

UNITED STATES OF AMERICA

+ + + + +

DEPARTMENT OF HEALTH AND HUMAN SERVICES

+ + + + +

FOOD AND DRUG ADMINISTRATION

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

+ + + + +

VACCINES AND RELATED BIOLOGICAL PRODUCTS

ADVISORY COMMITTEE

+ + + + +

MEETING BY TELECONFERENCE

+ + + + +

OPEN SESSIONS

+ + + + +

THURSDAY

JULY 10, 1997

+ + + + +

The Committee meet in Room 121, Building
29 at the National Institute of Health, 9000 Rockville
Pike, Bethesda, Maryland, at 11:00 a.m., Patricia L.
Ferrieri, M.D., Chairperson, presiding.

PRESENT:

PATRICIA L. FERRIERI, M.D.	Chairperson
ADAORA ADIMORA, M.D.	Member
MICHAEL APICELLA, M.D.	Member

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

PRESENT: (CONT.)

MARYLOU CLEMENTS-MANN, M.D.	Member
REBECCA COLE	Member
KATHRYN EDWARDS, M.D.	Member
MARY ESTES, Ph.D.	Member
HARRY GREENBERG, M.D.	Member
GREGORY POLAND, M.D.	Member
FERNANDO VILLALTA, Ph.D.	Member
ROBERT COUCH, M.D.	Govt. Empl.
RICHARD JOHNSTON, Jr., M.D.	Govt. Empl.
C.D. ATREYA, Ph.D.	FDA
ROLAND LEVANDOWSKI, M.D.	FDA
HIRA NAKHASI, Ph.D.	FDA
PETER PATRIARCA, Ph.D.	FDA

ALSO PRESENT:

NANCY CHERRY	Exec. Secy.
DENISE ROYSTER	Comm. Mgmt. Asst .
BILL EGAN, Ph.D.	CBER
NEIL GOLDMAN, Ph.D.	CBER
KATHY CARBONE, Ph.D.	CBER
BILL FREAS, Ph.D.	CBER
BOGDAN DZIURZYNSKI	MEDIMMUNE

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
 1323 RHODE ISLAND AVE., N.W.
 WASHINGTON, D.C. 20005-3701

C-O-N-T-E-N-T-S

	<u>PAGE</u>
BEGIN OPEN SESSION	
Call to order	4
Introduction to the Program	
Dr. Patriarca	6
Presentation by Dr. Nakhasi	7
Presentation by Dr. Atreya	12
Presentation by Dr. Levandowski	19
OPEN PUBLIC HEARING	86

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

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

(11:15 a.m.)

BEGIN OPEN SESSION

MS. CHERRY: First of all, before I read the meeting statement, I do need to remind everyone that this is an official meeting of the Advisory Committee. It is being recorded; we will have a transcript. And because we're not all on-site, I have to ask each of you to state your name each time you say something. That's very important for the recorder so that the transcript is accurate.

The only other announcement is -- and this time it's mercifully brief -- the meeting statement. This announcement is made a part of the record at this meeting of the Vaccines and Related Biological Products Advisory Committee, on July 10th, 1997. Pursuant to the authority granted under the Committee Charter, the director of the Center for Biologics Evaluation, and Research has appointed the following individuals as temporary voting members: Drs. Richard Johnston and Robert Couch.

Based on the agenda made available, it has been determined that all committee discussions at this meeting for the review of the intramural research program for the Laboratory of Pediatric and

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 Respiratory Viral Diseases, Division of Vira l
2 Products, present no problem for a conflict o f
3 interest -- or no potential, excuse me.

4 In the event that the discussi ons involve
5 specific products or firms not on the agenda for whic h
6 FDA's participants have a financial interest, th e
7 participants are aware of the need to exclud e
8 themselves from such involvement and their exclusion
9 will be noted for the public record.

10 With respect to all other meetin g
11 participants we ask in the interest of fairness that
12 they address any current or previous financia l
13 involvement with any firm whos e products they wish to
14 comment on.

15 That's the end of the meeting statement.
16 Other than that, welcome everyone.

17 CHAIRPERSON FERRIERI: Thank you ver y
18 much, Mrs. Cherry. We'll star t with the introduction
19 of the program by Dr. Patriarca. I might comment tha t
20 I can't hear you very well from CBER when you al l
21 announced yourselves; you were barely audible.

22 DR. POLAND: This is Dr. Poland.

23 CHAIRPERSON FERRIERI: Hi, Greg. We'r e
24 into the agenda, if you wish to look at it. We'r e
25 into the introduction of the program.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 DR. POLAND: Okay.

2 CHAIRPERSON FERRIERI: If the people a t
3 CBER could make a real point of seeing that all th e
4 audio is okay and the microphones so that we can all
5 hear you, please.

6 MS. CHERRY: Okay. I'm going to turn the
7 speaker just a bit now. It's aiming right at Dr .
8 Patriarca.

9 CHAIRPERSON FERRIERI: I can hear you ,
10 Nancy, but I thought the introduction was ver y
11 mumbled. Dr. Patriarca, can you start now, please?

12 DR. PATRIARCA: Okay. Can everyone hear
13 me?

14 CHAIRPERSON FERRIERI: I can hear you.

15 DR. PATRIARCA: Okay. I would very much
16 like to extend our welcome and thank the committee fo r
17 meeting today. The committee will be considering the
18 recommendations of a site visit team who evaluate d
19 three programs within the Divi sion of Viral Products.

20 For members of the committee who are not
21 familiar with our division, it is one of fou r
22 divisions within the Office of Vaccines and ha s
23 regulatory, review, and resear ch responsibilities for
24 both licensed and investigational products.

25 The division current has appro ximately 90

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 permanent and temporary staff and is comprised of five
2 laboratories which cover the areas of retroviruses ,
3 hepatitis viruses, DNA viruses , vector-borne viruses,
4 and finally, pediatric and respiratory viruses which,
5 from its name, obviously has a very broad mandate.

6 The three investigators that you will hear
7 from today are members of that laboratory. If there
8 are no questions from the committee I would like to
9 turn the program over to the three of them and allow
10 them to briefly present the salient points of their
11 work.

12 DR. PATRIARCA: Thank you, Peter. Any
13 questions from the committee members on-line at this
14 time? Otherwise, we'll proceed then, with the
15 program. Peter, will you be introducing --

16 DR. PATRIARCA: Yes. Dr. Nakhasi will be
17 the first speaker.

18 CHAIRPERSON FERRIERI: Thank you.

19 DR. NAKHASI: Can you hear me, please?

20 CHAIRPERSON FERRIERI: Yes, Dr. Nakhasi,
21 thank you. If you could continue to speak at that
22 volume.

23 DR. NAKHASI: Okay, thank you. Good
24 morning, everybody. My name is Hira Nakhasi and I
25 will be talking to you today with the work we have

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 been doing in our lab. And first of all I would like
2 to give you a brief introduction to the section which
3 I was heading so far, and the name of the section is
4 Section of Viral Pathogenesis and Adverse Reactions.

5 We have two responsibilities, both
6 research as well as the regulatory responsibility.
7 The goal of the section is to conduct research
8 pertaining to the safety issues of virus vaccines in
9 general, and of rubella virus vaccine in particular.

10 The safety issues of rubella virus
11 vaccines are: adverse reactions such as acute or
12 chronic arthritis in sero-negative women, and number
13 two, RV infection of fetus in the presence of maternal
14 immunity manifesting in congenital rubella syndrome.

15 The regulatory responsibilities of these
16 sections are: the personal review, investigation of
17 new drug applications, and product license
18 applications for viral vaccines. They provide
19 expertise in a number of areas critical to these
20 regulatory objectives of the division such as
21 validating purity, efficacy, and safety of recombinant
22 or live virus vaccine.

23 The subject of today's presentation, of my
24 presentation is, molecular mechanism of rubella virus
25 pathogenesis. In the following few minutes I will be

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 talking about the purpose of the research project ,
2 summary of the results, and the future directions.

3 The purpose of the research is -- before
4 I go into detail of the purpose of the research I
5 would give you a little background of the rubella a
6 virus. Rubella virus is an envelope virus consisting
7 of a single-stranded RNA of a positive polarity. It
8 is approximately 10,000 nucleotides long, goes for two
9 non-structural proteins and three structural proteins .

10 Rubella virus is a major human pathogen
11 and a causative agent of German Measles which appears
12 as a mild rash and a fever in children and young
13 adults. However, rubella virus infection during the
14 first trimester of pregnancy can cause fetal death or
15 multi-system birth defects known as congenital rubella
16 syndrome.

17 An effective vaccine has been developed
18 which has dramatically reduced the incidence of
19 rubella infection; however, a significant number of
20 natural infections are reported each year and in
21 addition, several cases of adverse reactions -- both
22 acute and chronic arthritis -- are reported following
23 vaccination.

24 The symptoms of arthritis are similar to
25 known features of other immune disorders. In the last

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 few years, the incidents of maternal infection and
2 consequent rubella -- congenital rubella syndrome has
3 been on the rise; thus rubella infection continues to
4 be of a public health concern. So as a part of our
5 goal to understand the mechanism by which rubella
6 virus causes atrophy and arthritis, we have initiated
7 the following studies.

8 And the approach we have taken is: 1) we
9 have identified cis RV -- cis-acting elements, or the
10 RNA elements in the RNA which are necessary for virus
11 replication; 2) interaction and identification of
12 factor or factors, which interact with these important
13 elements of the viral RNA; and 3) what role these
14 factors play in RV replication or the rubella virus
15 replication and pathogenesis.

16 Now, I will be giving you the summary of
17 the results, quickly. The following summary of these
18 results is the subject of six peer review papers and
19 two review articles.

20 We have discovered sequence elements at
21 the five prime and the three prime end of rubella
22 virus RNA that are essential for RV -- did I mention
23 RV, this rubella virus -- translation and initiation
24 of negative strand synthesis -- both in vitro and in
25 vivo.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 We have demonstrated the requirement o f
2 post-protein synthesis for rub ella virus replication.
3 We demonstrated that these elements interac t
4 specifically with host proteins with high affinity ,
5 and their binding correlates with our rubella viru s
6 replication.

7 Number 4, identify these host proteins as
8 autoantigens, la and calreticulum, and specifi c
9 interaction of la and calreticulum have bee n
10 demonstrated both in vivo and in vitro. In doing so,
11 we also discovered new functio ns of this calreticulum
12 protein which were not discove red before, such as RNA
13 binding and autophosphorylation activities.

14 In a retrospective clinical study ,
15 antibodies to one of the la autoantigens -- l a
16 autoantigen -- in persistent RV-infected people were
17 observed, suggesting possible mechanism of rubell a
18 virus-induced arthropathy by rubella virus interactin g
19 autoantigens.

20 Now, where do we go from here? The futur e
21 directions? In the light of t he association of acute
22 or chronic arthritis with RV vaccine in lo w
23 seronegative women, a vaccine with reduced incidence
24 of joint complications is warranted.

25 Our studies suggest that interactions o f

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 autoantigens with rubella virus RNA may have a role in
2 a rubella virus arthropathy; therefore, steps will be
3 taken to analyze this interaction and to develop
4 strategies for vaccine as follows.

5 Analyze the role of autoantigen
6 interaction of the rubella virus RNA, both at the
7 molecular level and at the immunological level ;
8 identify the viral determinants of tropism for joint
9 issues using chimeric viruses; study the interaction
10 of viral proteins with host proteins to understand the
11 mechanism of molecular mimicry; and to develop subunit
12 DNA vaccine expressing viral antigen.

13 Thank you very much for your attention.

14 CHAIRPERSON FERRIERI: Thank you, Dr .
15 Nakhasi.

16 MS. CHERRY: Before we go, let me just say
17 for the record that while Dr. Patriarca was speaking,
18 Dr. Goldman came into the room.

19 CHAIRPERSON FERRIERI: Thank you. Good
20 morning, Dr. Goldman.

21 DR. GOLDMAN: Good morning, Dr . Ferrieri.

22 CHAIRPERSON FERRIERI: We will move on
23 then, with Dr. Atreya.

24 DR. ATREYA: Good morning. Can everybody
25 hear me? Hello?

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 CHAIRPERSON FERRIERI: We can hear you --
2 I think we will hear you.

3 DR. ATREYA: Okay. Good morning. My name
4 is C.D. Atreya, and today I will be providing the
5 agreed overview of my research project and the title
6 of the research project is, "Molecular Mechanism of
7 Rubella Virus-Induced Pathogenesis". I give you a
8 brief introduction.

9 Recent estimations are that 10 to 25
10 percent of unimmunized women of child-bearing age are
11 susceptible to viral infection worldwide, even though
12 these numbers are very low in this country. It is
13 well established that gestation rubella infection
14 contracted in the first trimester of pregnancy
15 frequently causes congenital rubella syndrome, and in
16 spite of the fact that this rubella virus is a
17 pathogenic agent, in cases of CRS that are reported
18 over here, there has been no real, recent initiative
19 to elucidate the molecular mechanisms of teratogenesis
20 induced by rubella virus.

21 Since viral vaccine safety issues are
22 related, I have initiated studies on the molecular
23 mechanism of rubella-induced teratogenesis. One of
24 the rationales for this investigation is to gain
25 knowledge that could be utilized in developing

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 strategies to produce low risk rubella vaccines i n
2 future.

3 Our hypothesis and rationale is that the
4 clinical significance of CRS is the reduction i n
5 number of cells in affected organs of the fetu s
6 leading to developmental abnor malities. At molecular
7 levels, this could be possibly due to the host virus
8 interaction that inhibits cell growth and possibl y
9 cause cell death in the developing fetus.

10 Since an early developing fetus at an y
11 given time, there are cells that are proliferating ,
12 undergoing terminal differentiation, as the last cell s
13 pause to receive a specific signal, either t o
14 proliferate or to undergo differentiation. Specific
15 questions were asked as part o f the research project.

16 Number one, does rubella prefer a
17 particular stage of the cell f or its infection or its
18 application? And secondly, th e newly discovered host
19 protein that interacts with th e rubella virus -- that
20 is, the calreticulum -- does it play a role in viral
21 replication? Number three, are there any functions,
22 functional inter-reactions among the host and viru s
23 encoded proteins that could ultimately lead to rubell a
24 virus-induced teratogenesis?

25 To answer these questions there ar e

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 certain experimental approaches that we followed .
2 Number one, identify a suitable cell stage tha t
3 supports the rubella virus route. Number two, testing
4 the role of calreticulum, the host protein, in th e
5 viral replication by offering its expressional levels
6 in the cell.

7 Number three, test for the presence o f
8 viral protein inter-reactions with cell cycl e
9 regulatory proteins. Number four, identification of
10 domains in the viral encoded proteins that coul d
11 facilitate inter-reaction with key cell growt h
12 regulatory proteins that could trigger and inhibi t
13 cell growth and cause cell death.

14 Number five, testing the viral protei n
15 inter-reactions with cellular proteins. Summary o f
16 the results so far: 1) we demonstrated that rubella
17 virus prefers quiescent cells for its replication; 2)
18 that studies with all expressi on of the host protein,
19 calreticulum, demonstrated tha t the protein regulates
20 viral replication by altering the cell growth;

21 Three, the highly considered amino-aci d
22 motif, which we called LXCXE, that functionall y
23 interacts with one of the cell growth regulator y
24 proteins, the retinoblastoma t umor protein, have been
25 recently identified in our lab; that is, present i n

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 one of the rubella virus non-structural proteins which
2 we call NSP90.

3 The NSP90 was shown to bind to the
4 retinoblastoma protein, both in vitro and in vivo .
5 Number five, the viral application in quiescent cells
6 positively correlates with the presence of
7 predominantly under-phosphorylated retinoblastoma
8 proteins, suggesting that this protein may have a role
9 in viral replication.

10 With these kinds of results so far I'll be
11 dwelling on a few moments on the future direction .
12 Number 1, we'll test the functional role of NSP90
13 retinoblastoma protein inter-reaction in the virus
14 lifecycle. This will be achieved by site direct
15 communications -- in the NSP90 protein, replacing the
16 rubella virus infectious CDNA plasmid -- can be
17 provided by Dr. Frey of Georgia State University.

18 Number two, using an animal embryo culture
19 or immunologic tissue culture that is reactive to the
20 rubella virus, the vaccine and wild-type strains as
21 well as the mutants in the NSP region will be tested
22 for pathogenic potential.

23 Number three, if the specific NSP mutants
24 from this study are found to be less pathogenic, they
25 can be tested as candidate vaccines in future.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 Thank you very much.

2 CHAIRPERSON FERRIERI: Thank you, Dr .
3 Atreya. Are there any questions at this point for Dr .
4 Nakhasi or Dr. Atreya?

5 DR. GREENBERG: One point -- Harry
6 Greenberg talking.

7 CHAIRPERSON FERRIERI: Can you please
8 state your name before speaking? This is true of any
9 of us.

10 DR. GREENBERG: Harry Greenberg. The
11 question is simply, what is the teratogenic potential
12 of the current vaccine?

13 DR. NAKHASI: Can you repeat the question ,
14 please?

15 DR. GREENBERG: Yes. The question I'm
16 asking is, a goal that was stated was to improve on
17 the current vaccine to make it less teratogenic for
18 the fetus. And I was just trying to inform myself on
19 what the problems were with the current vaccine as far
20 as causing birth defects; how that would be improved
21 upon.

22 DR. ATREYA: Yes. There are no real ,
23 systematic studies using the current vaccines related
24 to the teratogenic potential of them. And so one of
25 the goals is to test that potential compared to the

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 wild-type. And also our goal is to make the futur e
2 vaccine less immuno-reactive and immunogenic to th e
3 patient, or the specific.

4 MR. POLAND: This is Greg Poland speaking .
5 I think another answer to that question is, CDC ha s
6 collected I believe, about 300 cases of women who wer e
7 inadvertently administered vac cine in the early first
8 trimester of their pregnancy. And there have been no
9 birth defects related in that kind of observational-
10 type study.

11 And to my knowledge, there's no reported
12 case of a fetal defect in a woman -- in a non -
13 immunocompromised woman receiving the rubella liv e
14 vaccine.

15 CHAIRPERSON FERRIERI: Thank you, Greg .
16 That is my understanding as well.

17 DR. NAKHASI: If I may -- this is Hir a
18 Nakhasi.

19 CHAIRPERSON FERRIERI: Yes, please.

20 DR. NAKHASI: If I may add to that .
21 Recently, some of us might have seen that people, a
22 child who had received vaccine at the 12 months a s
23 well as 11 years of age, when she became of child -
24 bearing age, she develops certain autoimmune disorder s
25 and the fetus was affected in that situation. An d

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 there was a correlation to some extent that the - -
2 even in the presence of maternal immunity, that th e
3 rubella virus infection caused the fetal -- congenita l
4 rubella syndrome.

5 Now, the question is whether it is th e
6 vaccine or the viral type. I believe moreso it's the
7 viral type, but the question is, the vaccine did not
8 completely protect that fetus from being affected .
9 This study was done in Journal of Infectious Diseases
10 in 1997, March or April issue.

11 CHAIRPERSON FERRIERI: Thank you. I f
12 there are no other points then we'll move on to Dr .
13 Roland Levandowski, please.

14 DR. LEVANDOWSKI: Hi, this is Rolan d
15 Levandowski. Good morning, everybody. I'm going to
16 give a brief overview of the program for the influenz a
17 and respiratory viruses team. Our program has th e
18 same responsibilities as the other programs within th e
19 Center for Biologics; that is, we hav e
20 responsibilities for regulation and research related
21 to specific products. The product that our team work s
22 on predominantly is influenza virus vaccine.

23 The regulatory activities that we hav e
24 occupy the great majority of our effort, and I would
25 estimate that it's probably around 75 percent. Th e

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 things that we do for regulatory activities includ e
2 review and approval of INDs -- Investigational Ne w
3 Drug Application -- product li cense applications, and
4 establishment of license applications.

5 In addition, we have a lot of laboratory
6 work to do to qualify and rele ase the influenza virus
7 vaccines that are used in the United States, and that
8 includes things like testing a nd approving all of the
9 seed viruses that are intended for use i n
10 manufacturing and testing the potency of all lots of
11 vaccine that are intended to be marketed in the Unite d
12 States.

13 We also review the release pro tocols that
14 the manufacturers produce, and review their testing o n
15 the products for the influenza virus vaccines intende d
16 for use in the United States, which currently ar e
17 about 70 to 75 million doses yearly. That may be at
18 a plateau but it has been rising in previous years an d
19 had added to the amount of work that our group has ha d
20 to do.

21 In addition, we are involved i n
22 surveillance activities of a variety of types ,
23 including review of adverse reactions for influenz a
24 virus vaccines, doing inspections of manufacturers ,
25 and then being involved in other compliance activitie s

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 including activities related to the vaccine shortages
2 and recalls.

3 The laboratory activities that we perform
4 in relation to our regulatory work include a lot that
5 are related to selection of the strains that are used
6 in the vaccine, which many of the committee members
7 will be very familiar with. We do serologic testing
8 of a large number of strains every year to determine
9 whether these new strains are inhibited well by anti-
10 sera produced by the current vaccines.

11 In addition, we produce, qualify, and
12 distribute the reference strains and reference reagents
13 that are used for vaccine standardization -- not only
14 in the United States but in other countries including
15 Canada and some European countries.

16 And finally, we produce high-growth
17 reassortants that are used for manufacturing current
18 influenza virus vaccines. With the amount of vaccine
19 that's being produced these days it's likely that it
20 would be impossible to meet the production goals
21 without the availability of strains that have been
22 adapted for growth in eggs, and that's the function
23 that the high-growth reassortant serves, since many of
24 the wild-type strains reproduce fairly poorly in eggs.

25 The remainder of our time is devoted to

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 research activities, and that's approximately 2 5
2 percent of our time. Our rese arch is, by its nature,
3 applied and directly supports our regulatory duties,
4 not only for the current vaccines but to prepare us t o
5 deal with new vaccines that are in development, such
6 as the live attenuated influenza virus vaccine.

7 The goals of our research are t o
8 understand and develop high-growth reassortants that
9 could be useful for manufacturing. We have mad e
10 several new high-growth reassortants every year fo r
11 the past several years, and one of our reassortant ha s
12 been used in manufacturing world-wide in each of the
13 last three years.

14 We have established a program to produce
15 high-growth reassortants by other means, including th e
16 use of controlled introduction of single genes or what
17 is being termed popularly as reverse genetics. W e
18 have currently been investigat ing introduction of the
19 matrix gene of A-Puerto Rico/8/34 into wild-typ e
20 strains to make high-growth reassortants, and th e
21 reason we've been pursuing thi s is because the matrix
22 gene has been associated with the high-growt h
23 properties of the other high-growth reassortants whic h
24 have been made by classical, reassorting methods.

25 We're at an early stage in that progra m

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 and so there's not really much to say except that we
2 have produced some reassortant by that method.

3 We're also developing a system to produce
4 high-growth reassortants for influenza B viruses .
5 Currently, there are no high-growth reassortants that
6 produce for influenza B viruses, and this could be of
7 importance because we have occasionally had strains
8 that grow very poorly in eggs and we have only been
9 very lucky to find an alternate strain that could be
10 used.

11 The strategy that we're using to develop
12 these high-growth reassortants takes advantage of the
13 fact that there are two antigenically divergent
14 lineages of influenza B which are represented by
15 BAMAGATA 1688 and BVICTORIA 287. And again, we're at
16 an early stage of investigation here since we've
17 started this program only last August.

18 But we have been able to demonstrate that
19 we can produce reassortants by using those two strains
20 and that we can identify the origin of the hemmagglutinin
21 and the neuraminidase gene, and we're working on
22 identification of other genes related to that.

23 Finally, we have developed a system that
24 will permit us to identify by molecular means, the
25 donor origin of all influenza A and B genes which will

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 help us to better understand and manipulate high -
2 growth properties for the reassortants.

3 In addition, this will prepare us to be
4 able to qualify live attenuated vaccines which will be
5 important because the attenuation of these vaccines is
6 dependent upon the presence of specific genes within
7 those reassortants.

8 Our future goals for this program would be
9 to continue to prepare for production and use of new
10 influenza virus vaccines, including the live
11 attenuated vaccines, as I've already indicated. We
12 would like to be able to develop additional, high -
13 growth reassortants for influenza B and also to expand
14 our program of making high-growth reassortants for
15 influenza A viruses, particularly as those may be
16 needed for preparing for the next antigenic shift in
17 influenza A viruses and being prepared for the
18 possibility of a pandemic.

19 And one further thing that we related to
20 both of those that we would want to do would be to
21 continue to, as we can, to investigate the specific
22 properties that are responsible for the high-growth
23 phenotype so that we can improve what we're doing at
24 this point.

25 I'll think I'll stop there, and thank you .

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 CHAIRPERSON FERRIERI: Thank you, Dr .
2 Levandowski. Are there questi ons for Roland from the
3 committee members? Please announce your name before
4 you speak.

5 MR. POLAND: This is Greg Poland. Roland ,
6 haven't you already been successful in producin g
7 influenza A high-growth reassortants?

8 DR. LEVANDOWSKI: Yes, we have produce d
9 influenza high-growth reassortants for H3N2 and H1N1
10 influenza A strains. We have not worked at thi s
11 point, but would anticipate doing so, other strain s
12 that might be potential strains for a new shift i n
13 influenza A viruses, including the H2, H4, and H 7
14 subtypes.

15 MR. POLAND: Okay. Thank you.

16 CHAIRPERSON FERRIERI: Other questions fo r
17 Roland?

18 DR. EDWARDS: In terms of the DNA vaccine
19 --

20 CHAIRPERSON FERRIERI: Dr. Kat hy Edwards,
21 for the transcriber.

22 DR. EDWARDS: Sorry. Are those also goin g
23 to be evaluated in your division, or will those b e
24 evaluated in another division?

25 DR. LEVANDOWSKI: Yes, those will be - -

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 well, it will probably have multiple evaluations, but
2 we will certainly be involved in evaluating vaccines
3 as they relate to influenza -- the use for influenza.

4 DR. EDWARDS: Okay, thank you.

5 DR. CLEMENTS-MANN: This is Mary Lou
6 Clements-Mann. In terms of the DNA vaccine, would you
7 also be looking at the safety of those vaccines, or
8 looking at some of those issues in your lab or more
9 the immunology --

10 DR. LEVANDOWSKI: Well, if you're asking,
11 will we be involved in clinical trials, it's not clear
12 to me that we will be involved in any kind of clinical
13 trials. We will of course, review any clinical trials
14 that are being done for both safety and
15 immunogenicity. We do not have the specific program
16 to look at aspects of DNA vaccines in our laboratory;
17 however, we do have the ability to evaluate these
18 plasmids, at least to know what they are and to know
19 what genes are present in those plasmids as they
20 relate to influenza.

21 DR. CLEMENTS-MANN: Okay.

22 CHAIRPERSON FERRIERI: Other questions
23 from the panel?

24 DR. GREENBERG: Harry Greenberg. Roland,
25 I assume that your methodology that you plan to use to

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 genotype the live influenza viruses, the reassortant
2 viruses, are some sort of PCR -- how far that' s
3 progressed. That's strikes me as not totally simple
4 to do.

5 DR. LEVANDOWSKI: I'm sorry, I missed the
6 middle portion of your question; it was sort of cu t
7 out. Maybe you could repeat that, please?

8 DR. GREENBERG: The question -- I assume
9 that you are using a PCR-based assay to do genotyping
10 on the influenza live reassortant-type vaccines. My
11 question was, do you have such an assay in hand or is
12 that just beginning to be developed?

13 DR. LEVANDOWSKI: We have all th e
14 techniques in hand to do it. If you're asking have w e
15 done it for every gene for the live attenuated strain ,
16 the answer to that is no, but it's a straightforward
17 proces s to apply the procedures that we use alread y
18 for influenza A viruses, as we do them for inactivate d
19 vaccine strains or for influenza B.

20 The short answer is yes, we can do it .
21 Now.

22 CHAIRPERSON FERRIERI: Other question s
23 from the panel? If not, I wan t to thank everyone who
24 presented. We will need to clear the room now i n
25 order to move on to the closed session, so we'll take

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 a few minutes and during that time panel members, if
2 they want to tell a few of their favorite jokes --

3 MS. CHERRY: It's only going to take a
4 moment, and we're going to keep Drs. Neil Goldman ,
5 Peter Patriarca, and Bill Egan in the room at th e
6 table, along with the transcriber.

7 (Whereupon, the foregoing matter went off
8 the record at 11:47 a.m. and r esumed at 11:48 a.m. in
9 Closed Session.)

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1 MS. CHERRY: And we have checked th e
2 hallway. We are officially now open for open public
3 hearing but there is no one there beating at our door .

4 CHAIRPERSON FERRIERI: Praise the Lord.

5 MS. CHERRY: So that being the case, I
6 guess we are ready for you to adjourn.

7 CHAIRPERSON FERRIERI: Yes, I would move
8 for adjournment and want to thank everyone for hangin g
9 in. It didn't take us the two hours and 45 minutes;
10 we're short of two hours. And I think we did a very
11 complete job here, so it was g reat being with you all
12 again by remote, and I look forward to being able to
13 talk with all of you in August.

14 Nancy, we're still on for the other site
15 visits?

16 MS. CHERRY: We go through the same kind
17 of fun again in August, yes.

18 CHAIRPERSON FERRIERI: Yes, terrific ,
19 Nancy. We'll be talking some more about those other
20 items then, Nancy.

21 MS. CHERRY: Absolutely.

22 CHAIRPERSON FERRIERI: Okay. Well, bye-
23 bye everyone.

24 MS. CHERRY: Thank you, all.

25 DR. GOLDMAN: Thank you very much.

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25

CHAIRPERSON FERRIERI: Goodbye.

(Whereupon, the teleconference meeting of
the Vaccines and Related Biological Products Advisory
Committee was concluded at 1:04 p.m.)

NEAL R. GROSS

COURT REPORTERS AND TRANSCRIBERS
1323 RHODE ISLAND AVE., N.W.
WASHINGTON, D.C. 20005-3701