:6 services 8:6 80:7 95:9 170:1 180:20 181:1,5,13,15 183:19 301:20 304:5 305:6,7,16 307:4 310:18 session 11:6 12:7 25:8,10,17 42:20 43:1 57:19 66:15 79:11,14,21 124:19 295:21 set 76:2 124:9 192:18 238:16 241:2,6 242:3 243:7 261:12 273:6 288:17 328:5 333:5 348:22 sets 338:2 setting 108:6 128:2 154:8 281:12 283:16 284:17 321:18 343:13 settings 39:20 54:8 71:20 169:18 273:10 setup 45:2 65:1 273:19,21 seven 176:19 195:4 213:1 severe 87:13 90:6 114:17 267:5 277:14,22 278:2,9 278:12 279:17 286:1 290:20,22 291:1 323:14 324:15,20 325:1,3 325:6 338:18
---	--	---	--

severely 100:6	82:9 88:3 118:7	179:1 226:12	91:3 112:11 115:7
severity 150:16	124:13 132:5,11	242:5	124:7,8 126:17
284:10,11,22	139:11 161:19	shunting 121:17	127:10 128:20
295:5 314:14	172:1 179:14	sick 16:6 19:3	130:12 135:20
327:6,7	193:21 223:17	32:15 33:16 71:9	148:19 158:3
shake 261:18	226:2 227:7 230:2	71:19 74:8,13	179:2 212:5,14
shallowly 121:7	234:18 237:2	85:16 86:11 136:5	213:18 215:7
share 32:7 169:6	239:6,14,16	sicker 75:5 117:2	258:11 263:14
170:5 171:15	245:13 247:14,14	117:2	265:12,22 266:7
179:18 180:11	254:3 256:18	side 34:2 35:20	305:17 317:7,8
264:20 267:15	272:20,20,21	63:15 101:17	318:22 319:11
300:9,9 302:6	274:21 283:10	157:4 168:5	340:18 342:11
sharing 66:13	329:18,18	182:10 226:12	352:18
130:5	showed 40:21 49:5	227:9 228:9,11	similarities 127:12
sharp 290:14	50:20 76:13 89:9	231:4,9 252:7	295:3
sharply 278:18,18	93:7 118:19,20	348:1	similarly 127:13
shaves 251:2	135:7 195:4	siderophores	160:20 342:12
sheep 259:2	232:16 233:4	147:21	simple 65:16
282:22 286:7	239:18 245:15	sides 246:6	80:20 168:4
288:2	263:5 325:14	sigma 54:13	simplest 51:2
sheer 265:14	334:18 343:18	sigmoid 208:22	simplify 50:15
shift 208:14 336:2	showing 16:8	sign 290:13	simply 180:3
shifted 210:17	33:22 68:18 86:1	298:21	192:16 206:7,10
shine 153:17	86:6 87:3 88:5,21	signal 121:9	single 9:13 15:13
shipping 89:20	89:3,7 90:1 194:3	139:20 319:22	16:22 17:15 21:18
shock 34:17 278:3	228:3 232:9 237:1	signals 164:6	42:21 43:14 44:8
278:5,13 279:7,8	242:19 271:16	signed 24:11	77:7 110:13 145:3
279:17 288:12	274:1	significance 107:2	161:16 173:18
314:12,13 315:5,7	shown 43:21	207:4	187:12 318:21
316:6 323:14	52:12 60:5,8	significant 17:5	singular 155:4
324:9	76:13 115:11	67:18 68:4 74:9	sink 236:2
short 54:9 56:19	139:17 141:13	89:18 107:3 129:1	sirnas 167:4
62:15 78:19 108:2	144:16 148:6,11	154:8 165:18	site 15:15 18:6
138:20 168:16	148:13 162:18	231:5,21 271:12	35:3 36:2 38:16
330:12,16 340:1	177:20 178:16	significantly	119:4 120:10
shortcomings	222:16 230:6	23:15 120:6	144:7 147:9 150:7
23:21	238:20 239:20	270:19 271:9,14	170:21 172:10
shortened 208:13	265:16 268:7	275:22 276:20	206:21 207:19
shorter 88:20	270:15 328:15	signs 85:10 87:3	213:22 214:2,3,3
shorthand 46:5	shows 73:18 86:14	114:16,16,22	215:7 216:16
shortly 98:14	88:17 115:9,10	silver 1:12,15	217:2,22 218:5,18
show 17:5 32:18	117:11 127:11	silverman 339:19	220:22 221:2
37:8 48:7 49:4	147:12,18,20,21	similar 59:17 60:7	229:14,17 256:11
50:7 53:6 60:11	148:2 161:20	76:12 77:20 90:21	260:9 262:7 345:6

345:18 sites 19:17 37:16 39:16 40:12 41:10 51:11 55:1 65:19 77:1 82:18 127:9 146:6 147:10 150:19 306:18 337:3 siting 74:2 sits 332:10 sitting 110:8 situation 46:12,16 47:1 78:21 110:10 131:2 145:12 148:5,15 150:10 236:10 248:3 250:4,6 255:17 262:10 318:3 329:4 situations 22:8 128:19 212:5 334:21 six 31:21 49:21 67:20 111:22 219:15 255:19 269:11,14 271:5 273:4,5 size 47:4 55:17 78:17 79:2 114:5 120:9,13 132:6 255:22 331:18 sizes 120:11 skeptical 284:16 skilled 177:6 skills 356:7 skin 35:5 36:4 38:5 51:10 68:3 121:17 145:19 146:16 154:11 160:10 169:9,9 175:11,11,12,12 261:10 267:6,6 342:8	skip 154:18 skips 31:15,19 36:9 skyrocket 249:3 slant 299:11 sleep 4:10 sleepy 234:14 slide 24:5 29:10 29:11,13 30:20 31:6,18 32:4,15 33:6,21 34:7,22 35:11,17,20 36:8 37:6,22 39:6 40:5 40:14 41:12 43:22 55:3 57:4 59:22 73:18 75:8 81:18 85:5 86:1,14 87:15 88:21 92:13 147:12 148:6,11 153:17 162:15 169:6 177:20 211:18 230:5 235:19 237:1 242:19,22 248:22 254:4,17 282:18 284:19 285:4,12 285:17,22 286:4,6 286:10 294:8 295:9 297:4,9 298:2 301:14 304:14,14 311:8 slides 16:9 28:18 67:13 89:6 118:7 125:3 135:7,21 168:14 280:16 296:7 299:3 333:3 slightly 54:15 276:17 slow 225:5 small 24:9 39:14 41:2 49:17,18 61:16 62:1 76:14 111:1 128:6 137:9 233:15 235:21	246:1 251:10 259:21 275:1,4 281:21 282:6,17 283:11 285:15 287:3 294:12 320:11,22 321:6 333:5 351:18 smaller 48:9,11 208:16 216:21 260:18 312:17,20 318:22 319:20 320:13 326:4 328:20 smallpox 129:15 129:19,20 130:11 130:15,16,18 131:3,15 197:21 297:13 snda 83:2,4,15,16 84:4 societies 294:3 soft 146:16 154:11 160:10 206:16 soil 186:20 soldiers 200:19 234:22 249:10 sole 307:8 solely 215:9 solicit 309:4,13 solid 219:22 soluble 253:7 solution 53:13 solutions 125:19 130:7,8 134:5 solve 125:21 130:1 130:12 somebody 152:7 196:17 297:9 313:1 somewhat 45:5 83:17 88:8 100:9 131:22 217:1 sons 34:21	soon 255:15 314:14 sophisticated 192:19 332:9 sordid 152:4 sorry 16:8,8,10 29:1 36:17 66:11 291:18 294:15 325:18,18 sort 29:12,13,18 30:2,12 35:15 44:20 53:7 55:1,3 55:6 74:5 87:18 131:9,16 132:18 133:18 134:11 135:18 138:18 140:2 151:20 156:18 157:5 163:12,16 165:9 165:10 166:8 187:19 191:19 193:1,19 243:2 267:1 303:8 311:22 316:20 317:20 319:5,6,8 319:10 320:14,18 322:5 329:2 331:1 331:10,22 332:2,5 338:10,17 342:1 350:15 351:11 sorts 259:1,2 273:16 320:16 334:20 sounds 313:3 341:20 346:18 349:6 source 113:3 143:12,13 148:20 174:15 304:20 307:9 sourced 113:2 sources 37:21 143:9 151:15 187:3
--	---	--	--

south 237:10	125:19 139:8	sponsored 316:10	263:17 288:16
southeast 113:2	140:6 212:8	sponsors 95:21	289:12 291:16
space 22:22 73:7	267:21 283:15	96:2,8 100:14,14	292:17 323:15,20
157:1 270:10	284:5,13 300:12	104:5 110:18	331:4 333:10
296:14 306:19	312:22 326:11	111:16 303:18	337:6,11 345:5
308:10 319:10	345:1,9,12,12	304:16	standardization
spain 6:7	352:5	spontaneous	345:1
speak 125:3	specifically 59:8	143:1 159:19	standardize 91:18
160:19 176:18	97:11 113:3	spookiness 153:6	199:11
179:17 347:1	214:16 222:21	spot 161:10	standardized
speaker 28:8	291:10 310:2	spots 73:12	150:22 215:22
57:19 66:15 79:22	316:3,7 326:17	spr741 247:17	239:22
110:21 124:19	345:6	spread 55:2	standpoint 121:1
151:2 205:3	specificity 60:1	spring 1:12,15	237:13 328:2
221:19 233:22	129:17 130:15	33:8	staph 28:14,15
234:2 264:11	specifies 129:17	sputum 32:16,19	36:3 38:5 175:18
280:5 291:19	specimen 60:3	33:12 90:16	264:14 271:21
295:20 301:19	spectrum 38:4	square 244:3	315:11,19 337:6
308:16	40:16 44:1,3,3	258:21	staphylococci
speakers 2:3	57:5 68:20 69:6,9	squeak 56:16	119:3
42:22 74:22 79:21	71:12 131:17,19	ssti 322:20 343:7	staphylococcus
282:11 283:9	212:10 303:8	st 263:6	266:15 274:2
287:13 294:15,16	speculate 214:12	st2 263:5,6	313:19 314:5
342:3	spellberg 151:13	stability 186:12	337:6 352:10
speaks 158:16	158:15 162:18	300:21	353:5
349:6	spend 104:4	stable 51:9	start 16:7 26:2
special 306:15	191:20,22 193:3	staff 321:9	29:12 74:12 78:21
specialized 157:17	193:19 298:2	stage 197:15 203:2	88:12 95:7 121:6
186:22	spent 31:14 50:13	297:18 307:10	125:4 135:16
species 9:13 15:14	58:2 66:22 223:20	339:11	162:22 163:1
17:1,15 21:16,18	spero 247:16	stages 101:20	165:12,16 166:20
23:10 42:22 43:14	spero's 248:1	196:3 198:12	167:3 174:17
90:11 93:2,5 94:5	spiked 354:4	304:11 307:22	175:16 186:1
111:19 112:17	spirit 29:5	stakeholders	193:15 194:4
113:1,8 125:19	spleen 114:22	309:5 332:18	195:17,21 196:8
130:14 132:2,6	115:17,21 119:10	stand 301:3	202:13 210:1,4,11
134:16 139:8	176:8 231:21	standard 18:13	222:8,22 227:2
140:6 152:10,11	246:19 276:1	34:5 37:16 46:14	236:20 245:3,10
237:5,7 265:19	spleens 229:18	47:3 48:22 49:11	246:14 247:11
268:9,11 351:4,6	splint 253:20	49:22,22 50:5	252:13 292:4
351:13	sponsor 50:18	51:21 52:19 54:6	299:14 313:2
specific 18:15	54:11 82:21	54:7,7 75:16 78:4	317:9,14 321:14
23:12 24:20 59:10	104:21	98:22 144:8	322:3,4 329:7,8
59:10,11 69:4		182:21 193:1,1	

started 17:2 35:2 106:15 112:20 117:3 125:9 130:22 155:20 156:22 157:8,13 197:12 204:18 234:17 235:15 238:1 242:7 243:11 266:16 267:13 271:19 287:4 292:12 314:4 starting 82:1 119:21 130:1 249:3 257:10 287:11 starts 317:11 stasis 209:22 210:19 211:4 212:3 213:5 214:7 215:3 217:18 218:5 state 1:2 15:6 144:20 309:6,20 356:19 stated 326:12 statement 24:19 95:7 111:14 152:3 158:15 states 181:3 204:3 236:15 265:5 281:10 294:10 339:4 stating 29:14 station 251:1 stationary 344:15 stations 251:13 statistical 47:13 75:20 107:2 207:4 300:4 331:11 statistically 107:2 331:22 stats 244:12	status 33:15 303:3 stay 29:3 147:8 150:8 244:1 staying 254:15 stays 156:15,15 steadily 332:16 steady 175:22 283:1 steep 50:3 step 78:5 136:18 307:5,7 344:1 346:3 351:19 stephen 322:16 steps 12:6 25:15 103:17 136:22 137:1 204:15 310:8 stewardship 30:17 41:22 61:6 184:8 sticking 190:21,22 stimulation 124:5 stimuli 153:19 stockpile 96:9 297:3,15 stocks 349:2 stokes 2:19 stones 341:7 354:11 stood 110:11 stool 107:1 194:2 stop 94:10 301:10 stopped 35:18 story 66:6 storyline 50:16 straight 292:17 strain 23:12 92:21 92:22 112:15,16 116:14 142:17 143:1,3 144:14,15 146:1 160:5 167:11 171:12 173:16 174:9 182:12 190:4,10 191:15 195:3	210:15,19,20 211:15,15 212:19 230:10 233:10 237:16,21,22 238:9,17 239:9,11 244:3,6,15 245:19 248:5 252:13 257:20 263:4,5,8 263:11 268:21,22 287:15,20 298:17 340:16 343:11 345:12,13 346:1,4 346:5,6,15,16,18 347:13 348:16 349:8,11,12 355:2 strains 48:20 58:20 59:14 60:4 60:7 61:3 63:8 69:1 70:1 93:1 111:20 143:14 148:7,8,16 149:5 149:11,17,20 150:17 160:2,13 162:19 165:22,22 166:1,2 167:13,15 169:5,11 170:18 170:18 171:7,8,14 171:15 172:21,22 174:3,7 177:21 181:21,22 182:6 183:2,15,17 190:6 190:7,8,12,14 191:15 196:12,14 196:15 197:9 198:9,15,20 199:22 200:5,9,11 200:13,15 201:4,8 201:22 211:1,2,7 211:14 212:9 216:6,8 221:8 238:2,13 240:2,3 240:16,17 241:1,3 241:17 242:13,16 243:13 245:15,16	245:17 250:18 257:15,18 287:19 288:7,7,11 299:17 347:16 348:7,14 348:22 strange 157:9 strategic 297:2 308:21 strategies 167:19 205:10 strategy 7:6 27:7 30:15 74:12 184:8 208:17 302:19 stream 82:6 streamlined 139:19 strength 47:13 143:10 stress 122:16 197:4 stresses 344:8 stressful 110:10 stretch 159:15,15 strict 289:20 strictly 246:8 strides 30:19 stringent 228:22 strive 182:19 205:10 strong 45:16 77:11,11 99:12 130:14 294:5 stronger 45:16 strongly 70:21 98:20 100:17 107:6 struck 84:22 structure 169:9 175:11,12 267:6 struggled 36:9 stuck 56:14 students 279:20 279:20
--	---	--	--

studied 17:13 21:2 59:22 61:14 65:22 95:18 151:20 158:13 162:15 213:9 219:12 studies 21:7,13,20 22:7,14,14 23:2 29:8 40:8,22 41:2 41:13,14 55:12 61:15,15 71:22 72:16 74:2,17 81:15,19 82:13,16 83:7,9 84:20 85:4 88:2,4,5,7,9,12,22 89:6 90:17 91:20 92:1,5,7,12 93:21 94:3,7 104:11 105:5 106:4 107:17 110:5,9,10 112:11,21 113:10 113:19 114:6,9 116:2,11 117:5,7 117:10,12 118:14 119:20 120:11 121:10 122:17,21 123:8 124:2,8,9 124:16 128:7 149:3 160:16,17 176:7 179:16 182:15 190:12 206:7 208:7,10 211:19,20 213:16 213:20 215:1 218:4 227:17 232:5 237:10 265:9 287:4 298:4 299:8,10 301:3 305:11 309:9 310:4 312:13,16 319:20,21 322:10 332:11 333:5 351:18 353:17,19 353:19,20,21 354:1,6	study 20:4 22:9 23:5 29:9 46:21 49:9,12 50:19 51:1,6 52:7,20 53:8,16,22 54:1 55:21 61:16,17 62:3 64:5 65:1,14 66:4 75:12 76:2,3 76:10 77:7,16 78:4,17,20 79:2,2 81:4,4 82:10,11 82:14,18 83:5,8 83:22 85:6,13,20 86:19,21 88:13,14 89:1 94:1,7,9 104:16 105:6 107:9 113:15,16 114:2 116:16 118:15 119:12 124:2 128:12 156:18 159:3 160:11 162:1 171:18 174:8 194:9 196:22 206:2 207:11 209:6 210:14 213:13 216:5 221:6,22 237:2,4 238:10 239:12 267:11 281:3 285:5 286:16 290:19 291:1 293:19,20 294:11 298:16 311:2,5 313:19 314:2,9 325:14 327:4 339:10,12 341:1 studying 18:2 42:8 49:7 54:1,2 153:12 216:4,6 235:17 322:2 346:15 stuff 35:5 199:15 239:19 244:21	254:11 261:3 262:3 320:22 sub 55:9 121:15 247:8 subacute 122:8 subclinically 247:9 subcutaneous 121:11,14 175:13 230:18 232:17 subject 169:2 subjects 55:17 77:9 79:1 92:10 100:20 103:14 submandibular 324:4 submission 24:22 84:4,7,11 submissions 67:1 310:13 submit 83:11 309:15 310:12,19 submitted 83:13 84:15 submitting 112:9 suboptimal 19:21 subsequent 84:3 88:2 117:5 subset 166:13 subsets 55:11 subspecies 111:20 substance 21:6,10 substantial 60:16 74:16 112:12 119:16 331:5 substantially 98:17 substantiated 326:11 substantive 74:16 substitute 203:3 subtle 242:11 success 156:11 171:3 218:13	219:6,6 successful 110:4 139:7 155:4 219:14 304:1 308:11 328:11 succumb 100:5 105:15,17 108:9 succumbed 86:3 228:12 231:1 succumbing 108:9 sudden 154:20 suddenly 325:15 sufficient 76:9 266:3 sufficiently 21:19 48:21 350:18 sugars 162:2 suggest 106:11 217:8 suggested 79:5 98:20 100:17 108:8 195:7 236:8 suggesting 98:13 275:8 277:16 278:19 279:2 suggestions 92:2 suggestive 70:22 105:18 suggests 49:18 270:21 suit 96:7 suitable 65:8 267:2,10 299:15 299:20 suitably 47:21 suited 61:5 sulbactam 66:18 67:9,15 69:3,10 70:13,15 77:2 sumathi 6:18 9:7 12:7 15:9 28:21 62:9 84:8 124:22 140:14 280:19
--	--	---	---

summarize 90:8 109:13 140:2 262:14 summarized 89:12,13 summarizing 40:15 summary 84:19 117:12 162:15 179:20 summer 16:18 50:12 51:18 57:10 217:11 311:4 suny 240:21 342:14 super 244:10 superficial 175:13 superimpose 212:16 superimposed 242:20 superior 48:8 106:13 superiority 17:6,9 19:8,13,18 20:1 38:20 40:22 48:6 48:12,17 49:2,2 49:18 53:16 62:12 76:11 78:5 superoxide 163:3 supplemented 20:17 support 13:16 93:17 106:11 180:14 184:17 194:10 206:20 282:9 285:15 295:19 299:9 301:20 302:21 303:4,10 305:10 306:13 309:14 supported 200:13 supporting 27:8 94:16	supportive 77:3,9 134:11 284:22 supposed 153:16 161:8,10 288:20 sure 26:3 37:8 41:6 45:22 46:4 154:17 160:6 247:2 262:4 294:22 313:8 324:16 334:2 343:9,12 surface 145:19 256:3 surfaces 120:21 surgery 32:8 188:6 318:3,5 surgical 113:16 188:6 225:4,7 267:8 338:20 surgically 113:17 surprising 118:22 218:9 surprisingly 114:12 surrogate 100:9 104:5 131:9,10 333:17 surveillance 30:17 survival 21:22 88:5 98:17 104:17 104:19 106:8 107:3 108:7 109:6 109:8,11 166:10 172:12,14 174:2 176:5,6 183:3,6 207:1,5 228:11 229:7 231:16 238:5,10 239:12 247:22 248:2 269:9,17 271:8 295:4 survive 114:21 116:7 247:12 269:18 270:16	271:6,7 274:13,13 275:18 survived 85:6,18 86:20 115:13,19 228:13 276:5,17 survives 86:13 surviving 85:18 survivor 86:12,16 86:17 survivors 86:4 88:10 324:14,14 susceptibility 53:14 132:8 239:2 266:1 susceptible 36:18 54:8 155:1 160:3 171:11 178:18 182:4 188:2,20,22 190:15 221:7 240:18 252:13 257:21 288:9 292:12 353:2,10 suspension 177:3 290:8 sustaining 185:2 swelling 256:9 swim 243:6 swimmer's 146:9 swimming 146:11 swine 266:10 swiss 58:13 sword 314:22 symbol 270:16 symbols 219:22 220:2 228:11 270:17 274:9 symptoms 32:17 syndrome 288:22 316:6 318:12 synthesis 166:8 syringe 225:15 system 110:4 145:17 148:3 221:21 227:20	228:7 252:2 255:19 258:3 284:1 303:7 systematically 62:3 198:11 systemic 199:5 252:1,2 326:22 systemically 249:13 systems 93:17 148:2 157:17 166:21 259:15
			t
			t 2:1,1 3:1,1 4:1,1 5:1,1 6:1,1 7:1,1 8:1,1 9:1,1 10:1,1 11:1,1 12:1,1 13:1 13:1 14:1,1 table 125:1,11 tailored 61:6 taipei 181:10 taiwan 73:20 181:4,10 take 25:21 75:20 79:8 85:15 87:5 128:6 130:16 135:11 137:1 140:16 167:20,22 171:1 188:10,10 195:3 198:22 199:1 221:12 225:17 236:10 237:16 240:5 245:8 247:22 251:21,22 255:2,8 256:1 259:14 260:16,20 263:3 264:6 269:20 273:15 295:16 298:17 300:5 302:4 304:6 307:4 310:8 319:10 324:8 329:16,16 355:15

taken 47:13 73:18 87:11 89:11 102:15 105:9 136:19,22 279:5 314:10 316:17 356:3,9	target 15:13 17:12 37:11 59:8,10 61:16 72:8 77:18 116:2 181:13 209:16 210:7,19 210:21 211:4,9,16 212:3,4,9,17 215:19 216:14 217:2,6 219:21 220:4,6,11,12,15 233:18 352:10 353:10,11	telemeters 113:16 116:17 telemetry 85:21 88:1 117:12 121:1 121:11 tell 80:14,16 110:7 133:1 153:12 173:19 180:21 195:14 206:22 216:10 222:11 223:2 320:2 342:1 346:21	85:14 144:9 174:1 178:15 184:3 186:10 199:5 204:21 305:6 316:21 327:9 332:13 336:3 341:4
takes 87:21 94:2 111:21 137:11 262:6	targeted 59:12	telling 141:8 254:12	test 18:17 39:13 52:13 54:18 64:9 82:17 91:1,4 95:14 123:9 170:19 181:6 192:20 198:9 200:11 233:13,17 238:5 252:18,19 268:9 281:18 304:9 306:6 314:18 321:17 352:21
talk 25:3,13 29:7 32:5 37:14 39:4 42:20 50:8,10 58:12 91:12 95:4 96:5,21 97:15 99:19 100:10 111:9 126:2 129:6 129:19 137:14 142:15 145:10 151:3,19 165:21 189:20 205:19 237:17 247:5 263:13 287:16 296:6 299:4 301:16,19 304:7 339:16 342:4 343:3	targeting 9:13 42:21 43:14 120:12 134:16 164:12 222:5 233:19 267:21	temperature 86:2 86:9,12,17 90:14 102:3,17 113:18 116:18,21 117:2 117:20 118:4,6 121:11,13,15 153:20 228:4,5,9 228:15,18 229:4,9 229:11 266:4 290:15	tested 82:5,13 104:15 109:2 147:16 149:20 178:15 263:15,20 268:6 283:4 316:7
talked 56:15 131:6 134:7 172:21 173:1 194:11 202:9 223:13 331:8	task 298:12,15 299:1	temperatures 101:10 102:19 142:1	testing 38:3 93:18 116:13 154:17 173:20 181:5,15 181:16 183:15 195:10 203:5 222:2 223:17 236:4 252:19,20 252:21 264:16 267:10,16 302:9 305:9 306:2,12,14 330:5 337:7,11 353:1
talking 44:3 47:5 50:13 59:6 95:16 134:10 169:14 174:18 184:20 200:1 258:16 307:20 316:1 319:5 328:14 331:2 336:14 338:9 341:19 342:1,21 343:12	tazobactam 34:4	temporarily 250:2	tests 38:22,22 323:15,16 324:1
talks 48:2 140:22 255:5 281:7 303:2	team 58:4 110:17 124:16 222:15 223:22 225:19 250:20,21 251:9 251:18 293:18	temporary 195:13 245:2 248:17,21	texas 8:8 168:20 170:2 286:13
	tease 172:13	tend 149:10,11 223:15 227:16 324:10 354:20	thailand 73:20
	technical 143:21 165:5 168:12 301:6 310:16	tension 277:20	thank 25:22 28:21 28:22 42:14,16,16 43:12,15 57:17,18
	technically 225:4	term 122:18 138:20 139:2 152:16,17 284:7 330:13,16 340:1,3	
	technique 177:4,4 177:12	terminal 99:11 105:3 142:4	
	techniques 263:14	terminally 119:15	
	technology 184:11 184:15	terms 31:19 39:16 41:12 51:12 54:15 55:7 68:16 80:17	
	teeter 168:7		
	tegaderm 251:12		

58:8,9,10 63:16 66:12 67:4,5,5 79:6,7 80:14 94:10,12 95:2 110:19,20 111:7,7 124:17,18 125:7 140:13,18 141:5,5 143:22 151:5,13 168:10 176:13,16 176:16 180:16 183:20 184:2 185:5,17 191:6 221:17,18 233:21 234:1 264:9,19 280:2,3,19 291:21 295:9,11,13,14,16 301:18 302:2 308:14,15 311:12 336:6 349:9 353:14 355:4,6,8 355:11,12,13,18 thankfully 262:22 thanking 125:4 222:8 thanks 43:19,20 66:10 95:2 124:22 140:15 176:14 180:17 183:22 185:19 189:18 205:14 296:4,5 311:14 theme 45:6,14 themes 39:19 theodor 287:1 therapeutic 89:3 95:19 97:10 99:7 108:6,14 181:7 206:8 222:1 223:16 224:9 227:17 229:6,6 239:13 252:17 303:19 304:18 therapeutically 329:12	therapeutics 5:10 9:17 25:7 27:12 43:3 66:16 80:8 112:10 116:9 199:18 222:4,22 229:10,12 232:16 233:13,17 235:20 235:22 236:4 247:16 297:8 300:2 302:9,22 303:5 304:4,9 305:9 306:2,7,14 308:13 therapies 18:22 19:12,21 34:5 59:12 96:21 167:4 170:3 171:13 175:9 233:5,7,11 284:22 287:6 therapy 16:7 19:9 19:19,21 34:10 36:6 45:17 48:15 48:16 49:12,19 54:5 61:5,20 72:8 72:15 73:4 77:2 78:22 131:14 136:17,17 137:10 137:11,13 164:8 164:10 165:15 170:19,19 172:11 195:9 207:13,17 210:1,4 thermal 315:10 thigh 182:7,13 183:11 206:15 207:12 208:8 210:13 213:1,5 214:5,10,20 217:16 344:3,4 353:18,19 thing 42:10 46:4 56:13 76:16 82:8 82:10 83:20 84:14 84:21 126:6,22	132:13 133:16 137:18 154:15 157:6 161:4 195:11 196:12 199:22 200:1 201:9 203:16 226:10 228:1 235:12 249:17 250:18 253:2,16 254:16 300:16 318:1 347:3 things 31:16 38:5 38:6 44:19 45:10 48:19 56:20 80:17 83:4 100:12 107:9 117:6 121:2 128:1 132:10,19 133:13 135:19 139:2 150:21 153:11 154:18 157:9 159:8 161:15 162:16 191:20 193:14,18 196:5 203:9 223:3 226:3 229:5 232:14 234:21 235:17 237:12 241:18 243:6 247:13 249:13 252:19 259:3 262:7 263:20,22 273:16 300:14,20 320:12 320:16 322:22 327:18 338:9 339:18 340:2,10 344:2 348:3 349:18 think 29:16 30:9 37:7 38:2 39:18 39:19 40:6,17,19 41:7 42:6 44:18 47:8 57:2 58:21 64:16 66:1,10 74:6 79:11 97:2,5	97:7 98:18,20,22 99:6,10,12,16 100:12,17 101:7 105:20 107:17 108:1,22 110:11 124:7 125:22 126:6 127:1 128:1 128:3 131:1 132:3 133:3,12,12 134:5 134:13 135:6,16 136:14,18 137:4,6 138:3,4,8,18 139:10,15 140:2 140:15 150:2,3,21 151:19 153:2 155:7 158:4,14 161:3 165:2,3,15 165:17,20 166:15 166:16,19,20 167:3,9,16,17,20 167:21,22 168:1,2 168:6,7,8 176:13 186:4 187:8,17,21 188:15,17 189:6 191:21 192:20 193:5,5 194:22 196:9 197:7,17,19 198:1 199:19,21 200:1,9 202:19 203:4,7,8,14,16 204:1,17 209:11 215:11,14 216:6 219:8 220:18 221:15 228:21 233:2 234:16 236:10 246:3,22 250:7 256:5 262:15 287:18 294:21 295:2 297:21 298:20 300:16 301:9,10 302:3 304:8 311:15,19 312:2,7 312:12,18 316:21
--	---	--	--

317:1,5,9,22 318:7 319:15,16 319:18 321:3,22 322:3,7,11,15,20 323:6,7,10,11,17 323:21 325:22 326:10 327:21 328:6,19,22 329:3 329:4,10 330:5,8 330:15,18 331:3 332:3 333:1,20 335:2,14 336:13 339:8 340:2 341:9 342:15,22 343:1 343:14,17,21,22 344:2,20 345:7,10 346:14 347:8,20 348:3,7,15 349:19 350:15 351:2,3,7 351:11 354:15 355:3,14 thinking 40:7 92:11 125:14,18 127:5 139:1 153:4 156:22 167:3 202:15 331:1 338:14 third 48:5 66:15 107:1,16 180:6 237:14 296:8 thirds 298:1 thorny 189:12 thought 29:11 32:4 51:5 54:14 54:18 55:1 100:2 107:8 109:21 126:2 133:7 135:15 136:10 151:21 156:20 186:1 233:7 254:21 257:15 265:11 333:3 346:2 350:8	thoughts 25:20 67:12,14,15 312:19 thousands 143:6 threatening 21:4 24:15 146:18 threats 30:22 31:3 31:5 three 29:11 42:22 45:4,4,8,11 50:9 55:5,5 57:12 107:9 108:13 167:22 195:15,16 198:11 207:3 208:20 230:17 237:16 242:8 269:3 270:14,16 272:8 275:16 277:13,17 279:9 318:21 321:20 325:2 threefold 180:2 threshold 266:3,8 throat 169:21 thromboembolus 318:4 throughput 266:20 267:4,8 throw 131:17 341:7 throwing 354:11 thushi 2:5 13:19 308:17 tidal 272:5 273:10 tie 206:10 tier 39:22 46:12 46:15,20 47:1,6,6 47:8,14 297:22,22 tiered 46:9 tiers 325:2 tigecycline 30:7 33:3 217:17,21 218:4	tight 166:22 226:22 347:11 tightest 209:2 till 228:20 time 19:20 30:21 32:22 34:20 36:3 36:14 42:10 47:17 49:12 56:18 62:15 70:11 78:18,19 79:3,6,11 81:19 83:1,14 85:4 86:1 86:10 87:5,7,10 87:20 88:6,7,18 88:20 89:1,2 90:1 90:13 94:5 96:7 96:19 97:6 99:9 99:17,18,22 101:20 104:4 106:6,11 107:11 110:6 112:20 113:20 114:11 116:6 117:14,15 117:20,22 119:5,7 122:11,22 128:7 132:9 137:10 143:5 155:19 156:8 157:3 161:19 165:1,16 173:18 174:22 176:7 179:10,13 185:8 188:19 191:20,22 199:20 200:8 201:6 208:21 209:2,8 210:16 211:5 212:2 218:18,18 218:19 221:17 223:20 224:2 226:19 229:7 230:22 232:3 233:21 237:12 239:7 244:20 245:1,1 251:8 252:3,6 253:13	254:12 256:20 262:13 263:21 272:16 275:13 276:14 282:10 287:5 293:2,17 296:6 298:2 300:17 301:9 302:5 311:19 318:2 325:11,13 325:14 340:22 343:8 349:8,18 timed 53:17 timeframe 82:16 86:22 97:1 118:12 timeline 81:18 82:1,9 93:22 timelines 93:21 timely 31:9 141:7 times 45:15 59:1 88:22 89:16 94:8 106:5 150:20 207:3 245:4 250:6 250:9 269:3 289:15 291:3 318:17 327:15 timing 100:21 tina 4:13 13:18 26:4 301:20 tina's 198:21 tiny 55:12 324:3 331:15 tissue 36:13 126:15 146:16 154:12 160:10 175:5 187:16 189:5 195:21 202:22 203:1,12 206:16 245:14 254:14 256:10,21 278:12 327:5,6 tissues 119:9 123:5,6,11 124:12 186:21 189:3 202:13 210:1
---	--	--	---

titer 174:1 275:18	ton 249:21	327:16	translation 80:2
titers 172:9,10	tons 244:9,12	tracheobronchial	213:20 308:22
175:14	tony 280:1	120:20	translational 26:6
tnf 266:5	tool 192:16 195:16	tracheobronchitis	145:1 302:12
today 15:17 24:7	tools 44:22 139:15	32:12 33:10	303:11
25:2 28:8 29:1	139:16 144:21	track 176:8	transmissible
31:2,9 32:3 40:3	194:12	253:17 274:10	29:17
42:12 44:1 45:2	top 81:13 101:10	tracked 329:19	transmitted 89:20
45:13 47:5 80:15	101:14,14 102:16	tracking 278:8	transparency
95:3 96:6 97:15	107:13 117:12	tract 33:10 37:16	130:5 139:12
99:19 111:8 112:5	177:22 241:13	68:3 114:17	transplant 37:2
125:8 130:11	242:20 249:12	120:14 146:13	194:2
134:10 135:6,8,22	261:12 282:18	176:1 224:18,21	transponders
137:14 141:19	topic 16:16 79:19	224:22 283:22	228:5
142:16 165:18	303:8	tractable 38:4	transporting
169:12 176:18,21	topics 29:8	tradeoffs 56:22	167:7
179:13,17 180:2	tops 256:16	57:14	transposon
184:3,9,20 185:11	tortured 55:11	traditional 62:10	144:12 145:7
185:18 193:6	total 101:12 102:4	104:2 208:20	transposons 145:6
205:15 206:14	208:11 213:3	traditionals 303:5	transpulmonary
222:12 223:3,9,13	290:10	traffic 276:22	273:21
227:14 230:4	totally 189:1	277:2	transurethral
233:4 234:16,18	198:19	trafficking 277:6	174:14
236:18 239:6	totter 168:7	trained 225:20	trauma 146:7
243:19 264:8	tougher 173:6	traits 155:19	travels 355:19
267:15 272:20	tour 204:20	transcriber 357:1	treasurer 296:2
274:1 302:4	tox 110:9	transcript 357:3	treat 18:22 24:15
305:21 311:8	toxic 21:5,10	transcription	37:19 69:4 88:2
327:22 333:1	toxicity 34:10	166:12,13	92:8 117:10 164:3
334:19 336:9	toxicology 305:11	transcriptional	171:11 173:13
343:3,10 355:9	305:11	144:22	232:21 252:11,11
today's 15:5 17:1	toxin 97:14,19	transcriptome	255:13 309:22
23:17,18 41:5	98:12 99:13 105:4	144:6	312:22 331:17
141:15 310:9	105:7 147:19	transition 33:4	337:13,17
told 45:7 152:18	300:15 347:12,14	34:11 129:5 304:2	treated 33:2 36:5
259:22 287:2	347:16 352:11,15	translate 72:1	51:21 68:7 81:12
tolerated 33:4	352:20	180:15 244:8	90:8 104:19
78:1	toxins 149:15	295:2	105:14,17 124:3
tom 7:20 240:21	348:2	translated 287:6	239:15 245:11
342:13 345:20	traber 286:11	316:8	253:12 257:5
tomas 8:4 189:18	trachea 225:12	translates 18:12	269:10,18,21
191:4	246:7,12 292:3	91:8	270:14,18 271:15
tomorrow 309:1	tracheal 173:9	translating 281:11	274:5,12 275:12
	291:15 292:22	284:17	275:16,21 276:1,4

276:12,16 277:13	133:5 134:3,3,6,9	356:6	168:16 185:19
279:9,12 316:4	134:14 136:7,12	truly 29:18 65:21	189:13 244:1
329:14	136:13,14,17,20	137:21 184:20	245:17 248:13
treating 48:14	137:2,8,10,15,15	truncated 100:4	turned 161:9
52:1 170:3	137:19,20,21	try 73:3 104:21	tweak 253:5
treatment 19:5	138:7 193:20	125:21,22 130:1	two 22:20 27:18
55:22 67:9,16	194:3 218:12	132:18 134:8	31:22 34:3,21
81:12 93:14 96:22	219:1,5 306:18	136:5,6,19,22	49:14 53:5 55:4
97:18 99:2,7	310:1 328:10,13	137:22 172:1	55:11,11 57:11
103:18 104:18	328:14 335:22	173:10 188:10	68:5 73:22 81:9
106:18,20 107:4,4	341:12	204:6 234:12	85:6,7,17 86:2,15
107:10 109:2,6,11	trials 19:8 21:10	261:18 281:1	86:20 88:9 100:1
109:12 127:3	37:22 38:14 40:7	283:6 296:6 311:3	104:17 105:12
131:15 173:12	45:9,19 46:13	320:12 327:22	118:7 134:11
174:17 175:16	48:9 53:6 55:4	329:11,15 335:17	138:19 140:21
176:4 182:17	62:12,13,18 92:5	trying 66:13 91:7	144:12 167:13,14
210:14 215:1	92:9 128:5,6	92:18 105:6	170:8 187:19
217:13 218:11	129:4 134:18	125:16,18 126:10	188:12 191:8,20
219:1,5,6,6,10,14	137:1 138:6 140:6	130:12 131:14	197:2 198:11
220:1 230:18,19	140:9 187:8,9	132:16 134:8,13	200:2 206:13
230:21 231:16,18	189:8,9 193:17	136:11,12 138:3	210:14 212:16
232:17 233:6	215:16 217:13	152:7 171:11	213:8 214:11
255:10 256:9	218:1,3 219:10	191:21,22 192:6	223:18 225:19
262:11 268:16	220:1 260:16	193:3 228:22	226:2 230:3
271:3,3 315:20	306:15 326:7	250:1 263:8 312:9	236:16,18 237:19
327:13	327:10 328:17	319:8 321:4 331:3	245:9,20 251:6
treatments 94:21	345:18	336:9,15 350:13	252:12 263:10
97:10,10 247:8,9	trick 56:12,20	354:5	264:20 266:20
255:11	trickle 204:18	tub 146:17	267:17 274:6,16
treats 19:5	tricky 177:5	tube 192:20 272:7	274:22 276:7
tree 120:20	tried 96:6 109:22	273:1,2 285:19	293:10,13 298:1
tremendous	129:9 238:2	291:13 292:5	309:10 318:11,18
129:17 336:17	288:21 354:2	314:8	318:21 321:19
trend 231:7	tries 63:18 328:10	tufts 3:12 9:10	329:22 353:15
trial 9:12 16:4	trigger 23:14 76:8	28:5,5,11,12	type 16:3 34:14
17:5,9,18,18 18:6	88:1 93:13 117:10	tularemia 10:7	104:11 111:20
18:10,14,20 19:10	triggered 164:7	80:13 111:10,12	145:22 148:3
19:16 20:14 23:7	triggering 162:12	111:18 116:1	154:16 170:13
24:9 41:8 42:21	164:11	145:13 351:16	175:6 209:18
43:13 47:2,3,4,17	trouble 265:15	tularensis 111:20	212:19 220:17
47:17 48:21 49:18	true 62:2 172:3	111:20 117:21	233:19 255:19
52:18 53:3 61:21	237:9,11 244:17	tuli 124:8	267:11 288:1
62:1,11 64:3,7,9	253:20 259:9	turn 31:6,18 34:14	300:15 304:15
84:7 128:8,17	262:3 344:13	37:6 120:7 140:9	317:7 318:1

339:12 types 38:15 41:10 122:17 148:7 150:19 170:4 180:10 182:4 190:9 209:4 266:18 303:5,15 305:8 309:6 typewriting 356:5 typhimurium 199:1 typical 52:11 84:6 86:10,13 146:1 187:22 234:19 235:3 262:11 268:3 270:2 296:14 typically 15:14 52:9 87:21 88:6 178:9,13 246:6 299:13 300:10 303:21	unc 227:8 230:9 uncertainties 139:17 140:4 uncertainty 18:11 128:12,21 134:4 135:2,11 137:4 138:11 139:6 unchallenged 103:12 uncommon 72:11 underestimate 66:3,3 undergoing 145:18 undergraduate 279:20 underscore 198:21 understand 17:11 40:11 74:10 76:18 92:6,17 97:21,22 99:2 133:21 158:2 159:22 160:20 162:9 179:11 193:12 199:8 201:21 235:8,11 312:9 326:8 332:7 354:10,11 understanding 23:19 96:13 97:12 98:6 99:17 101:2 133:8 134:22 158:5 248:4 understood 21:15 undertaken 145:9 undertaking 32:6 underwent 32:8 unethical 21:8 unexpected 167:9 unfeasible 284:8 321:17 unfortunately 27:19 29:20 108:12 161:16	258:13 260:11 269:12 330:1 uninfected 275:2 uninterpretable 140:10 unique 16:6 69:18 113:6 129:15 155:5 158:3 united 181:3 204:3 236:15 265:4 294:10 339:4 units 71:11 73:14 114:8 115:13,19 130:19 146:2 290:8 306:12,13 universe 334:11 university 2:14,21 3:12,22 4:11 5:19 6:7,16 8:8 11:10 11:14 12:12,15 13:6,12 26:11,14 26:15,18,21 28:5 28:12 141:2 168:20 170:2 205:7 222:12 234:6 264:12 286:13 289:20 322:16 unmet 16:21 24:16 45:8 67:18 72:9 75:11 96:17 336:10 unpleasant 49:3 unreasonable 287:3 unreserved 52:3 unstable 186:15 untreated 68:9 183:6 239:15 252:7 253:12 299:22 update 67:19	updated 144:8 updating 83:18 upper 86:2 224:17 224:21 290:14,15 298:1 uptick 235:6 urgency 165:18,19 urgent 16:7 31:5 urgently 31:8 urinal 257:10 urinary 33:10 37:16 68:3 146:13 urine 33:12,17 175:4,7 usaisr 340:14 use 18:13 22:10 24:20 30:3,5,6 37:15 39:17 40:17 41:20 48:17 72:12 84:9 87:22 91:2 92:21,22 103:14 106:22 112:8 113:1 122:20 126:18 127:13 130:12 139:22 153:5 154:7 170:17 171:3,7 173:8 176:22 178:13 182:12 189:5 190:5 192:20 193:8,11 193:21 198:20 200:11 205:19 207:3 216:18 223:15 224:8 226:4 227:17 229:2 232:14 235:21 238:1 239:3 241:17 242:3 243:16 247:12 248:5 250:16 254:1 255:11 259:21 263:8 265:2
u			
u.s. 58:16 63:5 67:22 68:12 71:8 73:13 94:18 95:21 96:9 110:17 234:3 294:6 307:16 321:11 339:2 ubiquitous 141:21 ugly 48:13 ulceroglandular 111:22 ultimate 296:21 ultimately 32:19 33:5,8 37:4 119:8 120:10 316:3 332:18 unable 231:12,17 unappreciated 165:1 unasyn 69:13 70:18			

266:14,18 271:22	utis 169:19	219:3 224:5,19	venous 273:22
281:14 285:8,9,13	v	227:3 241:19,21	ventilate 273:5
285:18 286:6,14	va 26:20	variable 212:21	313:21,22
287:10 288:6	vaccination 97:2	variables 206:3	ventilated 13:9
289:21 291:14	vaccine 66:21 67:3	210:6 216:15	146:22 272:5
300:8 306:4 307:7	97:5 116:13 222:1	225:1	280:18 286:2
315:16 319:21	306:12	variation 116:21	287:8 290:3
320:19 323:3	vaccines 80:8	117:19 118:3	291:15 292:6
329:10 330:3	96:18 112:4,10	209:20 211:13,18	294:21 313:16,18
332:8 334:6 338:3	116:9 183:9	variations 191:13	313:20 324:16
339:12 341:1	197:22 302:22	347:19	339:1,1
346:1 347:13	305:13 306:7	varied 115:5	ventilating 282:7
350:6	308:13	191:15	317:19
useful 37:11 39:13	vader 44:21	varies 120:7	ventilation 156:12
41:11 46:8 51:3	valentine 352:12	variety 20:18	156:14 273:11
117:4,8 118:19	352:22	37:21 40:11 55:1	284:7 285:22
126:21 158:21	valid 62:19 63:12	129:2 141:13	288:4 289:3 293:2
203:4 207:9 209:7	329:21	153:22 154:2	295:6 314:9
304:16 322:1	validate 47:10	163:8 182:3	318:20 321:9
326:3	265:2 326:3,4	192:20 205:21	ventilator 18:9
users 338:7	validated 39:9,12	209:21 212:11	51:17 73:15 74:1
uses 221:22	39:20 92:10	216:9 314:6	218:7 267:14,19
334:15	181:19 349:1	variola 130:16	271:20 272:10
usual 34:16 47:12	validation 39:8	various 30:10	273:4,6,20 277:1
65:15	45:19 178:15	37:19 43:10 82:13	284:13 285:20
usually 71:10	179:4 181:14	143:9 144:11	288:21 289:4
128:6 173:5	182:15 267:3	165:12 176:11	293:10 318:15
196:19 225:3	319:21	265:1 272:18	323:13
293:9 318:17	valley 296:18	304:10 305:8	ventilators 273:4
321:6,8 326:16	valuable 25:19	334:17	ventilatory 282:8
327:14,18 330:10	287:6 326:9 327:9	vary 120:6 190:5	318:9 330:17
uti 52:12 169:8	value 50:2 63:14	208:3 284:21	ventricular 34:18
170:14,22 174:10	109:9 192:7	varying 146:17	35:1 36:21
174:19,20	215:17,17 216:8	208:4 209:22	verification 110:7
utility 15:18 64:20	319:20 338:1	211:22 242:16	versus 107:4
127:3	values 44:4 218:20	243:13 247:7	109:11 173:1
utilize 133:20	valve 267:12	vasoactive 285:6,7	239:15 253:12
206:21 240:13	337:8,14 338:13	286:20 288:11	262:11 312:20
319:18 320:13	valvular 338:1	314:13 315:16	319:7 324:14
utilized 109:22	vancomycin 36:6	vast 88:15 89:9	vertical 214:6
129:20 131:12	vap 218:4 291:9	vectors 144:21	vesicles 157:10,15
132:2 140:11	291:11 323:5	vehicle 231:19	167:7
utilizing 75:17	variability 211:3	vendors 190:22	vessels 119:6
98:13 258:4	211:15 218:10	191:1	

veteran 2:20 veterinarian 122:21 veterinary 5:5 110:22 video 177:11 view 151:8 163:17 192:18 272:22 viral 94:15 129:11 virome 163:12 virulence 127:18 147:11 148:8 150:18 151:10 155:6,18 157:2,5 157:16,18 158:7 158:13 159:22 160:17 161:2,3,6 161:9 163:1,5,5 163:11 164:12 166:3,14,18 167:18 168:5 201:10,11,11,12 221:6 236:9 238:6 238:7,11 239:1 240:21 243:9,10 243:13 255:18 268:1 347:7,15 virulent 112:15 126:9 144:16 149:20 155:17 164:2 166:3 190:3 190:8 201:5,8 239:10,11 240:5 244:15 virulosome 155:8 166:16 virus 32:18 130:16 130:16,19 131:3,9 viruses 131:7 visit 29:3 visual 219:19 visualized 177:9 visually 86:19	vitro 70:12 77:14 119:22 147:16 158:9 181:4,15,16 188:20 230:5 242:14,17 305:8 310:4 vivo 70:12 77:12 77:14 94:20 147:17 158:12 181:5,15,16 189:1 305:8 voice 66:11 volatile 240:15 volume 272:5 273:10 volunteers 21:9 w wait 98:21 103:1 174:21 335:20,21 waiting 100:5 walk 44:17 75:8 wall 157:10 wallnofer 7:8 9:16 27:9,9 43:2 57:20 57:21 58:2,8,9 66:13 325:20 walter 7:15 12:20 155:21 200:19 234:5 254:12 255:1 258:20 263:13 283:3 want 38:17 44:17 46:4 47:18 48:17 52:19 57:7,13 69:7 78:14 80:16 81:22 83:20 85:5 92:21 100:15 101:7 110:16 122:12 123:11 125:4 129:5 130:15 140:13 153:1 170:16,17 170:19,22 171:8,8 171:9,22 173:12	175:1 176:16 183:20 188:9,14 191:12 195:21 196:15,22 197:4 197:10 198:4 222:20 223:3 224:22 229:15 230:1 231:9 232:12 236:6 238:20,22 239:11 243:19 247:14 252:18,22 255:14 258:1,7 261:22 264:3 276:6 294:22 299:14,17 300:8,9,9,11,12 301:6,11 304:6 312:7 322:20 325:6 328:17 339:22 341:7 342:15,20 347:13 349:17,19 353:15 355:11,13 wanted 24:4 41:5 54:9 67:11 74:5 82:17 93:20 103:13 105:21 112:7 131:17 170:5 176:21 203:18 224:3 228:1 233:13 236:14 237:1,2 238:6,16,18 239:10 244:16 245:13 249:8 251:18 254:3 255:6 256:18 259:11 268:8,10 276:8 302:6 325:20 349:20 353:14 355:1,8 wants 189:13 313:1	war 235:7 warawa 222:14 ward 163:20 warm 153:1 washington 1:12 6:16 26:22 watching 125:2 water 142:1 146:10 186:20 273:9 wax 144:19 243:10 waxy 158:20 160:15,21 way 40:8 41:8 42:1,7 45:1 46:7 47:6 48:18 56:22 57:10 62:7 63:20 65:22 71:1 73:3,8 122:10 130:9 132:11 158:1,3 160:20 165:9,16 166:15,20 167:16 170:6 176:2 183:8 192:11,18 193:17 193:22 200:10 201:19 241:16,18 242:21 243:2 250:16 252:8 253:14,18 254:6,7 254:11,13 255:21 273:3 286:3 298:5 317:20 319:14 320:21 331:3,12 332:1,6 337:19 350:18 355:17 ways 30:6 37:19 39:7,17 100:1 128:20 138:5 158:22 166:17 167:4 170:5 172:20 175:12 189:8 192:10 224:12
---	--	--	---

wbc 272:16	weight 114:22	william 8:8 168:19	257:12,22 258:4
we've 15:12 16:16	122:5 257:2,5,6	willing 18:11 46:3	258:15 259:7
30:4 31:14,19	269:20,22,22	window 62:16	262:19,19 263:4
53:18 125:10	270:2,3,4,4,12,12	89:4 239:13	279:19 298:21
126:18 127:13	270:20,20 271:9,9	252:17	301:5 306:3
129:9 130:14	274:15,15	winter 33:8	311:22 320:1,12
133:19 170:6	weights 257:1	wisconsin 2:14	320:15 322:17,18
178:22 185:7,9	weiss 8:8 168:19	12:12 26:16 205:7	325:16 328:15
186:6 187:4,18	169:1	205:7	329:17 333:4,8,8
188:19 190:3,6,6	welcome 15:4	wise 344:17 348:3	333:9,9,15,16
190:10,20 191:8	204:16 342:3	wish 52:4 161:4	334:16 341:10,17
199:22 208:10	346:12	248:22	344:21 345:3,11
214:1 220:18	wells 70:16 154:18	woman 143:3	345:12 346:2
227:14 228:7	went 35:20 36:1	women's 8:4	347:22 353:17
230:3 232:17,18	83:2,14 84:11	189:19 191:5	354:9,17
233:12 235:5	89:14 121:21	wonder 278:4	workable 74:7
239:7 245:1 247:7	124:12 126:4	wonderful 184:12	worked 45:5 93:5
252:6 256:18	152:4,4,5 157:7	280:8 354:13	151:14 253:4
257:14,22 259:21	165:4,4 166:2	wondering 202:8	271:20 305:22
260:7 263:15,20	240:19 250:13,14	202:13	330:2 331:19
263:21 297:16	262:21	word 332:20	354:5
309:10 312:3,4,11	western 2:21	words 331:7	workhorse 182:8
329:22 331:8	11:13 26:19 151:2	work 23:22 40:19	206:13
340:4,21 341:4,5	wet 153:1	44:18 53:9 65:2	working 34:20
341:18,20 343:2,3	whirlwind 204:19	78:12 82:7,10,21	35:19 73:6 82:3
346:2 347:6	white 84:15 99:21	95:4,8,13 96:1	82:22 92:22 99:5
354:17	101:9,12 102:5	97:16 98:13,18	109:15 126:8
weaknesses 91:22	103:12 104:1,15	99:19 100:8 101:5	131:2 139:6
202:17	107:13 118:10	104:10 111:12,15	155:21 161:17,19
web 311:10	119:13 163:20	112:13 121:16	172:4 174:6
webcast 125:2	165:4 195:14	125:5,7,16 126:4	176:10 185:7
webex 168:11	243:21 244:1	129:10 136:1	189:22 190:20
webpage 311:11	245:16 249:1,4,19	151:16 172:17,18	235:13 236:1
website 144:5	265:10 268:13	172:22 178:14,17	250:19 253:1
168:15 185:16	276:11,13 309:15	178:18,22 179:4,9	256:2 263:19
305:1 308:4,6,7	310:12,13,15	180:14 181:20	266:16 267:13
week 31:6 122:3	wide 80:6 197:8	182:3,4 184:5	271:19 300:18
143:16 196:18	216:9	192:19 193:4	302:17 306:19
251:16 266:22	widely 69:11	198:6 203:12,12	314:3,4 330:9
267:1,9 321:19,20	123:5 225:2	205:21 216:20	343:13 347:6
340:9	wider 18:12	224:1 229:12	works 76:19 93:10
weeks 114:21	widest 55:12	233:8 234:17,19	165:7 173:4 174:9
251:17 271:18,19	wild 145:22	239:21 247:2	174:13 209:13
314:5	212:19 259:16	248:4 253:9,9,10	244:2 302:14

342:12,14 workshop 1:1 15:5 16:18,19 17:1 18:1 23:18 39:5 50:12 56:9 58:11 129:18 130:2 134:7 176:17 179:18 281:18 303:9 310:9 316:10 355:15 world 30:1 31:13 51:3 60:4 68:13 73:13 100:15 128:5 130:5 154:7 154:10 157:7 159:5,5,6,6,7 166:2 237:14 263:7 307:15 world's 237:13 worldwide 67:1 68:19,22 71:8 287:18 worm 158:20 worms 243:10,22 244:9,10 worried 225:5 335:4 worry 224:15 296:9 worse 33:15 35:3 218:6 worsening 35:7 worst 40:13 worth 53:8 wound 7:14 160:11 164:5 169:21 170:15 175:16,19 195:22 200:22 202:22 234:4,15 237:3,4 237:8,18,19,20 239:7,16 242:2 248:16 249:12	250:5,11,13 251:4 251:7,8,21 252:8 252:10,13 253:2 253:11,17 254:6 254:13,15 255:5 255:16,20,22 256:1,12,19 257:3 258:8 259:11,12 260:9 261:20 262:6 322:15,19 322:21 323:1 340:18,18 343:2 wounded 200:19 235:1 wounding 260:15 wounds 146:19 175:15 251:3 252:5 256:7 260:14,16 261:13 262:20 323:4 wow 102:1 333:3 wrair 7:15 write 349:17 written 57:1 90:11 122:8 163:1 177:10 wrong 191:14 344:2 wrote 91:16 x x 7:6 9:15 27:7 43:1 50:9,11 51:2 51:6,19,22 53:10 54:6 64:3 100:3 152:13 208:9 226:13 333:8 xdr 65:21 238:21 y y 152:13 226:15 yeah 125:14 194:8 201:16,18 203:15 204:4 292:1 319:3 321:5 325:18	333:18 334:13,18 335:1 year 16:18 17:3 24:12 32:7 34:15 37:3 49:6 51:14 53:7 68:1 70:6 111:13 134:7 236:15 251:17 265:4 300:21 304:20 309:2 310:6 years 15:12 16:17 32:9 35:16 42:6 43:6 46:7 58:2 66:22 94:15 110:22 113:5 114:3,4 151:8,15 151:20 153:5 164:22 170:5 180:10 181:7 185:9 187:13 234:16,18 240:3 263:16 265:21 282:17 294:7 298:7 304:20 322:18 335:18 345:2 yellow 82:8 yersinia 23:12 90:15 222:10 yorkshire 258:16 young 34:20,21 156:8 340:14 younger 156:9 z z 152:14 zealand 99:21 101:9 103:12 104:1,15 107:13 265:10 268:13 zebrafish 144:19 160:19 zero 87:7 245:1	zika 297:16 zinc 163:14 zurawski 7:12 12:20 194:21 203:7 234:2,11 259:20 322:15 339:15 342:10 343:17 347:1 354:10
---	---	---	--