UNITED STATES FOOD AND DRUG ADMINISTRATION

PATHOGEN REDUCTION TECHNOLOGIES (PRT)

FOR BLOOD SAFETY

PUBLIC WORKSHOP

Silver Spring, Maryland

Friday, November 30, 2018

1 PARTICIPANTS:

2 Welcome:

3 C.D. ATREYA, Ph.D.
OBRR, CBER
4 Food and Drug Administration

5 SESSION 4: Emerging Innovations Relevant to
Pathogen Reduction Technologies and Alternatives:
6
STEPHEN WAGNER, Ph.D., Moderator
7 American Red Cross

8 Blue Light Inactivation of Pathogens in Platelets
and Plasma: A Pilot Study:
9
MICHELLE MCLEAN, Ph.D.
10 University of Strathclyde

11 A Nucleic Acid Binding Photosensitizer With
Flexible Structure for Pathogen Inactivation in
12 Red Cell Suspensions:

13 STEPHEN WAGNER, Ph.D., Moderator
American Red Cross
14
Pathogen Reduction in Blood Products: Refrigerate
15 and Use PRT:

16 COLONEL ANDREW CAP, MS, M.D., Ph.D., FACP
U.S. Army Institute of Surgical Research
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Panel Discussion:
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MICHELLE MCLEAN, Ph.D.
19 University of Strathclyde

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1 PARTICIPANTS (CONT'D):

2 SESSION 5: Funding Opportunities for Future Pathogen Reduction Technology Research:

3

SIMONE GLYNN, M.D., MPH, Moderator
4 NHLBI
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Panel Discussion:

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MAJOR BRYAN KUJAWA, M.D.
8 U.S. Army

9 SESSION 6: Summary Presentations:

10 Session 1:

11 SIMONE GLYNN, M.D., MPH, Moderator
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12 National Institutes of Health

13 Session 2:

14 BILL FLEGEL, M.D., Moderator
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Session 3:

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RAYMOND GOODRICH, Ph.D., Moderator
17 Colorado State University

18 Session 4:

19 STEPHEN WAGNER, Ph.D., Moderator
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Concluding Remarks: Insights for Future Research
21 and Development:

22 PAUL NESS, M.D.
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1 PARTICIPANTS (CONT'D):

2 Closing Remarks:

3 NICOLE VERDUN, M.D.
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1 P R O C E E D I N G S

2 (9:00 a.m.)

3 DR. ATREYA: Good morning, everyone. I
4 hope you enjoyed yesterday's sessions very well
5 and this is welcome to day two of the workshop.
6 And I am looking at anybody else in the hallways
7 to come inside and then, when we start as soon as
8 possible. And hopefully, we'll have very pleasant
9 discussions today, and it will end around 1:00.
10 And then, after that you guys are free. Thank
11 you.
12 Steve, you want to come here and do it after -- you
13 have anything to say your words, then we can keep on
14 that point.
15 DR. WAGNER: Good morning. My name is
16 Steve Wagner. I'm with the American Red Cross and
17 welcome to session four which is emerging
18 innovations relevant to pathogen reduction
19 technologies and alternatives. And our first
20 speaker today will be Michelle MacLean from across
21 the pond, as you will. And it's entitled "Blue
22 light inactivation of pathogens in platelets and

1 plasma; A pilot study."
2 DR. MACLEAN: Okay, thank you.
3 DR. WAGNER: Wrong one. We'll get it
4 eventually, yes. Okay. You're good.
5 DR. MACLEAN: Okay, thank you very much,
6 and first thing, I'd just like to, again, thank
7 the organizing committee and C.D. for inviting me
8 here today. It's an honor to be able to come here
9 today to tell you about some of the academic
10 research which we've been doing at Strathclyde
11 University in collaboration with C.D. and Monique
12 here at the FDA. And I'm going to talk to you a
13 bit about the work we've been doing looking at
14 blue light for inactivation of microbial pathogens
15 within platelets and plasma.
16 Now just to give you a bit of background
17 initially about myself and the team that I work
18 with; I, myself, am an applied microbiologist and
19 bioengineer. And I work at the University of
20 Strathclyde which is in Glasgow in Scotland. And
21 the area that we work in is very much associated
22 with the development of novel technologies in both

1 optical and electrical engineering technologies
2 for infection control applications.
3 And one of the main technology areas
4 that we have worked on over the last quite a
5 number of years now is the use of violet-blue
6 light for antimicrobial applications. Now in
7 terms of germicidal light, it's well known the
8 germicidal properties of ultraviolet light. And
9 over the decade or so there's been a growing
10 awareness of the antimicrobial properties of light
11 in the kind of violet-blue region.
12 Now the peak antimicrobial efficacy we
13 found through a number of studies which we've
14 conducted at the university, but the peak
15 antimicrobial efficacy is found to be in the
16 region of 405 nanometers. So we're looking at
17 wavelengths down towards the kind of cusp of the
18 ultraviolet region of the lower end of the visible
19 spectrum. These violet-blue light regions have
20 been found to possess some quite broad spectrum
21 antimicrobial effects.
22 Now in terms of the use of these

1 wavelengths, it has a number of benefits.
2 Although it is less germicidally effective than
3 ultraviolet light, and this is due to the fact
4 that it's low-energy wavelengths. That also has a
5 benefit in that these wavelengths can be used at
6 levels that permit safe application for exposure
7 to mammalian cells and people. So this safety
8 benefit has opened up the interest for this
9 technology for a variety of application areas.
10 And two of the kind of most prominent
11 areas that are being investigated currently are
12 the use of these blue-light wavelengths for
13 environmental decontamination. Now this is an
14 area that we have worked a lot on at the
15 University of Strathclyde. And to give you a bit
16 of background about this, we have developed
17 lighting systems, broad spectrum white light
18 systems which contain high output of light in the
19 kind of 405 nanometer range. And these lighting
20 systems permit continuous environmental
21 decontamination in areas where there's people
22 present.

1 So the fact that you can have this
2 decontamination effect being safely applied 24/7
3 in areas where there are inhabitants has proved
4 very beneficial. And we're working a lot for this
5 for development and commercialization within the
6 healthcare sector. This has, over the last year
7 or so, been commercialized as a separate
8 application.
9 But there is also a growing interest and
10 other research groups have been looking at it for
11 wound decontamination. Again, the problem of
12 antibiotic resistance is growing, so the
13 development and emergency of new technologies
14 which can help limit the spread of infection are
15 being investigated. And there are a number of
16 groups, particularly in the US, who have been
17 looking at the development of lighting systems for
18 exposing wounds for wound treatment. So these are
19 some of the areas that are going on looking at the
20 antimicrobial effects of these light wavelengths
21 for practical application.
22 To give you a bit of background about

1 the antimicrobial effects of light and how the
2 actual mechanism of inactivation works, I have a
3 diagram here which displays it. But ultimately,
4 it relies on a photodynamic inactivation process.
5 So within organisms that are exposed, organisms
6 contain these molecules, porphyrin molecules, and
7 these molecules have an absorption maxima in the
8 region of 405 nanometers, so typically between 400
9 and 410 with peak around about 405.
10 And when these organisms are exposed to
11 light of these wavelengths, the photons are
12 absorbed by the porphyrin molecules, and this
13 results in the photoexcitation of the molecules.
14 And once these molecules have become photoexcited,
15 they can then react with elemental oxygen, or with
16 components within the cells to produce a range of
17 reactive oxygen species. And once these reactive
18 oxygen species are developed, they can then work
19 throughout the cell to cause a range of
20 nonspecific damage. So this can include things
21 like membrane damage, DNA damage, and also lipid
22 damage.

1 So the fact that it is -- doesn't rely
2 on DNA-specific damage, it's very much
3 nonselective. So essentially anywhere within the
4 cell that has this ROS come into contact you'll
5 ultimately get the damage. So this is ultimately
6 the mechanism that we've been finding and there's
7 a growing body of evidence surrounding this in the
8 scientific literature.
9 What we want to mention as well is that
10 so far we have found these light wavelengths to
11 have very broad spectrum antimicrobial effects.
12 Within our group at the university, but also wider
13 groups across international research groups,
14 there's a lot of work now looking at the
15 antimicrobial of these wavelengths. And
16 ultimately, what we've found has been that it's
17 got broad spectrum efficacy against a wide range
18 of gram positive and gram negative organisms, also
19 against yeasts and fungi, and we've done a bit of
20 work looking at viruses as well. And I'm going to
21 come back to talk about viruses in a few slides.
22 Because with viruses, although you get an

1 inactivation, it's very situation-dependent, so
2 I'm going to talk more about that.
3 But currently, from what we have found,
4 we're yet to find an organism that doesn't show
5 susceptibility to inactivation through this
6 mechanism. So it does demonstrate in great broad
7 spectrum application.
8 So through the work that we were doing
9 at the university, there's a large range of
10 advantages of these light wavelengths which I can
11 talk about. So I mentioned the broad spectrum
12 antimicrobial efficacy. So this was opening up
13 various application areas, but in addition to
14 this, a key aspect is that these wavelengths,
15 because they are longer wavelength than
16 ultraviolet, it does mean that they have greater
17 penetrability. So they can penetrate into
18 materials and into substances to a greater depth
19 than shorter wavelength energy.
20 So this, again, helps look at different
21 applications areas. And additionally, I mentioned
22 that the non-requirement for photosensitize are so

1 -- the photosensitizing agent in the case of this
2 technology is actually molecules which are within
3 the microbial cells themselves. So there's no
4 necessity for the addition of additional chemicals
5 or molecules into the inactivation and treatment.
6 And again, operator safety, operational
7 safety, so the fact that these wavelengths are
8 from within the visible spectrum means that there
9 is increased safety and improved safety; it means,
10 again, it opens up a variety of different
11 application areas. And we've also done a lot of
12 work looking at the effects of these light
13 wavelengths on polymers. Some light wavelengths
14 are associated with the breakdown of polymers, but
15 from the work that we've looked at, the effects on
16 polymers are negligible.
17 And again, these application areas
18 altogether, these advantages led to discussion
19 with colleagues C.D. and Monique at the FDA, and
20 we've opened up the potential that this might be
21 an option for looking at the treatment of blood
22 products. So this is how the, kind of,

1 application area came into investigation.
2 So the key objectives of what we start
3 to look at -- there was a range of different
4 stages we had to go through. So first of all, it
5 was, essentially, investigating the potential for
6 antimicrobial efficacy of these light wavelengths
7 for decontaminating contamination, microbial
8 contamination within blood products. Now we have
9 specifically focused on platelets and plasma, and
10 again, this is a lot to do with the
11 transmissibility of the technology. Whole blood
12 and red blood cells are red in color and they're
13 very opaque and they don't have -- allow the
14 degree of penetrability of light that we would
15 require for an application in this area. So we're
16 very much focusing on platelets and plasma in
17 terms of what we're looking at today.
18 We also wanted to look at the potential
19 for decontamination of blood products within blood
20 transfusion bags. So the penetration and the
21 penetrability of these light wavelengths means
22 that it could pass through the material of the

1 blood bag themselves. And it allowed the
2 potential for using these light wavelengths to
3 actually decontaminate blood which is already
4 pre-bagged within the transfusion bags, therefore
5 minimizing the handling and processing risks.
6 And importantly, an aspect which was
7 picked up very strongly yesterday is the fact that
8 we have to determine whether these light
9 wavelengths can actually obtain the antimicrobial
10 effects whilst retaining the integrity of the
11 blood components themselves. And this is,
12 obviously, a really important aspect for any PRT
13 that's being developed.
14 So our current areas of investigation
15 following on from these three points, in terms of
16 antimicrobial potential, we're looking at
17 inactivation of microbial pathogens, both in terms
18 of bacteria and viruses. We've been evaluating
19 energy levels that are required for
20 decontamination. And also, as I mentioned, we're
21 looking at decontamination within sealed bags. So
22 these are all aspects which we were investigating

1 in terms of looking at the actual potential of the
2 antimicrobial technology.
3 For blood product quality, it was really
4 important for us to start looking at evaluating
5 the quality of the platelets and plasma
6 post-exposure. And a key aspect of what we're
7 trying to currently determine is the upper and
8 lower threshold limits that we can use for this
9 technology. So we're going to try to determine
10 what the lower level of treatment that's required
11 in order to obtain the effective antimicrobial
12 dose, but we also need to ensure that we establish
13 what the upper threshold is so that we don't cause
14 unnecessary damage to any of the blood components.
15 So these are all areas which we are
16 currently working on, and I can show you some of
17 the data which we have on this today. A final
18 aspect which I'll touch on later in the
19 presentation is the prototype development.
20 So the laboratory, the research group
21 that I come from is an interdisciplinary research
22 laboratory. We work. There's a combination of

1 physicists, electrical engineers and biologists
2 all working together. And the element of what
3 we're looking at together with the antimicrobial
4 and the biological effects on the cells is looking
5 at the development of a prototype which could
6 potentially be used for trialing some of these
7 antimicrobial processes on. And I'm going to get
8 into some details about that as well.
9 So as I mentioned, the first thing we
10 had to establish was the potential for
11 antimicrobial efficacy when organisms were held
12 within the platelets and plasma suspensions. And
13 I have some data up here which has been taken from
14 some of our publications, and the photograph, you
15 can see, is essentially looking at some bacterial
16 inactivation. Now a lot of our early studies
17 looked at small volume samples and high radiance
18 light. And what you can see here is an
19 inactivation curve. So we've got low population
20 by dose and we can see inactivation curves.
21 So this initial curve, which I want to
22 highlight, is the inactivation of staphylococcus

1 aureus in a salt, saline solution, in a phosphate
2 buffer and saline. And here we also have two
3 curves looking at the inactivation of
4 staphylococcus aureus in both animal plasma and
5 human plasma. So we wanted to establish the
6 efficacy, first of all, could the inactivation be
7 achieved in plasma, and also comparing it against
8 inactivation in a substance such as inert saline
9 solution helped us evaluate how the
10 transmissibility of the plasma effects the
11 inactivation potential.
12 So we looked at some key organisms, some
13 key bacterial organisms and found that
14 inactivation could be achieved albeit at higher
15 doses that are necessary for this. What other
16 aspect I wanted to highlight here is to come back
17 to the viral inactivation.
18 From the work that we have done in our
19 research group, we've looked at inactivation of a
20 virus in different situations. Now because of the
21 inactivation mechanism relying on the presence of
22 porphyrins within the microbial cells, this wasn't

1 going to prove successful for viruses because they
2 don't contain these endogenous molecules. So what
3 we looked at was actually seeding plasma with the
4 viruses. And what we actually found was that you
5 actually got a good inactivation effect. And the
6 likely explanation for this is that the plasma
7 itself contains photosensitive molecules which can
8 actually absorb light in the appropriate
9 wavelengths. And this causes a photodynamic
10 oxidative effect from the outside of the virus
11 rather than internally as was the case with the
12 bacterial yeast cells.
13 So as you can see, this is an example of
14 a norovirus surrogate that we've used for this in
15 plasma. So the data is showing that there is
16 potential for viral inactivation. This is
17 something we need to look a lot more into, but
18 again, the mechanism is slightly different in that
19 it's relying on the presence of components within
20 the blood components themselves. And there will
21 be elements that we have to really investigate
22 quite thoroughly to make sure that this isn't

1 actually causing any damage to the plasma or the
2 platelets themselves as well. So this is all EDS
3 that we're looking further into just now.
4 So what I want to move on now is
5 actually looking at the antimicrobial efficacy and
6 compatibility with plasma in terms of looking at
7 it in terms of within the blood bags. So I
8 mentioned about the penetrability of the light and
9 the fact that you can actually get light, adequate
10 light penetration through the blood bag material.
11 And this image that you can see here highlights
12 the transmissibility of light through the blood
13 bag material. Again, we're up at the 405 region;
14 as you decrease with shorter wavelengths then the
15 penetrability decreases significantly.
16 But the ability of the light to pass
17 through this blood bag meant we had the
18 opportunity to investigate whether this could
19 potentially be applicable for in situ
20 decontamination of platelets and plasma within the
21 bags themselves. And we published work a couple
22 of years ago and this is some of the data from it.

1 So to do this, we would essentially set
2 up a light set-up which used LED arrays and it's
3 typically 405 nanometer narrow band LED arrays
4 that we use. And we have to model the irradiance
5 profile to ensure that the bag is getting an
6 appropriate irradiance across the entire surface,
7 and then artificial seeding of the plasma bags was
8 undertaken. And you can see the successful
9 inactivation that was achieved over the time
10 periods.
11 Again, in another of the studies that
12 we've done, we've used fairly low-level
13 contamination with a view to trying to inactivate
14 the low density contamination that is likely to
15 appear within the blood supplies. From the
16 previous slide you saw, we did work, initial work,
17 on much higher population densities. So we're
18 able to decontaminate using high -- decontaminate
19 high contamination levels. But for all the work
20 we're doing currently, we're looking at the low
21 levels to see what energies are required.
22 So this example that you can see here is

1 what we found with the plasma and I'll show you in
2 later slides that the inactivation capability
3 within platelets was actually very similar. So
4 the similar kinetics were achieved in both
5 instances.
6 So that was specifically looking at the
7 quality of -- sorry, the antimicrobial efficacy of
8 the light for decontamination. But as we
9 mentioned, it was really important for us to look
10 not just at that, but at the quality of the blood
11 components and if there's any changes in these
12 areas. So we set up some studies fairly recently
13 to look at the quality and looking at key
14 indicators within plasma to try to determine
15 what's happening, and also to try and help us
16 establish some threshold levels that we want to
17 try and start working towards for a more practical
18 application.
19 So for these experiments, we would look
20 at exposing different samples of plasma to
21 different durations and different intensities of
22 405 nanometer light. And following this exposure,

1 samples were then analyzed using SDS gel
2 electrophoresis and also Western blotting. And
3 the gel electrophoresis allowed us to look at
4 general changes in the protein quality and
5 contact, and then the Western blotting would help
6 us to look at specific markers that we had
7 selected to investigate.
8 So we set up, initially, two levels of
9 inactivation kind of processing. So we wanted to
10 look, first of all, at the high irradiance levels,
11 100 mW/cm2 irradiance is what we used and this is
12 a very, very high level exposure which we
13 selected. And for these tests we exposed the
14 plasma from one hour to five hours at this high
15 irradiance light, and then we analyzed the plasma
16 using the gel electrophoresis. And what you can
17 see is that after two hours of exposure to the 100
18 mW/cm2 light, there tended to be changes becoming
19 evidence in the banding pattern. So that helped
20 us to establish the kind of upper level of an hour
21 at that irradiance level.
22 We also looked at Western blotting, and

1 specific key markers we selected were two
2 immunoglobulins, IgA and IgG. And we also
3 selected fibrinogen and human serum albumin as
4 well as two key markers. The results from this
5 varied from protein to protein, and again, these
6 are very preliminary results. We're working on
7 repeating these within the laboratory currently.
8 But generally you can see changes.
9 Everything that's highlighted in the red was
10 starting to show changes from the control samples
11 which had been left sitting not exposed to the
12 violet-blue light for the same time periods. And
13 ultimately, it varied from marker to marker, but
14 the lowest was changes an hour becoming evident
15 with the IgA. So again, taking these results
16 together, this was suggesting that using a high
17 irradiance of 100 mW/cm2 one hour would be the
18 typical kind of maximum duration that you would
19 want to expose this to.
20 We then went on to do similar analysis
21 with a much lower irradiance of light. So in this
22 case, we're using 10 mW and simply sp -- 10 mWs

1 exposure were conducted for up to ten hours in
2 this case and differences in the banding patterns
3 were observed after about five hours of exposure
4 to the light.
5 And with the Western blotting, the same
6 procedure was carried out, 10 mWs/cm2 exposure up
7 to ten hours. And again, highlighted are the
8 points where some breakdown was becoming apparent
9 within the proteins. And three hours seems to be
10 the minimum time both for the IgA and the human
11 serum albumin. So together, this then helped us,
12 again, establish something of a lower threshold.
13 So three hours using 10 mW/cm2 was helping us to
14 kind of establish a low exposure.
15 So the next stage of what we want to
16 investigate was looking at dose dependency. Now
17 with a lot of energy and light-based technologies
18 in particular, there is likely to be a difference
19 in the affects you see in biological cells
20 depending on how you apply this energy to them.
21 So from the results, we were finding that about
22 one hour at 100 mW/cm2 and this gave a dose of 360

1 Joules. This appeared to be a high-level
2 threshold that we didn't want to apply more than.
3 But with biological cells, these can be
4 quite sensitive. So we wanted to investigate
5 whether if you applied this dose level, but you
6 apply it in different ways, for example, using
7 much lower irradiance over much longer time
8 periods, do you actually get a difference in how
9 the cells themselves, and the components, the
10 protein components are affected because this has a
11 lot of influence on how, ultimately, you would
12 want to deliver a particular dose.
13 So for this we conducted a range of
14 treatments, all of which equaled a dose of
15 360J/cm2. And the maximum, which we mentioned,
16 was one hour at 100 mW down to using ten hours
17 exposure at 10 mW/cm2. And we wanted to evaluate
18 the efficacy of these. And what we found was that
19 regardless of how you applied this dose, the
20 inactivation efficacy was apparent across all the
21 different dose regimes.
22 We did tests conducting inactivation

1 efficacy using seeded contamination levels as it
2 was 102 up to 105 CFU/mL within the plasma. And
3 at each of the dose regimes, the five different
4 dose regimes, we were able to achieve significant
5 inactivation, and this ranged from between 92 and
6 99.99 percent inactivation, so up to -- full of
7 reduction in the majority of cases.
8 So the established that this dose, if
9 applied in different ways, it was still proving
10 effective for the antimicrobial properties. And
11 the point that we're at just now is actually
12 looking towards how the dose being applied in
13 different ways is affecting the actual components.
14 And what we have here is just an example of one of
15 the gel electrophoresis that we have conducted,
16 and from these results, it's quite difficult to
17 see, but the initial results seem to be showing
18 that the hour at 100 mW seemed to be causing some
19 noticeable changes in the protein structure,
20 whereas the other regimes aren't causing this to
21 the same degree.
22 Again, this is just the first run of

1 this experiment which we've conducted. So we have
2 a lot more investigation to do. But it does show
3 that there is potential to apply the same dose but
4 in a much more gentle fashion to allow
5 compatibility with the blood products themselves.
6 So that was very much focused on the
7 plasma. I'm just going to touch slightly on what
8 we've been looking at with the platelets.
9 So again, a lot of our initial work
10 looked at the antimicrobial efficacy of the light
11 treatment within plasma and platelets. And the
12 result that you can see here is platelets that
13 were seeded with staphylococcus aureus
14 contamination, and we conducted a range of
15 different treatments of the sealed blood bags
16 ranging between 3 mW and 10 mW/cm2 radiance. And
17 what you can see here is a typical inactivation
18 curve which we're achieving of the treated sealed
19 bags. So typically, the inactivation with
20 increasing dose we're achieving complete
21 inactivation of the contamination.
22 Some of the aspects that we were looking

1 at for this work was to look at the effective
2 agitation. With platelets, the standard treatment
3 conditions and storage conditions are under
4 agitation. So we were looking at the inactivation
5 under the same types of condition and results were
6 promising. Results is the inactivation capability
7 is enhanced by the use of agitation because the
8 light -- this helps any contamination in the
9 platelets and plasma to actually be exposed,
10 probably more, to the light than they would be if
11 they were just sitting static. So the use of
12 agitation in standard storage is compatible and
13 actually helps improve the antimicrobial efficacy.
14 Now also some work was conducted, some
15 immune tests were conducting using platelet
16 samples which had been exposed to the light. So
17 what was -- we wanted to evaluate whether the
18 light treatment had any effect on the recovery of
19 the platelets. And this was done using scid mice
20 as the model. And for this, the platelets were
21 treated for eight hours and irradiance of 10
22 mW/cm2. And these were then infused -- transfused

1 into mice.
2 And control platelets, which had been
3 non-exposed, were also transfused into a mice
4 model. And as you can see from the data, the
5 light exposure didn't have a significant effect on
6 the recovery of the exposed platelets in the mouse
7 when compared to the control platelets. So this,
8 again, was very promising and looking at the
9 compatibility of the technology with the blood
10 components themselves.
11 Okay. So I mentioned briefly in one of
12 the initial slides about the fact that we're
13 interested as well from a university perspective
14 in trying to develop a prototype both in terms of
15 helping us with our research, and also looking at
16 the potential of this as an actual
17 pathogen-reduction technology that might be of
18 use, of interest to the industry.
19 But one of the stages we're at just now
20 is trying to decide what the best route and best
21 way that this technology might be applied. So we
22 see that as being two, kind of, routes of

1 potential application; the first being a rapid
2 treatment application. So it could be that the
3 technology could be applied as a high-intensity
4 short duration treatment early in the processing
5 stage in order to decontaminate platelets or
6 plasma before the storage of the components.
7 But also there is a potential for
8 continuous decontamination more in the
9 consideration of platelets. With platelets,
10 there's potential to have very low irradiance,
11 violet-blue light during the storage period. And
12 what this would do is, in addition to helping
13 decontaminate, it would help maintain any low
14 bioburden within the platelets themselves. So
15 over the five-day period of storage, there is a
16 potential for low contamination levels to actually
17 replicate over this time. So the potential of
18 having a blue-light treatment which could actually
19 be incorporated into the storage conditions
20 themselves is something that might be of great use
21 in trying to minimize the contamination.
22 So got some pictures here just for

1 showing the stages, again, our initial prototype
2 and what we're trying to build and evaluate within
3 the laboratory to help us with our research in
4 order to help us control the environmental
5 conditions in which the blood components are
6 exposed. And again, some of the work that we've
7 been doing, just highlighting using the cabinets
8 that we've been developing, again, just confirming
9 the inactivation efficacy of the pre-bagged
10 platelets and plasma within the systems.
11 And just to finish up, as we mentioned,
12 these are very early stage results, very
13 preliminary results. But they are starting to
14 establish that there could be potential for use of
15 violet-blue light in the -- as a
16 pathogen-reduction technique for platelets and
17 plasma. Preliminary analysis has demonstrated
18 that decontamination can be achieved at levels
19 that appear to be non-detrimental to the proteins
20 and the plasma, and also the survival and recovery
21 of light-treated platelets and untreated platelets
22 showed similar trends. So these were all showing

1 great potential.
2 But again, much is still to be
3 understood. Light interactions of biomolecules
4 are a very complex area, and there is a lot more
5 information that needs to be understood before
6 this could be developed further. Things like
7 assessing broad-spectrum antimicrobial efficacy,
8 particularly in terms of antiviral properties are
9 of great interest. But these are all things that
10 we're looking to evaluate and investigate over the
11 coming period.
12 So I thank you very much for your time.
13 And I'd also like to thank my colleagues back at
14 Strathclyde and also colleagues here at the FDA
15 for the work that we've been doing. So thank you
16 for your time.
17 DR. WAGNER: Okay. Thank you. I'm
18 going to be talking about a technology that we
19 developed many years ago between 2004 and 2006.
20 So you would not believe how surprised I was to
21 field a call from C.D. a while back saying that
22 you wanted to hear about it. But I guess

1 especially that it was in emerging technologies.
2 But I guess there's not been a lot of
3 emerging technologies between 2004 and now, and I
4 think the work that we did was probably ahead of
5 its time. I should mention that I'm in the
6 inventor of a patent on this and I guess the good
7 news is if you're willing to wait a few years, not
8 very long, it's going to be off patent, and so you
9 can use it for free if you so wish.
10 So this is a slide that basically
11 describes what happens when you add photochemicals
12 to solutions of blood. And what we've seen for
13 about 25 years is a cartoon which is represented
14 in the right part of the slide that shows
15 basically the specific interaction that results in
16 the inactivation of pathogens by the association
17 of a photochemical with DNA, and its illumination
18 producing an excited photochemical that produces
19 photochemical reactions that damage particular
20 DNA. But this is really not what happens.
21 This is not really the full story. This
22 is a cartoon, because in real life, for any of you

1 who have ever worked with microscopy, if you add a
2 dye to a cell, a suspension or a tissue culture,
3 you're going to get the dye-labeling where you
4 want it to label, but almost all microscopists
5 spin down the preparations in something called the
6 cytospin which removes the free dye from solution
7 because it's not -- it doesn't all go to the
8 nucleic acid.
9 And this dye that's free in solution can
10 undergo photochemistry just like the dye that's
11 bound to DNA. And it undergoes photochemistry
12 either by singlet oxygen-mediated reactions which
13 in themselves can change and morph to making other
14 reactive oxygen species such as hydrogen peroxide
15 or hydroxyl radicals or super-oxide. But through
16 electron transfer, for example, with the psoralen
17 molecules, you can make dimers. That is obvious
18 that it occurs in solution. And the reason it
19 makes dimers is that these molecules tend to be
20 flat and planar and hydrophobic and they tend to
21 stack on top of each other into solution and make
22 dimers. And actually, the dimers that they make

1 are exactly like DNA bases that are adducts, for
2 example, in psoralens.
3 And this is demonstrated if you do HPLC
4 of the material in a solution, for example,
5 psoralens, you'll see these dimers. And you'll
6 also see for psoralens some yield of singlet
7 oxygen. The particular psoralen that was picked
8 by the company that involved -- that's involved in
9 the current licensed product does make some
10 singlet oxygen. But it's been selected to reduce
11 the amount of singlet oxygen.
12 Now if you make singlet oxygen from a
13 photochemical, that can diffuse and it can diffuse
14 basically about 100 angstroms. And so any singlet
15 oxygen molecules that are close to the membrane,
16 you're going to see membrane damage from the
17 single oxygen that's produced in the solution.
18 And if it happens to morph into other things such
19 as hydrogen peroxide, which is much more
20 long-lived than singlet oxygen, which only has a
21 lifetime of microseconds, you're going to see
22 long-lived damage and peroxidation of membranes.

1 In addition to that, photochemicals
2 don't just bind -- don't just live in the solution
3 or bind to nucleic acids, because of their
4 chemical properties, they interact with cell
5 membranes. And that's because cell membranes are
6 generally slightly negatively charged, and most of
7 the photochemicals that are used to inactivate RNA
8 or DNA in pathogens have a means on them and have
9 a positive charge. So they can interact ionically
10 with the phosphates of nucleic acid. And they're
11 hydrophobic because they inter-collate between the
12 bases of nucleic acids which they are themselves
13 hydrophobic.
14 So you have this hydrophobic core and
15 then on the outside of the molecule you have an
16 amine group which is going to interact with
17 membranes. And if you make singlet oxygen in
18 membranes, you're going to have a lot of membrane
19 damage. And if you have a psoralen, for example,
20 on membranes, that makes -- goes by electron
21 transfer, then you're going to have electron
22 transfer that occurs in membranes as well.

1 So Dana Devine gave a very nice talk
2 yesterday about the types of things that happen in
3 blood cells when you interact -- when you do
4 photochemistry with platelets, and these things
5 also occur in red cells. And so you'll see
6 changes in the in vitro properties of red cells
7 and platelets with the treatment with the
8 photochemicals. For red cells you see potassium
9 leakage, you see hemolysis, and there are in vivo
10 changes where you may see changes in the 24-hour
11 recovery or survival.
12 And the same is true of platelet damage.
13 You'll see changes in activation of platelets.
14 You'll see changes in the metabolism, speeding up
15 of the metabolism of platelets. You may see
16 changes in aggregation if you look at aggregation
17 response. And this -- and you'll see it in vitro
18 and you'll also see it in vivo with 24-hour
19 recovery and survival. And you'll see it with
20 corrected count increment in platelets as well.
21 And all of these things have been documented in
22 studies.

1 Now around the time that Larry Corash
2 and Lily Lin were busy in their lab investigating
3 8-MOP before they started looking at other
4 photochemicals, this paper came out by Kathleen
5 Specht and Robert Midden. And they were able to
6 show that fatty acids that make up the lipids of
7 membranes, the unsaturated fatty acids have double
8 bonds, and when a psoralen interacts with them,
9 they put adducts on the fatty acids, and so you
10 end up with these fatty acids with the psoralen
11 adducts on it.
12 And this is true, actually, even with
13 amotosalen as you can see in the bottom of the
14 slide, about a third of the photoproducts that are
15 produced by amotosalen bind to high-molecular
16 lipids. So what happens -- lipids are really
17 important for platelet receptors. There are
18 boundary lipids which are important for signal
19 transduction. And here you are -- and they're
20 very sensitive to the fluidity of the membrane.
21 And so if you're adding adducts that are spinning
22 because they're in phospholipids, that's going to

1 change the fluidity of membranes.

2 And so the basic point I'm trying to

3 make is that there's no free lunch. If you're

4 going to get inactivation, you're also going to

5 get some damage to the components that we care

6 about.

7 Now all of these photochemicals that

8 I've spoken of up to this point are rigid

9 molecules made of fused rings of conjugated bonds,

10 whether they happen to be psoralens, whether they

11 happen to be acridines, or phenothiazines, and

12 basically, the photochemicals are normally in

13 ground state. And when you expose them to light,

14 they're excited to an excited singlet state. Once

15 in the excited singlet state, they can fluoresce

16 and give up their energy, or they can go to the

17 triplet state.

18 And it turns out interestingly in life

19 ground state oxygen is in the triplet state. And

20 so there can be an interaction with the ground

21 state oxygen in the triplet state and the triplet

22 state of the dye and that's what make singlet

1 oxygen. And singlet oxygen is really reactive.
2 It's about 42 kilocalories per mole more reactive
3 than regular oxygen. And so you have this
4 tremendous amounts of reactive oxygen species that
5 potentially goes and damages the things that we
6 care about, the cells. They react with targets.
7 Also in the triplet state, you can
8 obviously decay and get phosphorescence going back
9 to the ground state. But these rigid molecules
10 don't really go back to the ground state directly
11 because they're rigid. They can't rotate with
12 heat to release their energy. And so there's no
13 real way to get back to the ground state by bond
14 rotation.
15 And so the idea that we had in the lab
16 was what if there was a photochemical that was
17 flexible? If that was the case, then you would be
18 able to rotate about a single bond and release the
19 energy from excited triplet state to the ground
20 state. And so if you were -- if that molecule was
21 in solution, it shouldn't participate in
22 photochemistry. Now if it was originally bound to

1 a substrate, for example, DNA or RNA, and it was
2 held in a planar confirmation, then it could
3 undergo photochemistry.
4 And so this was a way that we thought we
5 might be able to introduce more specificity for
6 inactivation where the molecule could only be a
7 photochemical if it was bound -- rigidly bound to
8 nucleic acid. But it wasn't a photochemical if it
9 was out in solution. So unlike the microscopists
10 who are spinning down cells to remove the
11 molecules from solution in the cytospin, you don't
12 need to do that.
13 This is a molecule that we began to
14 study in 2004. It's called Thiazole Orange. It's
15 actually used for scanning of reticulocytes in
16 both red cells and platelets. And as you can see,
17 it can rotate about a single bond and dissipate
18 its energy. But you can imagine if it was held
19 fixed in nucleic acid in a planar state, then it
20 would act as a photochemical. And it also
21 fluoresces in that state.
22 This is just proof. These were stained

1 virocells that we didn't wash the virocells. So
2 you can see outside of the virocells there's no
3 fluorescence. So the molecules -- if there's no
4 fluorescence, the molecules can't act as
5 photochemicals, but if there is fluorescence, they
6 can. And as you can see, they stain both the
7 nucleus and the cytoplasm, the RNA in the
8 cytoplasm.
9 So another problem that people run into
10 with photochemicals is that, as I mentioned
11 before, the dyes interact with cellular membranes
12 because the dyes are all positively charged and
13 the membranes are slightly negative charged. And
14 they're also amphiphilic or hydrophobic-like
15 molecules at the core.
16 And so this has been a problem over the
17 years. And so when we've studied hundreds of
18 photochemicals in our lab, and when we studied
19 them, we always did assays to see how well they
20 bound to blood cells. And so basically, what you
21 do is you add the dye to cells, for example, red
22 cells. And then you spin the cells down and look

1 at the supernatant and you see how much dye is in
2 the supernatant. And then you do an identical
3 experiment where you add the dyes to the
4 supernatant without the cells there. And you can
5 calculate what percentage of dye is interacting
6 with the membranes.
7 And in this case, Thiazole Orange, about
8 20 percent of the dye interacts with membranes.
9 And in our hands, with almost all of the
10 photochemicals that we studied, of the 100 or more
11 that we've studied, usually the amount of dye
12 that's bound to the membrane is usually around 60
13 percent or so, about two-thirds of the dye are
14 bound to membrane.
15 And so we thought, gee, this looks like
16 it has some advantages where it's not interacting
17 with red cells as much as what we're familiar
18 with. And so these were the experimental
19 conditions that we did.
20 We had the dye at 80 micromolar. We
21 didn't add any quenchers. There's no glutathione.
22 There's no antioxidants. There's no nothing, just

1 the dye.
2 We exposed the cells and the suspension
3 to oxygen, because, after all, if you're try --
4 you saw that the photochemistry for singlet oxygen
5 requires oxygen. And if your red cells have all
6 the oxygen and there aren't -- there's no more
7 oxygen in the suspension, you're not going to get
8 inactivation of the pathogens as readily. And so
9 we added some oxygen.
10 We did this in petri dishes. You know,
11 this was not ready for prime time. We were just
12 studying it in the laboratory. And then when we
13 were done, we would pull the material from the
14 petri dishes after illuminating them with cool
15 white light. And we studied how well the red
16 cells were and how much inactivation we got.
17 So these are inactivation curves of
18 three model virus; vesicular stomatitis virus
19 which is the model for HIV, and pseudorabies virus
20 which is the model for HBV, and obeen (?) virus,
21 diarrhea virus in red cells. And you can see that
22 you get four or more logs after eight or so joules

1 per cm2. So what happens in red cells under these
2 conditions?
3 Well, not yet. Let's do some more.
4 What's the mechanism? So M13 is a bacteriophage.
5 It's non-envelope that I used many years ago when
6 I was doing Sanger sequencing as a graduate
7 student in the eighties. But and so we treated
8 M13 and we looked at inactivation, and we also
9 isolated nucleic acid from the M13 and transfected
10 that in, and lo and behold, the virus inactivation
11 kinetics were the same. So what does that tell
12 you? That tells you that nucleic acid of M13 is
13 the target here. It's not the protein capsid.
14 We also looked at HIV inactivation and
15 we saw inactivation -- robust inactivation in both
16 extracellular HIV and intracellular HIV. We saw
17 inactive -- we worked with Lisa Cardot. I don't
18 know if any of you ever remember Lisa Cardot or
19 not. And she looked at leishmaniasis and T-cruzi
20 and we saw inactivation of both of those. So it
21 looked like it was pretty robust.
22 I did some work in the lab and we looked

1 at bacterial inactivation because that was
2 something easy that I could do. And it
3 inactivates bacteria. It's a little odd the way
4 it inactivates bacteria. It's species-dependent.
5 And it doesn't go with gram negative or gram
6 positive, and it depends on the species. And I
7 still don't understand why there are differences.
8 Ray is sitting there shaking his head
9 yes. And we looked at red cell storage. And we
10 were able to store the red cells out to 42 days.
11 And we saw some nice talks by Dr. Cancelas
12 yesterday with riboflavin that only gets out to 21
13 days. And we were able to get out to 42 days.
14 And I might add, if you take the cells that have
15 been treated, and you wash them to remove the dye
16 from the supernatant, and then you store the
17 cells, the hemolysis is even less. It's basically
18 about.2 at day 42. So the degree of hemolysis can
19 be managed and it's pretty low.
20 We looked at potassium leakage, and no
21 surprises there. We saw a rapid potassium leak
22 and, you know, of the hundreds of photochemicals

1 that I've studied in the laboratory, or we've
2 studied in the laboratory over many years, I've
3 always seen increases in potassium. The rate of
4 increase of potassium is two to threefold greater
5 than basal rate, and that's very similar to what
6 you see with gamma radiation.
7 And with gamma radiation, we know that
8 the 24-hour recovery is slightly less than that of
9 untreated red cells. And they're only stored for
10 28 days. So until you do the recovery and
11 survival experiment, I don't know what to expect,
12 but I would be -- I would think that might
13 indicate that there is some damage. But it's a
14 lot less than what we've seen for most of the
15 photochemical -- well, all the photochemicals
16 we've studied over the years.
17 For ATP we heard Dr. Cancelas say that
18 ATP levels were predictive with riboflavin on the
19 survival and recovery. And as you can see here,
20 we didn't really see differences in ATP levels.
21 And in fact, the ATP levels were close to 4Mmol
22 per gram of hemoglobin which is actually quite

1 good. So we really didn't see that lesion in what
2 we were -- in our studies.
3 So unfortunately, I'd like to be able to
4 give you more information on this, but the project
5 and our work with pathogen reduction was
6 terminated. And we really haven't been able to
7 study this for probably about 12 or 13 years. And
8 so unfortunately, there's no end to the story. We
9 did go out to talk.
10 Ray, you know, I came out to talk to you
11 about this many years ago, and I went out to
12 Cirrus to talk to them, but they were very busy in
13 what they wanted to do. And so no one really
14 picked up on this technology. And so there it
15 stays.
16 So the conclusions, all photochemicals
17 used for pathogen reduction have secondary
18 reactions that damage non-target molecules. These
19 secondary reactions are responsible for some of
20 the damage to blood components that are observed
21 both in vitro and in vivo.
22 Use of a flexible photosensitizer that

1 only undergoes photochemical reactions when
2 rigidly bound to target can reduce damage to blood
3 components from photosensitizer free in solution.
4 An example of such a flexible photosensitizer is
5 Thiazole Orange which can inactivate a number of
6 viruses and bacteria in parasites in red cells
7 with the maintenance of several in vitro
8 properties during 42-day storage.
9 And I'd like to thank the people in my
10 lab at the time who were involved in the work,
11 Andrey Skripchenko who now is at the FDA and I
12 wish him well; Helen Awatefe; and Dedeene
13 Thompson-Montgomery. Thank you.
14 DR. ATREYA: And so to end the session,
15 we have Dr. Cap and he's going to talk to us
16 about pathogen reduction in blood products;
17 refrigerate and use PRT, and that sounds like an
18 order.
19 DR. CAP: All right, let's see if I can
20 get the right slides up here. Okay, great. I
21 want to thank the conference organizers, our
22 colleagues at FDA for inviting me to speak here

1 today, and I look forward to the discussion after
2 our talk.
3 You know, we heard some alternate
4 approaches to pathogen reduction here this morning
5 from our colleagues here, and I'm going to remind
6 you of another alternative that's perhaps a blast
7 from the past; talk about refrigeration. These
8 are my disclosures. What I'm going to tell you
9 today represents my own personal views and should
10 not be construed as official policy of the
11 Department of the Army or Department of Defense.
12 So the DOD is interested in pathogen
13 reduction like everybody else, but with a caveat.
14 And that is that our primary role in military
15 medicine is to support the warfighter and our main
16 mission is combat casualty care. And so that
17 means treating bleeding patients.
18 And so whatever we deliver in terms of
19 blood products on the battlefield has to be able
20 to provide a hemostatic resuscitation. So we
21 really focus on that when evaluating technologies
22 for storage or pathogen reduction or what have

1 you. Now that said, of course, we want to deliver
2 a safe product to our soldiers, and, you know, so
3 we're interested in basic risk reduction like
4 everyone else for platelet bacterial growth in
5 particular. And we're concerned about the short
6 shelf life of platelets.
7 We deploy troops to environments
8 sometimes where there's endemic risk, where the
9 risk profile that the soldiers face is very
10 different from what we have here in the United
11 States. And for short shelf life products like
12 platelets that means collecting them downrange,
13 and sometimes when we don't have enough blood
14 products, we use whole blood collected from our
15 walk-in blood bank. And those emergency
16 collections, of course, might expose recipients to
17 whatever endemic diseases are in the area.
18 Another thing that forces us to think
19 hard about pathogen reduction is what I'll call
20 the Zika scenario. So we had an urgent
21 requirement for new testing during the recent Zika
22 epidemic. And our blood system is relatively

1 small compared to the civilian, you know, overall
2 blood supply. However, it's very geographically
3 dispersed. And so for example, the Zika testing
4 requirement really hit us hard in platelet
5 availability in certain locations.
6 For example, we have troops in the
7 Western Pacific, and based in Okinawa we have a
8 blood collection center and getting samples tested
9 at participating laboratories in IND back in the
10 United States meant collecting and shipping back
11 and waiting for results and, you know, we had a
12 problem with platelets expiring before we ever got
13 the results of the testing back. So this could
14 happen again, and so this is a major concern for
15 us.
16 And then lastly, there's always the
17 unfortunate reality that we may be faced with
18 radiological injuries. And having a technology
19 that might allow us to provide white blood cell
20 inactivation in far forward locations in treating
21 those troops to avoid graft versus host disease in
22 heavily irradiated soldiers would be potentially

1 useful. So those are sort of the broad spectrum
2 issues that we think about with regard to PRT.
3 So getting into platelets, I'll just
4 remind everybody, we really do have a problem with
5 this product. So the platelet dose study, the
6 PLADO study led by Sherrill Slichter and
7 colleagues identified a dose-dependent increase in
8 transfusion-related adverse events. And not
9 surprisingly, fever was the big problem here. So
10 keep that in mind. Platelets dose-dependent
11 increase in, we'll say, potentially infectious
12 toxicity, and of course, this topic has come up a
13 million times at BPAC and every other forum
14 including this one.
15 Conversely, the PLADO study did not
16 identify a dose response effect on bleeding. And
17 so you can double the amount of platelets
18 transfused and there's no change in bleeding or
19 overall transfusions. And there's a similar
20 bleeding risk across a range of 10,000 to 80,000
21 which suggests that we may have a problem with
22 efficacy with this platelet product that we're

1 using.

2 And then we all know about the platelet
3 storage lesion. The PLADO study showed here,
4 again, no dose-response effect on bleeding, but if
5 you look at the effect of storage time of
6 platelets on bleeding, there was not a
7 statistically significant difference because most
8 patients don't receive fresh platelets. But you
9 can see there that it seems to be a trend that if
10 you get fresher platelets, you might have lower
11 bleeding. So I think the platelet storage lesion
12 is real in that room temperature storage leads to
13 loss of function, along with, obviously, an
14 increased risk of bacterial growth due to the
15 higher temperature.

16 We saw this in the PROMMTT study. So
17 this was a 10 center observational study of trauma
18 patients across the US and Canada that evaluate a
19 number of different things. And one of the
20 outcomes of this study was that we found an
21 association of older platelet age with total
22 increased adverse events but also sepsis. So

1 again, there's a signal here that we really have a
2 problem, and we saw some numbers yesterday, you
3 know, 1 in 30,000 platelet units may be at risk
4 for bacterial growth.
5 And it's hard to wrap your head around
6 those numbers, but, you know, but the reality is
7 that when you look at patient outcomes you
8 actually see this reflected. So I think, you
9 know, there really is a problem with bacteria in
10 platelets.
11 All right, so to summarize all that we
12 have a short shelf life, hard to maintain
13 inventories for everybody, it's really bad for us,
14 and we have to deploy units downrange. We can't
15 ship to forward locations. We're doing downrange
16 collections where we're using untested units, by
17 the way, with no bacterial testing available to us
18 in those locations. Limited donor pools plus the
19 platelet storage lesion, and that's a problem.
20 Now for us in treating bleeding
21 patients, we're sort of held to the, you know,
22 room temperature problem of storage because of

1 recovery and survival, but there's no evidence
2 that that matters in hemostasis. So we have a
3 real issue with this relatively high risk product
4 that's not delivering, kind of, what we really
5 want.
6 And I'll just point out that that's a
7 problem for many people in the United States. So
8 if you look at the map on your left that has sort
9 of a few dots, those are level one and two trauma
10 centers. And you notice they're pretty sparsely
11 distributed across the country. And if you look
12 at level three, four, and five trauma centers
13 which are really not trauma centers, they're kind
14 of concentrated in rural areas. And then if you
15 look at what are called critical access hospitals,
16 again, tiny little hospitals that do see trauma
17 out in the rural communities, none of these places
18 have platelets, folks.
19 And so 50 percent of the US population
20 lives greater than an hour from a trauma center
21 and basically has no access to platelets, whether
22 they're going to get fresh platelets or platelets

1 that are old and have storage lesion and bacteria
2 in them, it doesn't matter if there's no
3 platelets. And it's been documented that there's
4 high rural trauma mortality in the United States.
5 So you need platelets in trauma. And in case you
6 don't think you need platelets in trauma, there's
7 more and more evidence emerging from military
8 experience, but also civilian experiences.
9 There's data from Mitch Cohen's group in San
10 Francisco showing that in level one trauma
11 admissions, 46 percent of patients have platelet
12 dysfunction on admission.
13 Percent of them develop it early during
14 their ICU stay, and if you look at the panels on
15 the right, if you have poor platelet aggregation
16 response to these various agonists, you have worse
17 survival. So when you bleed and you're in shock
18 you need platelets is the bottom line. And if you
19 can't get them, that's a problem.
20 Luckily, we have a low-cost technology
21 that may help us with this. So here we go; cold
22 storage of platelets. It's been an option for

1 many, many years just not implemented due to short
2 shelf life.
3 In case you're skeptical that
4 refrigeration is really going to solve this
5 problem with platelet bacterial growth, you know,
6 I'm sure most of you keep your milk and fish and
7 steaks and other highly perishable items in the
8 refrigerator. You can do this with platelets as
9 well, and we did the experiment here to look at
10 platelets versus platelet poor plasmas as seeded
11 with bacteria, in this case, Acinetobacter. And
12 you see that at 4-C on the left nothing grows.
13 What was really fascinating about this,
14 though, was that the bacteria -- the platelets --
15 actually the platelet-containing products seem to
16 accelerate bacterial growth. So if you look at
17 the panel on the right, the top two curves are
18 platelets with bacteria seeded in them grown at
19 room temperature. And the bottom curves are just
20 plasma from the same donors grown with the
21 platelets in them.
22 And you know, there's a lot of

1 literature out there that says that platelets
2 contain antibacterial peptides and so forth and so
3 on. But what's interesting is that the platelets
4 facilitated the growth by four logs of
5 Acinetobacter. So this is really interesting and
6 we pursued this in a broader range of bacteria.
7 And you can see here on the left we looked at
8 Acinetobacter, E. coli, Pseudomonas, Staph aureus,
9 and Staph epi.
10 And Acinetobacter, Staph aureus, and
11 Staph epi are all facilitated, we'll say, by the
12 presence of platelets compared to plasma alone.
13 E. coli and Pseudomonas are just fine at room
14 temperature, of course, but they don't need the
15 platelets to help them out. In further
16 experiments we determined that this was due to the
17 lactate production. So some bacteria really like
18 three-carbon sugars instead of six-carbon sugars
19 and we'll preferentially use them. And of course,
20 all this can be obviated by putting them in the
21 cold because metabolism is pretty much not
22 happening. You're not consuming glucose as you

1 can see here. So this is all in press and in
2 transfusion right now.
3 So we've known the platelets -- so
4 getting back to the hemostatic piece of this, why
5 we want this, well, you know, 1973 Becker and
6 colleagues showed clearly that cold platelets
7 actually do work and both aspirinated volunteers
8 and in thrombocytopenia bleeding patients.
9 So what's needed to make this a reality?
10 Well, we can already do cold storage of platelets.
11 And FDA a few years ago granted a variance for
12 doing this in apheresis platelets as well as whole
13 blood derived platelets all stored without
14 agitation. I'll show you some data looking at
15 platelet additive solutions versus plasma. And I
16 think it supports use for either one of those and
17 we've stored them out to 21 days and they look
18 pretty good. And we've recently worked with FDA
19 on trying to develop a variance for 14-day
20 cold-stored platelets. And I'll show why that's
21 supported.
22 But for us what would be really helpful

1 is 21-day cold storage because of transportation
2 issues to get fully tested products from the
3 United States to our deployed locations. And I'll
4 just point out it's not as crazy as it sounds. I
5 just said 21-day cold-stored platelets, right?
6 That sounds like a long time, right, five to
7 seven-day storage now. So if you think about it,
8 we store liquid plasma out to 40 days, right? And
9 red cells out to 42 days. These are refrigerated
10 products. So we're talking about just a half of
11 that storage duration. It's not like, you know, a
12 tremendously long storage duration in terms of
13 bacterial growth and things like that.
14 And then the other thing is suppose they
15 sort of peter out and don't work that well at 21
16 days. Well, then you're basically transfusing
17 either liquid plasma or maybe liquid plasma with
18 some additive solution in it. At either rate, if
19 there's any efficacy of the platelets at all,
20 you're still doing better than what you currently
21 have which is nothing in many locations.
22 So keep that in mind. But how well do

1 the platelets really work? So here's some
2 rheometry studies looking at clot strength; fresh
3 versus current standard of care, five-day room
4 temperature, and then stored out 14 days in the
5 cold in plasma in this case. And you can see that
6 the clot strength is better maintained by
7 cold-stored platelets.
8 Todd Getz, when he was in our group, is
9 now at Red Cross, Steve -- did this work on
10 aggregation responses in additive storage
11 solutions in platelets. And you can see on the
12 gray bars that platelet aggregation response is
13 well-maintained out to 22 days in this case to a
14 variety of different agonists. And I'll just
15 quickly show you the dual agonists kind of behave
16 the same way compared to room temperature in the
17 black bars that drop off pretty quickly.
18 We've tried to figure out exactly what's
19 going on to -- that maintains this hemostatic
20 function. So one of the things we looked at was
21 mitochondrial function in the platelets, basically
22 thinking that all these shape change and

1 aggregation responses and release reactions and
2 all that requires ATP. So the platelets have to
3 be metabolically active. Platelets use both
4 glycolysis and mitochondrial respiration. But we
5 figured that probably mitochondrial respiration
6 was more vulnerable to the platelet storage lesion
7 over time.
8 And indeed, that's what we found. So
9 these are oximetry studies showing routine
10 respiration on the left and then oxidative burst
11 on the right. And you can see that function is
12 better maintained in the cold than in room
13 temperature which drops off after five days of
14 storage pretty dramatically.
15 Mitochondrial dysfunction is often
16 associated with induction of apoptosis and so we
17 studied that as well. And we can see in panel A
18 increasing mitochondrial depolarization. It
19 happens, you know, sort of across the board.
20 There's no free lunch as Steve said. But it's
21 worse at room temperature than it is in the cold
22 that's associated with caspase activation. Loss

1 of membrane integrity is determined by fluid and
2 staining of actin that shouldn't be exposed if the
3 platelet membrane is intact and then microparticle
4 formation. So bottom line is that we do think
5 that the mitochondria are sort of driving the
6 platelet storage lesion just due to increased
7 metabolic activity and the room temperature
8 compared to the cold.
9 There are some drawbacks to storing
10 platelets in the cold. So you know, as Dana told
11 you yesterday about PRT kind of activating
12 platelets, we all know that from quite a few
13 studies that there are some activation, sort of a
14 pre-activation stage of cold storage, and that
15 causes some aggregation in the bag. And if you
16 look at platelet counts over time you'll see them
17 decrease.
18 Interestingly, if you store them at room
19 temperature they don't do that. We have, again,
20 this is work that Todd Getz did when he was with
21 us, showed that if you store them in an additive
22 solution, interestingly, this clumping problem

1 goes away. And to make a long story short, just
2 in the interest of time, we'll say that this is
3 basically driven by fibrinogen binding and you
4 make -- the more fibrinogen you have in the bag,
5 the more binding opportunities there are. And so
6 you'll make small aggregates of two and three
7 platelets put together, and we've imaged these.
8 And they're still smaller than a red cell, so it's
9 not really a concern in terms of what it's going
10 to do when it gets into the patient. If there are
11 larger aggregates that don't break up when you
12 rewarm the platelets, those get caught in the
13 transfusion filter and don't really affect
14 function afterwards.
15 So we think this is really a non-issue.
16 Most blood bank technicians, of course, see
17 aggregates in the bag and they think
18 contamination, but that's not what's going on
19 here. This is just a little bit of fibrinogen
20 binding in the bag that can be mitigated by
21 storing in additive solution.
22 What about clinical function of the

1 cold-stored platelets? So our colleagues in
2 Norway worked with us to develop a pilot -- sort
3 of an early phase study in cardiac surgery. And
4 so basically, this is an intervention where they
5 took additive-stored platelets either at room
6 temperature in the cold for out to seven days, and
7 patients who were found to be bleeding after
8 reversal of Heparin and coming off of bypass were
9 transfused whatever they were going to be
10 transfused, red cells and plasma and platelets,
11 and they either got warm platelets or cold
12 platelets.
13 So we looked at aggregation responses
14 and there's some indication that there's slightly
15 better aggregation response in patients receiving
16 cold-stored platelets. Blood product usage was
17 overall similar, you know, kind of trending
18 towards lower in the cold stored, but the
19 important point is that the 24-hour test tube
20 output was actually lower in the cold platelet
21 arm. Now I just want to caveat this by saying
22 this is a small study, 20 patients per arm, and,

1 you know, it isn't really designed to demonstrate
2 that any particular platelet product is superior
3 to another.
4 But it's just to try to reestablish, if
5 you will, the biological plausibility of
6 cold-stored platelets being hemostatically active
7 because we have 30 years of transfusion medicine
8 textbooks that say they're dead, and they don't
9 work. And I hope I've convinced you that through
10 any number of in vitro studies they are alive.
11 They do work. The mitochondria function. Their
12 membranes are intact, they aggregate. And oh, by
13 the way, when you put them in the patient, they
14 actually can stop bleeding. And so even though
15 they are cleared faster, from a surgical bleeding
16 standpoint, a trauma bleeding standpoint, they
17 have clinical relevance.
18 And if you storm out to 14 days you get
19 kind of the same results here. So this is an
20 extension of the Norwegian cold-stored platelet
21 study in the cardiothoracic surgery patients where
22 they sort of did an adapted trial design and added

1 another arm to the study storing them out to 14
2 days in the cold. And you can see that they still
3 work. So it's consistent with the in vitro data
4 that I've shown you so far.
5 And here is the aggregation data, again,
6 in patients getting platelets stored out to 14
7 days. And you can see that, generally speaking
8 they're going in the right direction pre and
9 post-transfusion. Not every time, not every
10 patient, disease, or individual patients, but
11 you've got to remember, too, these are actively
12 bleeding patients getting a resuscitation that
13 contains all sorts of things; red cells, plasma
14 and so forth.
15 So again think about this as like a
16 biological plausibility study. Are these
17 platelets doing something? I think we can say
18 yes. They're doing something and it's positive
19 for hemostasis.
20 What about whole blood? I told you that
21 we collect whole blood in theater. So here we
22 studied the hemostatic properties of

1 Mirasol-treated whole blood and this panel is a
2 little confusing to look at, but basically, if you
3 look on the left panel, that's platelet
4 aggregation response. And the top curves are cold
5 stored. The bottom curves are room temperature
6 stored because there was actually a thought that
7 maybe we would store whole blood at room
8 temperature for a short period of time after it
9 had been treated with Mirasol.
10 And we just took that out over 21 days
11 to see what that would look like, and obviously,
12 it does not look good. So that's not really an
13 option. But if you compare the top two curves,
14 the top curve in non-pathogen reduced, the bottom
15 curve is pathogen reduced, or Mirasol treated I
16 should say. And there's no real difference
17 between the two curves. There's a little bit of a
18 drop with the Mirasol treatment but it's not
19 significant. And if you look at
20 thromboelastography on the right you basically see
21 the same thing. And I'll just point out to you
22 that clot strength is preserved to 21 days of

1 storage. So even though you lose aggregation
2 function, you still get some pretty decent
3 contribution to hemostasis. If you just did red
4 cells and plasma and you looked at the TEG MA it
5 would be 20, not, you know, between 50 and 60.
6 So again, there's no free lunch.
7 There's a price to be paid both for duration of
8 storage, and for use of PRT, but certainly it's
9 better than nothing. And at least it improves the
10 margin of safety.
11 Now I have up in the title there why
12 aren't we doing this now? I think it's
13 interesting that we have data, in vivo data, from
14 the AIMS study in Ghana showing decreased
15 transfusion trans-minimal area. From the
16 standpoint of, I think, military use of a product
17 like this, we send soldiers who have been multiply
18 screened for transfusion-transmitted disease.
19 Many of them are blood donors to start with, but
20 if they're part of a unit where we're going to
21 depend on a walking blood bank, they are screened.
22 The donors are tittered for anti-A and anti-B.

1 They multiply deploy. They're multiply tested.
2 We know that they're not getting Hepatitis B and
3 HIV in theater.
4 But if they're operating in a malarial
5 zone, they could get malaria. They're supposed to
6 be taking their prophylaxis. They usually do,
7 but, you know, sometimes they don't. And so as a
8 risk reduction measure for at least malaria, I
9 think this is a reasonable alternative based on
10 the data we have now and something to consider.
11 And it doesn't compromise hemostatic function to
12 the point that I would be concerned about.
13 Now what about intercept on the platelet
14 side? So these are the preliminary data, but
15 basically what we have here is Trima collected,
16 stored in plasma, and either intercept treated or
17 not; all stored in the cold, okay? So there's not
18 a room temperature arm here, and here you're
19 looking at aggregation out to 21 days. And you
20 see that they're basically the same.
21 And here you have ROTEM on the left
22 showing clot strength and clot lysis. A little

1 bit of a possible decrease in clot strength with
2 the intercept-treated platelets, but it's not huge
3 and I think that we need more data to be sure
4 about what's going on there. But clearly, at
5 least out to 14 days, there's no major difference.
6 And if you look at thrombin generation
7 on the right, there's basically no difference. So
8 the US Navy has actually implemented intercept in
9 its treatment -- in platelet collection programs,
10 and I think this is going to be particularly
11 important in our very geographically dispersed
12 areas where, you know, we have problems with
13 testing turnaround in a Zika-like environment.
14 But in addition, there may be endemic transmission
15 of disease which we worry about, and also if we
16 can store them in the cold, which clearly, I think
17 we can without compromising hemostatic function,
18 that would allow us to deliver the platelets to
19 where they need to go.
20 So I think this also holds potential as
21 a way to improve our ability to deliver safe
22 component therapy that has hemostatic function far

1 forward. So if cold is good, how about frozen?
2 That not much bacteria growing in frozen
3 platelets at minus 65, cryopreserved platelets
4 have been around for a long time, how's their
5 hemostatic function? Well, they don't really
6 aggregate much. As you can see here this was
7 worked on by Lacey Johnson and colleagues in
8 Australia. They do shorten the TEG R time. They
9 generate plenty of thrombin. They do contribute a
10 little bit to clot strength. They make a bunch of
11 phosphatidylserine-positive microparticles which
12 contribute to that thrombin generation. How do
13 they work clinically?
14 Well, we don't have much in the way of
15 RCT data, although we do have a phase one led in
16 part by Dr. Cancelas in which we didn't see really
17 any increased adverse events. We did see some
18 good hemostatic function but in addition to that,
19 from a standpoint of combat casualty care, and
20 bleeding patients and trauma, the data that we do
21 have comes from the Dutch military where they were
22 supplying blood to one of the areas in Afghanistan

1 for quite some time. And they looked at their
2 massive transfusion protocol and the pre and
3 post-introduction of cryopreserved platelets. And
4 what they found was if you just resuscitated with
5 red cells and plasma, if you look down at that
6 bottom left panel there in terms of patient
7 outcomes, when you introduce the cryopreserved
8 platelets you see a decrease in mortality.
9 So it's not a randomized trial, but it
10 does suggest that these may be beneficial to stop
11 bleeding as well. Okay, if frozen is possibly an
12 option, how about lyophilized? So here we have a
13 picture that some of you have seen several times
14 from Mike Fitzpatrick.
15 You can allude -- in this case you have
16 shrimp larvae producing trehalose to protect
17 against dehydration. If you put trehalose in
18 platelets and freeze-dry them, you can make a
19 product that has quite a bit of shelf life and
20 stability, which is great. The process does
21 include a heat treatment step to -- I can't
22 remember if it's 60 or 80-C but, you know, perhaps

1 some measure of pathogen reduction, and perhaps
2 other pathogen-reduction technologies can be
3 applied prior to the freeze-drying.
4 Those products just, by the way, do also
5 have in vitro evidence of hemostatic function as
6 well as animal data that shows that they reduce
7 bleeding. So that's also a potential alternative
8 for the future. We'll see how clinical
9 development plays out with that product.
10 So bottom line is I'm showing you a
11 relatively low-tech approach to pathogen reduction
12 that I think works pretty well for platelets and
13 for whole blood which is to use cold. It's been
14 around for a long time. I think if you look at
15 dollars per quality adjusted life year it's going
16 to be cost-competitive. And importantly, I think,
17 maintains hemostatic function which, at least from
18 the military standpoint, and I think from a
19 standpoint of most people treating trauma or
20 surgical bleeding is a critical thing to consider.
21 Cold platelets are being used by the
22 Department of Defense in theater right now. Mayo

1 Clinic has a program. There's another -- I'm
2 thinking about investigating this, and then
3 cold-stored whole blood fully tested and
4 distributed for trauma care as used by the DOD,
5 shipped from the United States downrange, as well
6 as by the Norwegian military. And I have a couple
7 of major trauma systems listed here, but the list
8 has now grown to, like, 25 programs that are using
9 both cold-stored whole blood in both the
10 pre-hospital and in-hospital setting.
11 So I think this is a trend that is
12 catching on. And with that, I'd be happy to take
13 your questions. Thanks.
14 DR. WAGNER: Okay. So we're ready for
15 the panel discussion. Yes? Ray?
16 DR. GOODRICH: I don't want to
17 monopolize the microphone here, but I had several
18 questions. Maybe one I'll ask the panel members
19 to address, but one comment I think, Dr. MacLean,
20 the target molecule that you were describing in
21 porphyrins, actually in that actinic range between
22 4 and 500 nanometers, there may be other agents,

1 cytochromes, alloxazines, other types of compounds
2 that may absorb in that range. So it might look a
3 little broader.
4 My question is relative to just storage
5 of products today. Your data seemed to indicate
6 that just exposure to light, and in that 400 to
7 500 nanometer range, you will get that from even
8 the fluorescent lights that are in this room. Has
9 anyone evaluated things like the storage of plasma
10 in a liquid state or the storage of platelets
11 without any additives, without any components, and
12 what impact do you think you would see as a result
13 of the exposure of light in those settings?
14 DR. MACLEAN: Yes. In terms of the
15 light output that you will get that is contained
16 within your normal white light spectrum, the
17 levels that we're using are much higher. So
18 that's why you get the amplified response, but you
19 would need -- to get an effect from normal while
20 lighting you would need to expose it for a
21 significant length of time. From the work we've
22 done we've -- and with the platelets and plasma,

1 we haven't specifically looked into that, but from
2 the work that we've done in our other microbial
3 work comparing to controls with normal white
4 lighting, then you would really need to give
5 levels and durations that are probably not
6 compatible with the techniques, certainly, for the
7 blood applications. But those wavelengths are
8 part of your normal white light spectrum,
9 certainly.
10 DR. WAGNER: Steve?
11 DR. KLEINMAN: Yes. From the
12 perspective of transfusion medicine, those of us
13 who are not expert biochemists or biophysicists, I
14 think over the years when we've looked at the
15 technologies for PI in platelets, we've tended to
16 focus on do they add a photochemical. You know,
17 is amotosalen different from riboflavin, different
18 now from no photochemical in the THERAFLEX
19 procedure.
20 But what I'm learning here is that it
21 seems to me we should pay more attention to the
22 differences in the wavelengths of light because

1 they're different in the three systems, which I
2 think we kind of knew, but also the energy
3 exposure. The degree of energy that goes into the
4 system may have, I guess, and that's my question,
5 may have an effect on the functionality of the
6 component.
7 So I'm wondering with, you know, three
8 experts up there, if you could kind of address
9 that issue of how important is the wavelength in
10 the ultraviolet range into the visible range. How
11 important is the dose of energy that each
12 technology requires for thinking about how that'll
13 affect function? Obviously, we have to do the
14 studies. The data is important, but sort of from
15 a theoretical viewpoint.
16 DR. WAGNER: Okay. I think it matters.
17 Proteins tend to absorb at around 280. Nucleic
18 acid absorbs at 254. When you get out to the
19 400s, really what you're talking about is
20 endogenous photosensitizers. Riboflavin and the
21 flavins absorb out that far, but other things do
22 as well.

1 And so it does make a difference what
2 the light wavelength is. I think some wavelengths
3 are more damaging, for example, to platelets.
4 Visible light, I think, tends to be less damaging
5 to platelets. And normally, there's a law in
6 photochemistry that says that if you deliver the
7 light faster but give the same amount of light
8 versus delivering it slower, there should be no
9 difference. And we've looked at that in the
10 laboratory and found that not to be true in blood.
11 And so I don't really understand why.
12 But if you -- we had -- we were using LED lights
13 when LEDs first came out, and they delivered a
14 much higher Fluence rate and found that there was
15 more damage to the cells that we were studying in
16 blood than if we'd delivered it slower. And I
17 think it's because it -- in just in solution
18 chemistry it's all very simple. Of course, you
19 just have your buffer and you have whatever you're
20 studying. But when you get -- and you're studying
21 blood, there's so many different molecules and
22 there's so many different things happening that

1 all the rules that you learned as a graduate
2 student in this field don't necessarily apply.
3 And so it really requires
4 experimentation in the lab which is what they did
5 to tease out whether there is a light Fluence rate
6 effect. So from theoretical grounds, I really
7 can't give you any information.
8 Jim?
9 DR. AUBUCHON: Dr. MacLean, thank you
10 very much for sharing your very interesting work,
11 and wonderful Scots as well. Do you have data of
12 the content of treated plasma, or by individual
13 procoagulants, and also the effect of treatment on
14 platelets in terms of their response to various
15 agonists?
16 DR. MACLEAN: No, again, we're still at
17 quite early stage research. So the majority of
18 work we've been looking at has been very much
19 artificial seeding and spiking with the bacteria,
20 and we've just really started to start to delve
21 into the impact of other things that might be in
22 the plasma and the platelets. And that's

1 something we really need to do a lot of work on
2 because to find out if there is going to be
3 changes between different additives or different
4 dose regimes, indeed, then we need to look a lot
5 heavier into that. I'm afraid that it is still
6 very early stage.
7 DR. AUBUCHON: Thank you. My second
8 question, I don't know if you can answer, or
9 perhaps Dr. Benjamin can answer, it's been a long
10 time since my high school physics. How is the
11 amount of energy delivered in the systems that
12 you're developing compared to the amount of energy
13 delivered in the intercept system?
14 DR. MACLEAN: Okay. So in terms of the
15 light, or visible light, we are working at much
16 higher energy levels. The principles and the
17 workings of ultraviolet light, these energy levels
18 are much lower because the photons are much more
19 energetic. So for anything involving longer
20 wavelengths within the visible light spectrum, it
21 is much more higher energy that is required.
22 Again, Dr. Benjamin will be able to expand.

1 DR. BENJAMIN: Richard Benjamin, Cerus.
2 Just to confirm, I think we added 3 J/cm2 when you
3 were at the 100.
4 DR. MACLEAN: Yes.
5 DR. BENJAMIN: So it's a big difference.
6 How do you deal with heat?
7 DR. MACLEAN: Heat, in terms of the
8 systems we're building, we have very good thermal
9 management. It's all mathematically calculated to
10 get the right heat-seeking and fan operations. So
11 it is a big consideration with all energy delivery
12 systems, but it's carefully monitored throughout
13 it.
14 DR. BENJAMIN: So it is heat controlled
15 basically?
16 DR. MACLEAN: Yes, very much, yep.
17 DR. BENJAMIN: And is that at 4 degrees
18 or room temperature or --
19 DR. MACLEAN: We've done most of our
20 work at room temperature. So the platelet work
21 that you saw there was at room temperature, and
22 what we're currently building is a system to

1 control that within the 20 to 24-degree range to
2 make sure that everything's held at the correct
3 conditions.
4 DR. BENJAMIN: Thank you.
5 QUESTIONER: Did you try 4 degrees?
6 DR. MACLEAN: We've done, actually, some
7 antimicrobial work, not with blood, but the light
8 inactivation potential is significantly enhanced
9 when the light is applied at refrigeration
10 temperature. So the combined stresses -- bacteria
11 tend to be much more susceptible when you can hit
12 them with multiple stresses at the same time so.
13 QUESTIONER: Yeah, my question is for
14 Dr. Cap. So if we -- so you're talking in the
15 military sector, but in the civilian sector where
16 we're using platelets for both trauma patients,
17 surgery patients, as well as prophylactically in
18 hem-onc patients, would you see an evolution to a
19 dual inventory, both a cold-stored inventory for
20 one patient population, and a room temperature
21 inventory for another population?
22 DR. CAP: I'll be ambitious and say I

1 think you'll see that as a transitional phase
2 until we get rid of room temperature platelets
3 completely. But those studies remain to be done.
4 Nevertheless, yeah, I think so. You
5 know, we reintroduced whole blood, as I mentioned,
6 in trauma care recently. And it has taken off.
7 We have found that we are able to deliver a more
8 hemostatic product more quickly to bleeding
9 patients, and time is everything in bleeding
10 patients. I think if you have a dual inventory of
11 cold platelets and you put them where they need to
12 be in the emergency rooms, and, you know,
13 actually, in Mayo Clinic they're putting them on
14 helicopters believe it or not.
15 And you know, we'll have to see how
16 much, you know, what data come out of those
17 experiments, but -- or experience, but the reality
18 is time is everything. You've got to get the
19 hemostasis happening immediately, and the only way
20 to do that is to have functional platelets as
21 close as possible to point of injury.
22 QUESTIONER: Just as a follow-up

1 question, and this is terminology, I mean, the
2 usual whole blood product, when we have it, is
3 cold stored. Obviously, we store whole blood and
4 red cells in the refrigerator. So I'm wondering
5 why you're emphasizing cold-stored whole blood; is
6 this in distinction to what went on years ago when
7 people said, well, we're going to use fresh whole
8 blood and not even put it in the refrigerator?
9 DR. CAP: Right. So in the military
10 context when we're doing collections from a
11 walking blood bank, it's usually an emergency
12 scenario where there is no blood available, or we
13 ran out of platelets, for example, and we need to
14 provide platelets to a bleeding patient. And so
15 that's -- we consider that warm, fresh whole
16 blood.
17 I mean, really, you know, we're out of
18 the donor into the patient and that, obviously,
19 has some implications from a pathogen risk. I
20 mean, in our population it's very low, but in a
21 broader population it might be higher. But the
22 other point about the whole blood that's been

1 collected in a normal, you know, under typical
2 blood collection settings and fully tested, and so
3 forth, is that you would store it cold as you
4 said.
5 And by the way, what's in there is cold
6 platelets which we've been taught don't work. But
7 actually they work great. And it's a very
8 hemostatic product.
9 QUESTIONER: Yeah, no, and I get that
10 part. I guess is this because some years ago, at
11 least in military setting, people were saying warm
12 whole blood is better? Somehow not putting it in
13 the cold is better? I seem to remember hearing
14 that at meetings, and are you sort of trying to
15 react to that by saying cold-stored whole blood?
16 DR. CAP: No. So there's no question
17 that warm, fresh whole blood right out of the
18 donor is going to be your best product from a
19 fully functional standpoint, hemostasis, oxygen
20 delivery, everything. However, there are
21 trade-offs. So one, you have a constrained donor
22 population to collect from. I mean, you just

1 don't have, at any given time, large numbers of
2 donors available to give blood. So it's a
3 limited-supply product.
4 Number two, it's not fully tested. And
5 so what we've said is okay, how can we get most of
6 the benefit of whole blood in larger quantities
7 and have it fully tested, and potentially,
8 pathogen reduced at some point. And to do that,
9 you have to store it, obviously, so you store it
10 in the cold. And then the question is, if you
11 store it in the cold, are you still going to have
12 a hemostatic product, and the answer is yes.
13 So there's always a price to be paid, as
14 I said, for either storage or pathogen reduction;
15 the longer you store the worse the function.
16 There's no getting around that, but you can
17 mitigate that in the case of platelets by putting
18 them in the cold. And in the case of whole blood,
19 it's not that the cold-stored whole blood is
20 better than the fresh whole blood, it's that it's
21 available. Whereas, you know, you have very
22 limited supplies of fresh whole blood.

1 DR. WAGNER: Ray?
2 DR. GOODRICH: I'm going to go ahead and
3 ask my two other questions. First of all, Steve,
4 I wanted to make the comment if I didn't say it
5 that when we talked 14 years ago I'll say it now,
6 it's brilliant chemistry. My question to you was
7 did you ever do the experiments where you would
8 add the dye, separate it out, then do the
9 treatment? And if you haven't done it, what would
10 you expect from it?
11 DR. WAGNER: You mean spin stain with a
12 dye and then spin the red cells down and then
13 reconstitute and -- no, but I don't -- Andre, I
14 don't recall we ever did that, yeah. I was always
15 concerned with the degree, at the time, of
16 membrane-bound dye. You know, if 60 percent of
17 the dye is still bound to the membrane, for
18 example, we were doing a lot of studies with
19 methylene blue and dimethylmethylene blue, et
20 cetera, et cetera.
21 You start adding those, and if most of
22 them are bound to the membrane, you can wash until

1 the cows come home, but, you know, you're still
2 going to have a problem. And so we, over the
3 years, with some dyes started using dipyridamole
4 which seemed to bind to red cell membranes and
5 prevent the binding of the dyes. So it was a
6 competitive inhibitor, and that was interesting,
7 and we saw less damage.
8 But then you get into the problem of
9 adding two substances to the blood supply, both of
10 which you don't want to add. And so we never
11 really spent a lot of time on it.
12 DR. GOODRICH: Interesting.
13 DR. WAGNER: Okay.
14 DR. GOODRICH: And my other question was
15 for Andre (sic). You indicated that lactic acid
16 production in the platelets was responsible for
17 promoting bacterial growth in some of the -- if I
18 recall the slides correctly. I'm assuming that
19 that might be consumption in the Krebs cycle where
20 you're getting production or growth of the
21 bacteria or metabolism of that lactic acid.
22 Have you ever looked at the effects of

1 acetate and what does that say about platelet
2 additive solution if it could promote the growth
3 in bacteria in those cases?
4 DR. CAP: That's a great question, Ray.
5 We actually have not looked at acetate. You know,
6 we've done studies where we've taken platelets, I
7 mean, plasma without the platelets and seeded them
8 with bacteria and added lactate back and
9 recapitulated those growth curves. So we know the
10 lactate will do it. It's a good question whether
11 acetate would do it. It might. I mean, I don't
12 know why it wouldn't. It could be a problem.
13 DR. GOODRICH: And one comment earlier
14 on a question, that the question about energy,
15 it's E=H\nu where nu is the frequency or the
16 wavelength, the inverse of the wavelength. And so
17 if you're in the visible light region, you may
18 deliver lower energy photons but you may need to
19 deliver more of them to be an equivalent energy.
20 That doesn't really matter when you're
21 talking about photosensitizers because it's the
22 absorption characteristic of the compound that

1 determines the chemistry, not necessarily the
2 energy of the photon. If that photon is not
3 absorbed by the compound there will be no
4 chemistry. So it doesn't matter what its energy
5 is.
6 DR. WAGNER: Do we have questions from
7 the phone or online?
8 QUESTIONER: Yes. So we have two
9 questions. The first one is Dr. Cap. The
10 question is we have whole blood for trauma
11 containing hemostatically actively platelets, why
12 do you need cold platelets for hemostasis in
13 trauma?
14 DR. CAP: Well, that's a great question.
15 So from -- some of this is a military-unique set
16 of circumstances. Our blood system is essentially
17 self-supporting, so all of our donors are
18 collected on federal facilities, and essentially
19 it's mostly active duty military giving blood to
20 other active duty military. And so if we have a
21 requirement to supply components, for example, to
22 hospitals that we operate in the United States and

1 elsewhere, and we also want to produce whole
2 blood, you know, there's a tradeoff there.
3 I mean, you can't take a unit of whole
4 blood and have whole blood. I mean you have to
5 choose, it's either whole blood or components.
6 And so we can shift that balance a little bit, but
7 at some point, we run into some barriers in
8 getting as much whole blood as we want. So that's
9 one thing.
10 Second thing is, you know, in some
11 environments, it may be more convenient to have
12 components available. You could imagine a
13 scenario in which say if you don't have
14 pathogen-reduced whole blood, but you're operating
15 in an endemic zone, and you really are concerned
16 about disease transmission. If you can ship red
17 cells and plasma from the United States and even
18 if you have to collect platelets locally, if you
19 used a pathogen-reduction technology then you
20 could supply safe platelets.
21 So I think at the end of the day, there
22 is a role both for components and for whole blood

1 in trauma management. I mean certainly in the
2 ICU, sometimes you have to fine tune things. I
3 think in early resuscitation whole blood's hard to
4 beat. But you know, you could still have bleeding
5 in the ICU after the initial resuscitation where
6 you might want to give, you know, just a platelet
7 unit. So that's how we kind of balance all that.
8 DR. WAGNER: And there's one other
9 question.
10 QUESTIONER: This question is for Dr.
11 MacLean. So the question is have you tried to
12 inactive spore-related bacteria or bacterial
13 biofilm?
14 DR. MACLEAN: Yes, not in terms of
15 within blood, but back in the university we've got
16 quite a large bank of antimicrobial information
17 which we've published. We've got data published
18 on the inactivation of bacterial endospores. The
19 energies required for these are significantly
20 higher than for vegetative cells as you'd imagine.
21 We've also looked at fungal spores and
22 germinating fungal spores. And again, the

1 energies required for inactivation of dormant
2 spores are significant. But once you initiate the
3 germination procedure, you do get increased
4 susceptibility. And we've also looked quite
5 significantly at biofilm inactivation. And again,
6 excellent inactivation capacity there so it's --
7 DR. WAGNER: Thank you. I think if
8 there aren't any other questions for -- we have a
9 break now, C.D.? And we should be back at 11:10.
10 That's correct? Okay. Thank you.
11 (Recess)
12 DR. ATREYA: Hello everybody, now we are
13 ready for the session five which is funding
14 support for future (inaudible) research. Marion
15 White, Dr. Glen to be here on the podium, thank
16 you.
17 DR. WHITE: So, good morning and I'm
18 going to invite Ashley and Bryan to join me at the
19 table. So, what I thought we would do is first
20 introduce one another and let you know a little
21 bit about the programs that we are supporting
22 currently that might pertain or solicitations that

1 we may have and then after that open it to the
2 audience for questions. So, because of the way
3 you sat down, Bryan, do you want to go first?
4 DR. KUJAWA: Absolutely, good morning,
5 my name's Major Bryan Kujawa and I'm known as a
6 battalion surgeon assigned to attend special
7 forces group in Colorado Springs and, kind of, as
8 a major role that I do as a special forces
9 physician is I supervise the training and advice
10 for all the special forces medics who are really
11 our front lines for the initial transfusion
12 treatments for point of injury care that is being
13 prioritized right now.
14 So, I do want to mention that I am not a
15 researcher. I'm probably the only non-researcher
16 in the room and even thought the title of this
17 talk has funding in it, I have no ability to
18 authorize contracts, which I am sorry. It is
19 probably very disappointing to many people here.
20 So why am I here? Really, I think it is
21 a three- part answer. The first part is special
22 operations command is very interested in one,

1 trying to improve the safety profile for
2 transfusions for places that are very austere and
3 in remote locations and second, to increase maybe
4 the donor pool potential that we would have when
5 we are -- for deployed. The second part of that
6 answer would be to see the, kind of, the ground
7 truth of what is happening for PRT research right
8 now and if it can be applied for a special forces
9 mission in the future going forward. So, often
10 times things that are working in the lab and
11 eventually are being able to be utilized in a
12 hospital setting won't translate to a beneficial
13 technology in a deployed remote environment. And
14 the third answer to that question is when special
15 forces command buys you a plane ticket and tells
16 you you are going to the FDA you get on the plane
17 and you go and see what's happening at the FDA.
18 So, I see myself, kind of, as a
19 representative of the end-users; those being the
20 medical personnel that are doing transfusions for
21 deployed as well as the recipients of the blood
22 products. So, really I think it's helpful for

1 frontline researchers to know what's happening on
2 frontline military medicine and the paradigm has
3 really shifted from the golden hour ride
4 evacuation within 60 minutes as the biggest
5 determiner of decreasing mortality. And it's
6 probably better said that it is time until initial
7 transfusion that is the most important thing and a
8 lot of goodness has come out of the golden hour
9 but now we are shifting our efforts for immediate
10 point of injury transfusion capabilities.
11 So, special forces operates, of course,
12 at very austere and remote environments. There is
13 not an ability to access blood banking abilities
14 or a lab facilities. We might not have access to
15 cold chain storage along the way, so it's not
16 feasible and realistic that we can divide whole
17 blood into blood components. And even if it was,
18 we have to look at what PRT technologies that are
19 currently available. INTERCEPT being just one
20 example and right now as the machine exists, it's
21 too large and cumbersome for us to really deploy
22 with. Space is a premium in helicopters and

1 vehicles, and unfortunately the size would be a
2 limiting factor. So, remembering again that
3 really whole blood is lifesaving, we need to look
4 at how we can facilitate rapid transfusions in the
5 austere environment and really at that point of
6 injury which is where the special forces medics
7 are working.
8 So, their operating procedure, as Dr.
9 Cap briefly mentioned, is right now we give quick,
10 fresh whole blood and the donors really are team
11 members or support staff from other service
12 members. So, it's impractical to perform pathogen
13 testing at point of injury, of course. And as Dr.
14 Cap mentions, the military has a generally healthy
15 population that's pre-screened prior to any
16 deployment. Of course, that doesn't count again,
17 as Dr. Cap mentioned, any possible exposures
18 during a deployment and special forces
19 specifically operate with very small man teams;
20 usually around 12 plus or minus support staff.
21 So, a donor pool is an incredibly limited
22 resource. It'd be very nice if we could use local

1 population or perhaps partners, but as we are
2 operating in high-risk geographical locations
3 those personnel obviously would fail any donor
4 screening questionnaire we might administer them.
5 So, it'd be very nice if we could utilize PRT
6 technologies to be able to provide this ability
7 both safely and quickly.
8 So, one of the main things that special
9 forces is looking for: Proven technology for its
10 primary application, again which Dr. Cap
11 mentioned, really is massive hemorrhage from
12 catastrophic combat-related trauma and then
13 second, the equipment is very, very important. We
14 need something that's light, easy to use, able to
15 get dirty, operate in extreme temperatures, and
16 durable to survive any rough transport that it
17 might go through. So, technology such as Mirasol
18 certainly look promising, especially as Dr. Cap
19 mentioned, for malaria endemic regions, but we
20 need to field test such equipment to make sure
21 that it would operate in the areas that I
22 mentioned.

1 So, it was suggested several times
2 throughout the workshop that one approach probably
3 is not the only answer and for a military
4 application, perhaps, a combination approach for
5 that specific idea for deploy transfusions, would
6 be the best avenue for us to look at.
7 So, of course, in the ideal world;
8 perfectly, again, ideal world we could utilize PRT
9 without any concern for pathogen testing for local
10 population or any partners that we're working
11 with. So, for better or worse military, and
12 specifically wartime, has the tendency to drive
13 innovation for both patient care and for medical
14 technologies. And with the increased emphasis on
15 early transfusions I think this does have the
16 possibility to drive innovation. Again, in PRT,
17 not really from the hospital-cost benefit
18 point-of-view but more for a military application.
19 Thanks.
20 DR. GLYNN: So, Ashley, yeah, if you
21 want to --
22 DR. CECERE: Good morning, my name is

1 Ashley Cercere. I am a interdisciplinary
2 scientist at BARDA. I am sitting in for Dr. Mary
3 Homer who was unfortunately unable to attend in
4 person today.
5 So, a little bit about BARDA. So, we
6 stand for Biomedical Advanced Research and
7 Development Authority. We fall within the
8 assistant secretary for preparedness response
9 within the health and human services. So, we are
10 charged with doing -- supporting advanced research
11 and development and also potential procurement of
12 multiple medical countermeasures that fall within
13 multiple threat areas.
14 So, our blood products portfolio
15 actually fits within our radiation and nuclear
16 countermeasures division primarily to support in
17 the event of a radiation or nuclear event,
18 patients that are affected by acute radiation
19 syndrome or the associated trauma of the event.
20 Since these patients are expected to be
21 neutropenic and thrombocytopenic, these patients
22 are more susceptible to infection and -- as well

1 as sepsis and graft versus host disease.
2 So, I've been asked to give a little bit
3 of information on the programs that we're
4 currently supporting which you heard about a
5 little bit yesterday.
6 So, we are supporting the Cerus
7 INTERCEPT program for the S303 red cells. So,
8 we're supporting an efficacy clinical study that
9 was briefly mentioned yesterday in Puerto Rico as
10 well as other areas in the continental U.S. have
11 the potential to be impacted by the Zica virus.
12 In addition, we are supporting -- or
13 plan to support -- the studies have not initiated
14 yet, two phase three clinical studies in acute and
15 chronic anemia trials in the United States. We're
16 also supporting the second-generation system for
17 the red blood cell.
18 In addition, we have a contract with
19 Terumo BCT. We're primarily supporting their
20 MIPLATE trial which was also mentioned yesterday
21 in which they're using the Marisol
22 pathogen-reduced technology system to assess their

1 clinical effectiveness of Marisol-treated
2 platelets compared to standard platelets in
3 hyperproliferative thrombocytopenic patients as
4 well as supporting additional in vitro work.
5 As far as our open solicitations we have
6 an open broad agency announcement which means at
7 any point and time you are able to apply. This
8 can be located either on our website at
9 medicalcountermeasures.gov or on the Fed Biz Ops.
10 Our radiation and nuclear group is
11 listed under area number four for that. Remember,
12 specifically blood products at 4.2 in which we're
13 looking at products that enhance our ability to
14 respond to mass-casualty events such as radiation
15 and nuclear event.
16 That's about it.
17 DR. GLYNN: All right, so my name is
18 Simone Glynn and I am the branch chief for the
19 clinical therapeutics branch in the blood division
20 of NHLBI. So, NHLBI is one of 27 institutes and
21 offices at NIH and it is responsible for the NIH
22 supporting the researching blood transfusion,

1 blood safety, blood availability.
2 So, the research that we support goes
3 all the way from basic research to translational
4 clinical research and implementation research.
5 The main tool used to provide funds to researchers
6 is the RO1 grant and this is the one that I would
7 encourage you to apply for if you are interested,
8 certainly, in conducting basic research,
9 translational research related to any development.
10 If you are a small business, we, of
11 course, have a small business research program as
12 well so you can apply for a specific type of grant
13 applications if you are a small business. And if
14 you are interested, again, I encourage you to let
15 me know and then I can guide you to the right
16 program officer who knows all specific about those
17 particular grant applications.
18 In terms of clinical research, NHLBI has
19 undergone some, I guess, reorganization of how we
20 solicit clinical research applications. And by
21 clinical research we divide both, of course,
22 between observational studies and clinical trials

1 and I'm talking primarily about the clinical
2 trials.
3 So now when you have a clinical trial
4 application in mind, please contact us because we
5 will guide you depending on the phase of the
6 clinical trial application, whether it's
7 single-center versus multi-center towards
8 different solicitations that have different
9 requirements. And the whole reason for making
10 these changes in NHLBI were that we wanted to
11 assure that the reviewers would not only review an
12 application for its scientific value but also for
13 the feasibility of the application so that if a
14 clinical trial was going to be funded, chances
15 were that it was actually going to be doable and
16 feasible which is quite important to address the
17 important scientific question you have in mind.
18 And then just also to remind everyone
19 that we have training grant applications which I
20 think is also very important. So, if you have a
21 good mentor, again, you can apply for a K-type of
22 application and again, we do have some program

1 officers who specialize into those kinds of
2 applications.
3 So that's, kind of, in a nut shell and I
4 think now I'll open it to any question that
5 anybody would have. The one thing that I forgot
6 to mention is that we do have a memorandum of
7 understanding between our agencies so that we
8 actually do have routinely meetings between us so
9 that we can discuss potential applications and try
10 then to guide the researcher towards one of our
11 agencies depending on what the application is
12 about. So, I think that's been quite helpful.
13 We've had that in place for about two to three
14 years now, I think.
15 So, I don't know if we have any
16 questions. The other thing -- and it's outside, I
17 think, also is a handout. I did provide a handout
18 that, kind of, lists some of the major
19 solicitations that you might be interested in
20 looking at for NHLBI. It's available outside and
21 I think it will be available after the meeting.
22 So, nobody is interested in getting

1 funded.

2 (Laughter)

3 SPEAKER: I'll ask a question.

4 DR. GLYNN: Oh, thank you, Rick.

5 SPEAKER: You may not like it when I ask

6 it.

7 (Laughter). I think a comment that

8 was made to me is about bringing

9 new technologies forward in this

10 space. Obviously, the precedent

11 has been set that the amount of

12 investment that's required to turn

13 these into reality is enormous. I

14 -- estimating that combined we're

15 probably looking at more than a

16 billion dollars over the period of

17 time that this was first conceived

18 where they're actually getting into

19 routine clinical use. What do you

20 say to someone who has a new idea

21 that wants to come forward to bring

22 a product like this into existence

1 with that kind of a track record
2 and what kind of funding sources
3 are we talking about that might be
4 available to do that?
5 DR. GLYNN: Right, thank you for the
6 question. So, several things that come to mind is
7 it would be great, I think, if we could encourage,
8 again, researchers to try to think about
9 innovative ideas that hopefully then can come
10 up -- come to fruition.
11 So, the first thing, in terms of the --
12 a lot of the pre-clinical work to look at the
13 research hypothesis in both kinds of thing, that's
14 really RO1 amenable and -- so there we can try to
15 help with that certainly at NIH.
16 The question afterwards -- I think, the
17 hard part, right, is when you have a -- you know,
18 something that is ready to go into your -- into
19 human beings. So, you can do a phase one clinical
20 trial and that, again, we can provide some support
21 there in terms of either as a small business
22 application or, again, under the kind of clinical

1 trial applications that we can support at NHLBI.
2 In terms of a lot of pre-clinical, the
3 big animal model work, then I'm going to let
4 Ashley -- because we usually turn towards BARDA at
5 that time.
6 DR. CECERE: Well, I mean, as of right
7 now there's only product or one device that's out
8 there that's approved for one indication. So, I
9 think that we still are continuing to see what our
10 possibilities are. In addition, BARDA has always
11 believed in not having a single point of failure,
12 so I think we are always open to understanding
13 what technologies are out there. I think there's
14 been a lot of discussion about having a device or
15 a way of treating that can be done on all
16 components and so I think there's still a lot of
17 progress to be made.
18 I did want to highlight that on our
19 website we have the opportunity for companies to
20 ask for tech watches. We are continuously
21 interested in understanding the landscape for all
22 of these -- for all of the products that we work

1 on. It helps us in our decision matrix on moving
2 forward with programs. And we're also very open
3 to providing advice. We have experts that are
4 ex-FDA, clinical/non-clinical CMC and all that
5 stuff. And so, when we do work with our partners,
6 whether it's through official contracts or just
7 through communications, we really view it as a
8 partnership in helping not only the products that
9 we are supporting to get to licensure but
10 additional products as well.
11 And I forgot to mention, we usually pick
12 up at TRL 5 for radiation and nuclear. So, to
13 have at least had a pre-IMD meeting with the FDA
14 and have, kind of, a clinical path or regulatory
15 path forward, obviously we like to see clinical
16 data when possible.
17 SPEAKER: I'll just chime in and say
18 that, yes, I agree that DOD has -- make it clear
19 we have a great working relationship on all these
20 things and, sort of, take a whole government
21 approach, I guess you could say, to developing
22 these various technologies. Great working with

1 you all.

2 DR. BENJAMIN: Richard Benjamin, CERUS

3 and I want to reiterate how appreciative CERUS is

4 for the funding support we recently received from

5 BARDA, but there is another funding source that,

6 perhaps, we can consider would help here, and that

7 is if you create a market for a product more

8 innovation will come in to fill that space and,

9 you know, the length of time it has taken after

10 inactivation to become a reality in the market and

11 the length of time it then takes to actually get

12 the U.S. market to buy it and to -- you know, that

13 is an impediment, but I really want to recognize

14 the FDA for having this meeting because it's -- it

15 shows their commitment and I think a renewed

16 commitment towards pathogen inactivation because

17 things like the bacterial guidance that we are --

18 adopt guidance we're expecting help to create that

19 expectation that pathogen inactivation is what is

20 needed in the marketplace. It helps to create the

21 demand. It creates the physician who's actually

22 seeing the patients and the actual patients who

1 benefit from this to learn about the technology
2 and start to demand the technology because once a
3 product becomes successful in the market the money
4 will come from industry to drive the innovation we
5 are looking for. The second and third and fourth
6 generation products will not be there without a
7 successfully marketed first generation product.
8 So -- and then we can try and stoke the
9 fire or prime the pump with research funding but
10 that is what you're doing. Ultimately if the
11 initial products don't succeed in the marketplace
12 the subsequent products probably will never
13 arrive.
14 So, I just wanted to recognize the work
15 you've done over 20, 30 years, but also the FDA,
16 for what we see as a really renewed interest in
17 this area in helping us to move forward, and this
18 meeting is just a great example of that so thank
19 you.
20 DR. GLYNN: Thank you. So if there are
21 no other questions, please remember never hesitate
22 to contact us. That's what we are here for; to

1 try to guide you and help you try to, you know,
2 get to the next step of what you want to do, so
3 that's a major thing.
4 DR. ATREYA: Okay, if there are no
5 further questions, we will move to the next one;
6 that is session six. Let me get the slides. So,
7 session six is the summary presentations by each
8 moderator. Roughly it is -- add on 15 minutes for
9 each moderator to speak. First is Simone Glynn
10 again and I might try to brief you for that.
11 DR. GLYNN: So, hello everyone. So, my
12 session -- well, my session; your session number
13 one was titled Blood- Borne Infectious Agents and
14 Their Impact on Blood Safety.
15 So the first session started with Dr.
16 Busch presenting another view of the risks to
17 blood safety from infectious agents, and in his
18 presentation he reviewed the evolution of
19 responses to established emerging and re-emerging
20 transfusion transmitted infectious diseases and
21 highlighted the ongoing surveillance for and the
22 systematic responses to emerging infectious

1 diseases up to (inaudible) with sensitive
2 metagenomics, multiplex NAT and serological
3 testing strategies in Sentinel global donor
4 populations.
5 So, in his presentation, Dr. Busch
6 showed that over the past five decades; so, 50
7 years, so that's why he took a little bit longer
8 than his allotted time. For serological assets
9 targeting virus-specific antibodies and antigens
10 that were implemented proved effective for
11 screening our donors who are chronically infected
12 with a classic transfusion transmitted infectious
13 diseases. So, we're talking about syphilis, HPV,
14 HIV, HTLV, HCV and T. cruzi. And then the goal of
15 closing the pre-seroconversion infectious window
16 period led them to progressive implementation of
17 NAT screening for HIV, HPV and HCV over the past
18 20 years.
19 So, NAT screening, as I think we all
20 know, has proven quite highly effective in
21 introdicting [sic] the window period of donations
22 and reducing the residual risks for these major

1 agents to -- as we heard yesterday about 1 in 2
2 million in the U.S.
3 Now in addition, NAT screening has also
4 proven to be the preferred option for detection of
5 many emerging and re- emerging transfusion
6 transmitted infectious agents that cause acute
7 transmitted infections including parvovirus B19,
8 HEV, babesia and West Nile Virus and most recently
9 Zica. Such infections are effectively introdicted
10 by NAT and serological testing would not work in
11 this case and would result in loss of high rates
12 of seropositive donors would have result
13 infections.
14 So, the other thing is that he told us
15 was virus discovery using metagenomics
16 technologies has also led to identification of
17 transfusion transmitted pathogens that warranted
18 interventions but also to detection of
19 contaminating virus sequences. So, we heard about
20 XMRV, non-pathogenic (inaudible) human viruses
21 such as (inaudible) viruses and the known
22 transfusion transmitted viruses.

1 We then heard from Dr. Kleinman in our
2 second presentation who reviewed policy issues
3 pertaining to pathogen reductions. So, Dr.
4 Kleinman noted that pathogen inactivation
5 reduction should be viewed in the context of
6 shifting the blood safety paradigm from one that
7 is reactive to one that is proactive thereby
8 providing insurance against known and unknown
9 pathogens that may enter the blood supply or are
10 currently underrecognized or not recognized.
11 So, assuming that therapeutic product
12 efficacy is maintained and cost issues can be
13 addressed, the goal is to have all blood
14 components or whole blood treated by pathogen
15 inactivation which could then allow for a
16 relaxation of redundant donor lab screening,
17 modified donor questioning deferral, hopefully,
18 and simplified handling of post-donation
19 information.
20 A fully PI-treated blood supply would
21 then shape the response to threats from new
22 emerging infectious agents in that there would be

1 less pressure to give up new lab rat rescreening
2 assays.
3 So important considerations in
4 evaluating the role of PI and blood safety policy
5 are that one, not all infectious agents are
6 inactivated. We know we have a problem with
7 nonenvelope viruses and sometimes (inaudible).
8 And then the second problem is that each
9 manufacturers' process must be independently
10 evaluated for quantitative levels of inactivation
11 of numerous known pathogen as well as for its
12 therapeutic efficacy of the treated component and
13 potential adverse effects in the recipient.
14 Also, Dr. Kleinman noted that the
15 healthcare reimbursement system is to be able, of
16 course, to accommodate the cost.
17 So, this other view of policy issues was
18 then followed by a presentation from Dr. Snyder
19 who reviewed the current status of
20 pathogen-reduced platelets in the U.S. Dr.
21 Snyder mentioned that currently the only PI
22 manufacturing system approved by the FDA in the

1 U.S. uses Surolan, a UVA light-activated
2 photochemical as the agent of inactivation.
3 Approval is limited to a collection
4 using one of two apheresis devices and stored
5 (inaudible) a platelet additive solution or an
6 autologous plasma depending on the apheresis
7 device used for manufacturer.
8 Both PR products have a five-day shelf
9 life right now at room temperature and other
10 manufacturing systems are also under varying
11 degrees of development. So, we have the -- we
12 heard about the riboflavin one and the one that
13 uses the shorter wavelength for UV light or UVC.
14 Dr. Snyder then told us about the major
15 benefits of PR platelets include -- including a
16 multi-log inactivation of most blood-borne
17 pathogens as well as the inactivation of
18 lymphocytes thus protecting against transfusion as
19 (inaudible) graft versus host disease.
20 He also noted that despite FDA approval
21 and the acknowledgement if it's of a technology of
22 a medical field has been slowed to adopt and

1 integrate platelet technology -- PR technology
2 into day-to-day hospital operations for several
3 reasons which he went over. So these included, in
4 particular, concerns over the reports of lower
5 post-transfusion corrected count increments in PR
6 platelets versus conventional platelets; reports
7 of lower hemostatic efficacy of a PR platelets
8 risk of these transfusion associated GVHD because
9 irrigation is not recommended; unknown potential
10 for toxicity from repeated administration of
11 Surolan especially if this is a worry in neonates
12 and children; the possibility that the PR
13 platelets might increase the incidents of
14 transfusion reactions; the skin rashes in neonates
15 that are exposed to blue light therapy for
16 hyperbilirubinemia; the lack of long- term data on
17 the effects of repeated use of Surolans in adults
18 and children, especially neonates, and the
19 increased costs associated with the use of PR
20 platelets.
21 So, the FDA to date, he told us, has
22 provided draft guidance that has stopped short of

1 encouraging adoption of PR technology. Thus, the
2 use of PR technology is left up to the individual
3 hospitals as to whether they embrace or abstain
4 from use of these products.
5 So, he then went on to say that
6 currently the major ongoing credible threat to the
7 nation's blood supply comes -- in talking about
8 platelet products, comes from the potential for
9 bacterial contamination and (inaudible) a new
10 viral or other known bacterial agent threaten the
11 national blood supply, the time to ramp up
12 adequate PR manufacturing infrastructure to meet
13 the threat would likely take quite some time. So
14 more widespread adoption of the PR technology now
15 would do much to ameliorate this concern if this
16 scenario occurred.
17 So, overall the use of PR technology is
18 slowly increasing and they are addressing many of
19 the above-listed concerns have been published.
20 However, the lack of published data, especially in
21 pediatric and transplant patients coupled with the
22 lack of strong FDA endorsement of the technology,

1 and finally the increased cost of this technology,
2 has hampered widespread acceptance of these
3 platelets.
4 So, the possibility of another
5 blood-borne threat to the safety of the national
6 blood supply seems inevitable and how well we then
7 mitigate that threat may well depend on how these
8 issues regarding PR blood products are resolved.
9 And then he ended by saying that it's
10 really critical that early adopters of the
11 technology in the U.S. Make sure that they
12 publish their experience (inaudible) with the
13 utilization of platelets that have been treated;
14 especially their pediatric experience.
15 Finally, the last speaker for this
16 session, Dr. AuBuchon, reviewed the current
17 status of pathogen-reduced plasma in the U.S. and
18 he noted that available pathogen- reduced plasma
19 products are safe and effective despite some
20 content reductions. There may actually be a
21 reduction of some of a known infectious adverse
22 event risk associated with their use. However,

1 given the current level of safety of frozen
2 plasma, Dr. AuBuchon told us that he thinks that
3 there is little impetus to adopt pathogen-reduced
4 plasma at this time in the U.S. and, therefore,
5 widespread adoption of pathogen- reduced plasma
6 will likely require licensure and adoption of
7 systems for all of the blood components.
8 So that was a summary for the first
9 session.
10 DR. ATREYA: Oh, you're here? Okay, I
11 have the slides (inaudible).
12 DR. FLEGEL: So, your second session was
13 entitled Implementation of Pathogen Reduction
14 Technology for Blood Products in the U.S., and for
15 that purpose I mercilessly pilfered the slide set
16 of the speakers.
17 So, we had five presentations. The
18 first one was on -- by the American Red Cross
19 showing the experience of the introduction of the
20 technology in this largest blood service; the
21 second presentation, the introduction at the NIH
22 Clinical Center at a hospital setting with a

1 smaller blood donor service; a third presentation
2 on the effect on the quality and -- of the
3 platelets; the fourth presentation was on an
4 alternative pathogen-reduction technology for
5 plasma, the SD treated plasma, and the final
6 presentation on the health economics
7 considerations.
8 So David Reeve presented the experience
9 of the introduction of the technology in the
10 American Red Cross which was first implemented in
11 Puerto Rico in March 2015 using two different
12 blood collection apheresis devices, Trima and
13 Amicus, which differed slightly in the guard bands
14 that can be applied for those systems such that a
15 decision was made to move to the Amicus blood form
16 which was then introduced U.S. Stateside in July
17 2016 and is used since. There were mitigation
18 needed to make the production possible in the
19 larger scale. So initially the American Red Cross
20 primarily used duel storage kits; one-third was
21 large volume kits and the small volume kits were
22 hardly used. After the mitigation, however, the

1 small volume was used in two-third [sic] of the
2 cases. A large volume remained with one-third and
3 the stool -- duel storage is hardly used.
4 The conclusion is that pathogen
5 reduction of 100 percent of the product is not
6 practical based on the current guard bands would
7 then imply that, perhaps, one could work on
8 expanding those guard bands if possible. The
9 mitigation required to meet the guard bands was
10 feasible but labor- intensive and time-consuming.
11 Again, if the guard bands would be wider than one
12 would reduce the labor and the time and make it
13 more feasible and, in particular, less expensive.
14 The implementation of the pathogen reduction
15 technology will require adjustment of set points
16 and collection parameters on the apheresis
17 devices.
18 These conclusions are exactly mirrored
19 by that -- what we experienced at the NIH Clinical
20 Center when we tried to implement it there which
21 was actually implemented at a hundred percent of
22 our apheresis platelet collections in January 2016

1 and we are supplying the NIH Clinical Center with
2 our products -- a hundred percent pathogen-reduced
3 since. We still do use non-pathogen which use
4 platelets for those platelet products that are --
5 that need to be imported because physically we
6 cannot supply a hundred percent of our patients
7 with our own product.
8 In striking difference to the American
9 Red Cross, we are using dual storage kits only.
10 The implementation into this production took about
11 one year and as I said it can be done more quickly
12 but one should consider if one wants to implement
13 it one probably should consider a good year to do
14 that. So, if an emergency would arise it's not
15 possible to implement it quickly. One needs to
16 consider a certain longer timeframe.
17 The experience when we went live at our
18 NIH Clinical Center Hospital was that -- such that
19 we needed to educate and notify the nurses and
20 physicians ahead of time. Since this was done the
21 acceptance was very straightforward and as is
22 (inaudible) note the introduction of the

1 pathogen-reduced platelets at the NIH Clinical
2 Center overlapped with the occurrence of
3 (inaudible) in the U.S. which actually helped with
4 the acceptance by the prescribers.
5 So the task on the home stretch in the
6 time of the introduction of the product in January
7 2016 was to inform and educate the clinicians,
8 nursing staff, external customers. The current
9 situation is such that we had to adjust our
10 collection parameters quite a bit and it took us
11 awhile to get to the point that we actually
12 reached the aim for the loss due to the guard
13 bands of less than one percent. So at this point,
14 three years later, we actually hit that target but
15 it took quite a while to get to this low loss due
16 to the guard bands.
17 We are continuously evaluating at the
18 quality assurance of the platelet with tension
19 rate in the back. Obviously, platelets are lost
20 during the process but more than 90 percent are
21 retained and we approve that continuously with
22 testing a large number of the platelets and a very

1 positive aspect is that we cannot only eliminate
2 irrigation for those products, but on top of it
3 the quality of the teasel inactivation for
4 avoiding transfusion associated graft versus host
5 disease is actually better improved by that
6 technology. The education and notification was
7 done, again, to the external customers,
8 prescribers, and the nursing staff.
9 Which brings me to the third
10 presentation presented by Dr. Dana Devine from the
11 Canadian Blood Services with the impact of the
12 technology on platelet quality count and clinical
13 implications.
14 Dr. Devine reminded us that it is
15 expected that the quality parameters changed. The
16 treatment must balance between killing pathogens
17 and killing the transfused cells. The risk
18 mitigation must consider both infectious risk and
19 the risk to product efficacy.
20 And she noted that it was published
21 since that the reduction in blood component
22 potency has been postulated two percent greater

1 risk than benefiting countries with low risk of
2 transfusion transmitted infections. This, kind
3 of, addresses the risk benefit balance and we
4 certainly should have a eye on that topic beside
5 -- perhaps, cost efficiency considerations.
6 What we knew at the beginning, Dr.
7 Devine has stated that pathogen-reduced platelets
8 show a 15 to 25 percent decrease in survival and
9 recovery in normal volunteers. Licensing trials
10 that were done, obviously, to get it approved here
11 in the U.S. also showed the impact of treatment
12 and this is a tradeoff for increased safety.
13 There is a clinical assessment done of
14 the pathogen- reduced platelets showing that
15 patients with cancer had an increased platelet or
16 effectiveness and platelet transfusion
17 requirements. However, and probably no effect on
18 mortalities, severe bleeding or serious adverse
19 advents.
20 Also, descriptive studies did not
21 identify a significant problem in bleeding
22 patients. Dr. Devine noted that further studies

1 to that effect are really -- would really be
2 helpful. Entire quality evidence would be helpful
3 to understand whether or not using bleeding
4 patients is a real concern.
5 The fourth presentations was on an
6 alternative of pathogen-reduction available for a
7 long time focusing on the experience at the
8 University of Minnesota presented by Dr. Claudia
9 Cohn. So it's Octaplas is as treated plasma
10 frozen at 200 ml bags. It can apply it in an ABO
11 blood group specifically. It's pulled from 600 to
12 1500 donors. It's U.S. Donors only and this
13 should be the first point here; it's FDA licensed.
14 The randomized control clinical trials
15 shown here did not provide any evidence for a
16 difference in efficacy. It was, however, noted
17 that all of these five studies had very low
18 numbers. So they aren't really designed to
19 necessarily prove a difference of efficacy.
20 Also, hemovigilance data, primarily from
21 Europe with really large numbers of blood bags and
22 transfusion events, showed that there is no TRALI

1 report at all. Dr. Cohn noted that obviously this
2 hemovigilance data are passively collected and may
3 no -- not reflect every incidence but one is left
4 with the conclusion that the product is very safe
5 in regards to TRALI which otherwise obviously is
6 one of the number one concerns with this blood
7 product as a very serious, potentially lethal side
8 effect.
9 So in conclusion, Octaplas key
10 consideration, viral screening for enveloped and
11 nonenveloped viruses is provided. The effect of
12 pooling plasma and solvent detergent treatment
13 contributes to (inaudible) of side effects and
14 there is a long history of use worldwide since
15 almost a quarter of a century. So this product
16 offers another approach for plasma to blood safety
17 and pathogen-reduction technology.
18 The final presentation by Dr. Brian
19 Custer was on health economic considerations for
20 pathogen-reduction technology and he pointed out
21 that there are quite a number of interesting and
22 important operational gains that will eventually

1 offset the investment costs. However, he noted
2 that cost neutrality will be difficult to attain.
3 So there is something here on the right lower hand
4 left that, perhaps, will not be recovered and
5 would require a net investment for blood safety
6 even if the initial cost for implementing this
7 technology is overcome.
8 Not shown on the figure are additional
9 cost savings like prevention of test introduction
10 to emergent pathogens when used with transfusion
11 reactions and a potential for simplified inventory
12 management. I would note that at NIH and other
13 places for quite a long time we will have added
14 cost for additional inventory management due to
15 the dual system that will be required for life but
16 very long -- longer term that this may actually
17 come true and would get to one inventory only.
18 He -- Dr. Custer noted on the health
19 economic summary, broadly speaking, that
20 pathogen-reduction technology for plasma would
21 cost around 800,000 to $1.2 million per quality
22 adjusted life year regardless of the technology

1 that would be applied to that plasma. The number
2 for platelets alone are best because we have the
3 highest risk of -- with the bacterial
4 contamination and the platelet units such that a
5 quality adjusted life here has the price tag of a
6 quarter of a million dollars. This might be
7 approached and this can be considered if all
8 bacterial contamination is considered and the
9 culture is discontinued. So that's the best
10 figure for the pathogen-reduction technology that
11 he could calculate. If one combines this
12 technology for platelets and plasma then the
13 numbers are somewhere in between those for plasma
14 and platelets.
15 The summary is within the blood safety
16 context. The technologies are relatively cost
17 effective despite the numbers that he showed and
18 were shown on the last slide. As they are no less
19 cost effective than other widely adopted
20 interventions.
21 A budget gap is likely to remain until
22 pathogen- reduction technologies are available for

1 whole blood or red cells. That's a very important
2 consideration that additional research and
3 development is required to bring this to the red
4 cells which, after all, the number one blood part
5 product and will remain so. And he noted that --
6 Dr. Custer noted that the reimbursement remains
7 the key limitation in the U.S.
8 We then had a productive panel
9 discussion with quite a number of questions and I
10 think that those questions and the answers will
11 shift into the summary that will eventually be
12 published for this very interesting symposium. I
13 have to say that I learned a lot and it was very
14 worthwhile to come here for those two days. Thank
15 you.
16 DR. ATREYA: You don't have any slides
17 now?
18 DR. GOODRICH: I don't have any slides.
19 I'll just give out an overall summary from the
20 presentations that were made during the session.
21 Third session was pathogen-reduction
22 technologies for whole blood and red blood cells.

1 I was the first speaker in that session. My
2 presentation basically described some of the
3 issues that we originally envisioned, might be
4 present in the development and implementation of
5 these technologies into the future dating back to
6 a time in the early 2000s when most of these
7 technologies were in their early development
8 phases.
9 We discussed through that presentation
10 how some of those characteristics or some of those
11 issues have been resolved, how others remain. In
12 many regards the observations that have been made
13 with the platelet and plasma systems are very
14 similar with red cells and that changes do occur
15 as a result of these treatments. The clinical
16 trials are currently in process with the
17 technologies that are in development to determine
18 whether or not those in vitro or other changes
19 that are observed have significant outcomes
20 relative to the clinical results and the clinical
21 utilization of those products in a standard
22 treatment setting.

1 The message from that initial
2 presentation, my presentation, was that innovation
3 around existing technologies is likely to be the
4 most straightforward and likely path forward given
5 the amount of investment that has already been
6 made in this field in those particular areas.
7 What those modifications may look like is yet to
8 be determined.
9 Dr. Benjamin followed with the
10 presentation of data on the technique utilizing
11 amustaline which is a chemical method for
12 inactivating pathogens in red cell products
13 primarily, but it is -- it does not involve the
14 use of light. The primary focus, though not
15 exclusive, is on red cells. He detailed extensive
16 studies that have been conducted up to this point
17 in the clinical setting including results from the
18 REDDA study, the STAR study, the SPARK study, the
19 Recife study. These are studies that involve
20 phase three clinical evaluation of both acute and
21 chronic bleeding -- chronic transfusion patients
22 including acute cardiac surgery and chronic

1 transfusions in the case of thalassemia patients.
2 The results from those studies that have
3 been completed so far have indicated they have met
4 primary endpoint. The modified protocol which has
5 been utilized in creating these products
6 importantly has indicated that there are no
7 autoantibodies that have been observed and no
8 neoantigens present which was an issue with the
9 first iteration as Dr. Benjamin outlined for the
10 product configuration. The company has spent a
11 great deal of time and effort demonstrating that
12 this issue has not been problematic in the second
13 generation of the product development that has
14 taken place and has assays and methods in place to
15 be able to detect the antibody which was primarily
16 against the acridine moadin that is present in
17 these preparations.
18 The -- Dr. Razatos described -- followed
19 with the presentation describing the state of PRT
20 for whole blood by Terumo BCT which is a method
21 that uses riboflavin and light; described it as
22 the same process that's being used for platelet

1 and plasma. There is a significant increased
2 energy dose and treatment time that is associated
3 with that product. There were several details
4 that were provided on studies that have been done
5 by the organization. That AIM study, the JICA
6 study in collaboration with the Japanese
7 Development -- or Japanese Corporation, and also
8 the MERIT study which is a pending study that will
9 be initiated under the leadership of Dr. Erin
10 Tobin at Johns Hopkins University.
11 The primary focus has been on whole
12 blood although the -- there have been activities
13 related to red cells. She described it -- an
14 investigator-initiated study by Dr. Trachlin in
15 pediatric patients in Moscow at the Federal
16 Institute of Hematology and Oncology for pediatric
17 patients. She also described a -- the PRAISE
18 study which is a phase three study on thalassemia
19 patients which is being conducted in the United
20 States. She indicated during that presentation
21 that that study has been suspended as result of
22 issues due to the logistical aspects of supply and

1 that that is currently under evaluation by the
2 company as to how to proceed with that program.
3 Dr. Cancelas followed with a description
4 of his experience in working with both of these
5 technologies both in it from a preclinical
6 evaluation phase as well as from radiolabel
7 recovery and survival studies. He described the
8 data both on in vitro and in-vivo results with the
9 two PRT methods. With the amustaline process he
10 indicated that the procedure does require a
11 removal step. It is a centrigation [sic] and then
12 resuspension of the cells in an additive solution.
13 The product that was tested by this approach meets
14 the recovery standard established by the FDA.
15 There is a slightly reduced survival. This is at
16 day 35 of storage of those products. It is --
17 there is no significant increase that was reported
18 with the potassium and hemolysis of those products
19 over the storage period that they have been
20 evaluated.
21 In the case of the riboflavin and light
22 approach there is no removal step that's involved,

1 Dr. Cancelas indicated. That product, however,
2 does indicate that there is more potassium leak
3 and hemolysis when in the treated products. The
4 storage time for that product is reduced to 21
5 days as a result of those changes that occur
6 during processing. It does meet the recovery
7 requirement at day 21 as stipulated by the FDA,
8 but there is a -- also a reduced survival that's
9 observed in the products that are treated by that
10 process.
11 And that was the summary, essentially,
12 from that session.
13 DR. WAGNER: We heard from session four
14 which was emerging innovations relevant to
15 pathogen reduction technologies and alternatives.
16 The first talk was given by Dr. Maclean who
17 described the use of light alone with no added
18 sensitizer. The light that was used in the system
19 was blue light, 405 nanometers.
20 She first showed us data indicating
21 bacterial kill in plasma at 92 percent to 100
22 percent or 99.9993 logs of inactivation. They

1 then went through dose ranging studies to
2 determine what the effects might be on plasma
3 proteins. They use SDS-PAGE gels as well as
4 Western Blots and they were able to frame the
5 conditions under which protein gel patterns were
6 maintained and similar to controls.
7 They looked at two different light
8 fluence rates; a high fluence rate and lower
9 fluence rate and were able to identify that the
10 lower fluence rate seemed to provide better
11 retention of the protein qualities. They have
12 also done some work -- some preliminary work with
13 platelets and have been involved in developing a
14 system for delivering the light that -- so that
15 entire bags can be treated.
16 The next talk was given by myself. I
17 described a photosensitizer, Thiazine Orange,
18 which can be used for inactivation of viruses,
19 bacteria, and parasites in red blood cells. The
20 distinguishing feature of this system is that the
21 photosensitizer is flexible and only becomes
22 active when it is rigidly bound in a plane in

1 interacting nucleic acid.
2 The red cell studies involved looking at
3 hemolysis, ATP, and potassium leakage. There was
4 some enhanced hemolysis although levels were less
5 than one percent. In addition, there was a more
6 rapid potassium release and the clinical aspects
7 of this system are unknown at this time.
8 The third talk was given by Colonel Cap
9 and he reminded us that many hospitals in the
10 United States don't have access to platelets and
11 that platelet storage at room temperature made
12 platelet availability problematic, not only within
13 the United States but also for our troops overseas
14 in need of platelets.
15 She [sic] described studies in cold
16 platelets which showed better maintenance of
17 aggregation up to 21 days than room temperature
18 stored platelets. He described improved
19 maintenance of mitochondrial function of platelets
20 stored in cold temperature compared to room
21 temperature stored platelets and better clot
22 characteristics of platelets that were stored in

1 cold temperature compared to room temperature.
2 He outlined a study that was performed
3 in Norway on cardiac surgery patients who received
4 platelets and noted that the volume of the chest
5 drainage was less and certainly not worse than
6 patients who received platelets stored at room
7 temperature. He also described some studies that
8 were conducted by Dr. Goetz which showed that
9 platelets stored in the cold do have a tendency
10 with storage to aggregate to -- and reduce
11 platelet number, but this can be ameliorated by
12 storage in additive solutions.
13 He went on to discuss whole blood -- the
14 storage of cold whole blood for patients who need
15 both red cells and platelets who are bleeding and
16 described some studies that they had been involved
17 with which showed that cold whole blood -- the
18 platelets in cold whole blood maintained
19 hemostatic efficacy. In addition, he discussed
20 the problematic issues of bacteria present in
21 platelets because of their room temperature
22 storage and showed data that cold temperature

1 storage of platelets does not enable the growth of
2 many bacterial species in platelets.
3 So, thank you very much.
4 DR. ATREYA: Huh, which form is that?
5 DR. NESS: Yeah. Well thank you for
6 those of you who I have not met or you don't know
7 me. I'm Paul Ness from Johns Hopkins and I have
8 been given the difficult task, I think, of
9 offering some concluding remarks with insights for
10 future research and development. I think I need
11 to echo some of the comments of previous speakers
12 to say that I really thank the FDA for pulling
13 this together. I think it is a tribute to their
14 wisdom that they had gotten in one room for two
15 days almost all of the stakeholders in this issue
16 in terms of people who are interested in
17 regulating it, the companies who are willing to
18 produce it, the blood centers willing to make
19 these products, the hospitals willing to use it,
20 the funding agencies, the various users, and I
21 think that's really a tribute to their wisdom.
22 I've learned a lot through the meeting and I hope

1 -- I believe you all have too.
2 So, in terms of thinking about
3 disclosures, I've been around in this business for
4 quite a bit of time and I had been a consultant to
5 a company called New Health Sciences which is also
6 known as Hemanext. They are working on an
7 anaerobic red cell storage which we haven't heard
8 about much today but, perhaps, it may have an
9 adjunct to some of what we've talked about in
10 terms of tweaking the various processes that are
11 going forward. I've also been a consultant for
12 Terumo BCT in their processes. Actually, my
13 longevity with them is through four name changes
14 so that I've been involved a lot with the
15 discussions on Mirasol system and a lot of what's
16 been used. And it's -- you know, it [sic] really
17 a terrific opportunity to come here and talk to
18 you today which I have truly enjoyed or hopefully
19 I will truly enjoy; although in some ways it is a
20 little different challenge. Formally, I would
21 come to meetings and ask to be -- present some of
22 our original research, some of the results of the

1 clinical trials we've done while at Hopkins or in
2 conjunction with the Red Cross when I worked
3 there.
4 Today's lecture is, sort of, a different
5 type of lecture. One that as an earlier
6 investigator when I was young I always feared
7 that, you know, somebody was going to get up at
8 the end of a talk and give this type of summary
9 talk; didn't necessarily want to listen to
10 everything that he or she had to say, but I guess
11 when I look today in the mirror while shaving and
12 got my aching body out of bed and reminded myself
13 for dealing with my granddaughters who are very
14 happy to remind me that I'm getting old and not
15 any smarter, but I've finally have earned the
16 title and the obligation to give this type of
17 presentation.
18 So anyway, what I'm going to try to do
19 and I certainly don't think this is the be all and
20 end all of the talks that have been given, is to
21 raise some things for continuing efforts going
22 forward that I know that others have alluded to

1 and probably other thus far, and some of them may
2 be somewhat independent and some of them probably
3 are speaking for the broad consensus as the people
4 are here.
5 But in terms of the ideas of blood
6 safety and pathogen kill we've seen a lot of
7 information about the various levels of the kill
8 with the various systems that have been done; some
9 that have been tried, some have been true. And
10 the question that I think really remains is what
11 does this do and how does this correlate with
12 clinical efficacy? And we learned for multiple
13 descriptions that you kill more things, you also
14 have cell damage, so we're going to have to figure
15 out how we can balance those two things.
16 So what is the appropriate balance
17 between pathogen kill and blood component
18 function? And we know that we're buying into --
19 buy all of these technologies at 20, 25 percent
20 hit on cell function. Are there ways to tweak
21 that such that we can still maintain acceptable
22 cell function without having an acceptable cell

1 kill by compromising the existing systems or,
2 perhaps, going forward with new ones?
3 So one of the examples is this that I
4 wanted to point out is this is an old slide that
5 -- from the Marisol system and it shows the
6 various log kill measurements of viruses,
7 bacteria, parasites. And if you look over on the
8 far and the red column where there's parasites,
9 they -- it was predicted based on their in vitro
10 work that they would get a three to five log kill
11 for parasites such as malaria. We've seen this
12 slide in a number of ways although the point was
13 not made or raised particularly. This is from the
14 AIM Study that was conducted in Ghana. And as you
15 see -- as you look at the differences between the
16 untreated and the treated cells that the parasite
17 loads were much greater than the ten to three or
18 ten to the five predicted kill rates that the
19 Marisol process would have had.
20 So this gives some example, perhaps,
21 that what we are measuring, in terms of in vitro,
22 may not necessarily correlate with how effective

1 these things will be in vivo. And what we're
2 obviously going to hope to get is more in vivo
3 evidence as to kill. Now this is obviously going
4 to be very difficult to do because with the virus
5 lodes our studies that -- the risks are too low to
6 really measure them. And that's why I think if we
7 talk a little bit about Erin Tobins' study that
8 I'm working with him in Uganda, funded by the DOD,
9 this hopefully will give us some real evidence as
10 to what we really are killing in -- based on
11 recipient studies and that's the kind of study I
12 think we would want going forward.
13 The other thing I would raise as you
14 look at the third point, this issue of how much
15 cell kill do we need and how does it correlate
16 with clinical efficacy? I know some people
17 pointed out this paper to you, but Jeff McCullogh,
18 Harvey Alter, and I recently put together a large
19 review of this topic called the Interpretation of
20 Viral Lode in Relationship to Infectivity and
21 Pathogen Reduction Efficacy. It has been accepted
22 for publication and transfusion. I'm no longer

1 the editor so somebody else accepted it, but
2 hopefully this will add to the discussion of this,
3 I think, very important topic so that we will know
4 how we can balance, perhaps, cell kill with
5 clinical efficacy.
6 So in terms of platelets, this is a --
7 obviously important topic. We have a licensed
8 platelet system out there which is INTERCEPT and
9 we had a number of discussions, sort of, about do
10 the platelets really stop acute hemorrhage? And
11 we know that most of the studies that have been
12 done have been done in hemon patients where the
13 use of platelets is prophylactic and we haven't
14 seen necessarily any enhanced bleeding in these,
15 sort of, noninferiority-based studies, but we
16 really don't have a lot of reassuring information
17 that in the acutely bleeding patient,
18 pathogen-reduced platelets has current being
19 performed whether by the INTERCEPT system, whether
20 by the MIPLATE system, or the Mirasol system,
21 really will stop acute hemorrhage. And I think
22 this is something that we're going to have to look

1 at. We're given some information, for example, by
2 hemovigilance studies that imply that, for
3 example, red cell usage in countries that are
4 using these have not seen enhanced uses of red
5 cells. This, I think, unfortunately ignores the
6 fact that we're also in a ten-year patient blood
7 management program where all around the world
8 people are now learning to use less red cells for
9 clinical events. So we're really going to need
10 better evidence, I think, for the acutely bleeding
11 patients that these platelets do have some good
12 function. I think what Dana Devine implied, based
13 on the activation status of some of these
14 platelets, may be reassuring but I think we need
15 more clinical information.
16 Then again, I think the second topic
17 really is important that comes out and was
18 repeated multiply at times is can PRT damage to
19 platelets be mitigated so that we can enhance the
20 recovery, survival, and function? So do we have
21 to accept the 20 percent or so hit? Can we do
22 this in conjunction with other things? I think

1 we've talked about some intriguing possibilities
2 and, perhaps, going back to cold storage with
3 pathogen reduction to deal with some of these
4 issues. There may be other ways with other
5 anticoagulants, other solutions that we can do
6 this, but I think this is an important goal
7 because we want to deal with it.
8 We didn't spend much time at this
9 session talking about how effective PRT platelets
10 are in reducing alloimmunization. And just want
11 to remind you, if we look back at this study
12 called the TRAP study which was done many years
13 ago at seven hospitals in acutely ischemic
14 patients. You can see that various interactions
15 using either leukoreduction or UVB light reduced
16 the risk of alloimmune refractoriness in patients
17 from around an existing level of about 13 percent
18 down to about 5 percent. And this led to really
19 the standard of care that we now do when we reduce
20 leukoreduced platelets routinely for almost all of
21 our patients, particularly for those with
22 hematologic malignancies. It, sort of, doesn't

1 pay attention though to the fact that this study
2 shows, with leukoreduction, we still have a five
3 percent remaining problem. And if you're working
4 at a large referral cancer center you still see
5 patients coming in with alloimmune refractoriness
6 either because of previous pregnancies, previous
7 treatments with platelets, previous transplants.
8 So this really does remain an important goal. I
9 know that the Mirasol system is attempting to look
10 at that; the initial results from the prepare
11 studies. We're not as confirmatory as an initial
12 study they did in France called the Miracle Study.
13 We haven't heard a lot of information on the
14 INTERCEPT system as to what it does in
15 alloimmunization, but I think this is an important
16 potential direction and that -- an advantage, if
17 it's proven, that pathogen-reduction platelets
18 would give us.
19 And then the other question I think we
20 really need to totally verify is how effective are
21 PRT platelets in reducing other platelet
22 reactions? So this is a slide that I give when I

1 talk about platelet reactions and I think it's --
2 we've seen pretty convincing evidence that
3 bacterial sepsis and transfusion associated graft
4 versus host disease due to platelet transfusions
5 really are eliminated by pathogen- reductions. In
6 terms of bacterial sepsis or other means you could
7 probably handle this and we've shown that we can
8 do this with culturing or other tests, but these
9 are two proven advantages of the
10 pathogen-reduction.
11 Alloimmunization we just talked about,
12 and it's not -- we -- the results are maybe a
13 little discouraging but not yet clear. But in
14 terms of the other types of potential reactions
15 that patients suffer, we heard from Dr. Cap about
16 the high incidence of fevers in oncology patients
17 getting platelets. So will the pathogen reduction
18 systems reduce the (inaudible) due to white cells
19 or cytokines that are produced during storage?
20 And also this other transfusion reaction that can
21 occur; transfusion related acute lung injury which
22 has to do with either antibodies or lipids; will

1 these reactions be reduced by pathogen-reduction?
2 I think these are important things to add to the
3 value of pathogen reduction going forth to,
4 perhaps, make it a more comprehensive and easier
5 thing to sell to the skeptics in our hospitals.
6 In terms of plasma we heard a number of
7 talks about what is the effect of PRT on
8 procoagulant and prothrombotic constituents and
9 their balance in patients? And we know from
10 earlier episodes that, for instance, Protein S,
11 low levels in some of the plasmas led to
12 thrombotic complications. So this will be an
13 issue that we will obviously need to go forward.
14 The second question, I think, that we
15 heard about is will pooled PRT platelets or
16 products reliably reduce transfusion reactions?
17 And as, sort of, a corollary to that, can PRT be
18 added to plasma pools to improve current products?
19 So this is a list of, I think, issues
20 that are problems with the current plasma product
21 we're dealing with, FFP. And, you know, I heard
22 Dr. AuBuchon say that there's no compelling reason

1 why hospitals want something better. Well most of
2 us who deal with fresh frozen plasma in a hospital
3 setting think it's the world's worst product. It
4 has a whole host of issues that make it very
5 difficult to deal with. Obviously, it has ABO
6 antibodies meaning we have to have four different
7 types. If we want to use it for universal
8 patients, we have to use AB or sometimes A plasma.
9 This is very cumbersome. This could be handled.
10 It has variable content of coagulation factors and
11 it has to be thawed and after it's thawed it has a
12 limited shelf life. It has infectious risks. It
13 also causes allergic reactions very commonly in
14 patients who get plasma during routine transfusion
15 episodes or, perhaps, during apheresis as we
16 pointed out earlier. And there's a potential for
17 volume overload in patients and the bottles -- in
18 some cases it comes in glass bottles, in some
19 cases it comes in bags and they break so they're
20 not easy to use.
21 So there's been a lot of energy going on
22 with improving plasma. A lot of you have been

1 involved in the idea of having frozen or
2 lyophilized plasma that could be used, for
3 instance, for military use, but I don't think we
4 will ever get to the maximum of these potential
5 things to improve these products without
6 pathogen-reduction. So if you really want to get
7 rid of the allergic reactions which plague some of
8 our patients, you're going to need bigger pools
9 than currently are going to be provided. And if
10 you really want to have -- eliminate the
11 variability of coagulation factors you're going to
12 need bigger products. And if you have a
13 manufactured product it may potentially, for
14 example, be reconstituted in less volume so that
15 you could use it for stable patients who have
16 liver failure as opposed to just using it in
17 trauma.
18 So I really do believe there is a real
19 role for pathogen-reduction in plasma products. I
20 think we underestimate the inappropriateness and
21 the failure of FFP to really meet the clinical
22 needs our patient's have and so I hope this is

1 something going forward.

2 So -- and then the other thing that has

3 never really been mentioned is this final point on

4 this slide. We talked a little bit about making

5 whole blood to be treated making components from

6 it. We know that right now when we make

7 components; the blood centers make components,

8 that there is plasma left over. Some of it goes

9 into FFP. A fair amount of it goes as a recovered

10 plasma in de-fractionation. So is it going to be

11 acceptable to use whole blood PRT treated plasma

12 for the fractionation process? Will this be a

13 problem for manufacturers going forward? Will it

14 require different types of regulations because if

15 we can't use all of the plasma coming out of these

16 products it will be a financial disincentive to

17 those people who use it.

18 So in terms of, sort of, summarizing

19 with the red cell issues, can damage to red cells

20 with current systems be limited by new processes

21 or additional manufacturing steps? And we heard

22 that some of them are meeting the criteria fairly

1 well; some of them, the Marisol system seems to
2 fall short. Are there ways that we can treat the
3 -- tweak the system with different anticoagulants,
4 with different ways to deliver the light source to
5 deal with these issues? I think this is very
6 important.
7 A second issue that we talked a little
8 bit about is do PRT processes effect
9 immunohematologic procedures? We know that the
10 first-generation red cells were affected by
11 antibody production. We saw some reassuring data
12 that the second generation of -- on the intercell
13 process doesn't seem to have these problems,
14 although Dr. Benjamin admitted that there are some
15 problems that will still exist. We don't think
16 they're clinically significant but if we have
17 products that are going to be made difficult to
18 administer with our current immunohematologic
19 processes, this is something we're going to have
20 to deal with and have to understand.
21 And then I think the other thing we
22 haven't really talked about is does the addition

1 of PRT in red cells reopen the age of blood
2 controversy? So in a previous meeting I attended
3 and spoke at we talked about whether the age of
4 blood controversy is resolved. And we pointed out
5 that there are a number of randomized clinical
6 trials in adult and pediatric patients that showed
7 no real difference between fresh and blood stored
8 for longer periods of time looking for adverse
9 effects and function issues.
10 But not everybody has totally bought
11 into this. Populations at high risk have not been
12 comprehensively studied. For example, trauma
13 patients, sickle cell patients, that we have some
14 data that we published and I presented on
15 retrospective studies in patients who received
16 older blood which is actually -- they didn't do
17 quite as well as patients who got more routine
18 blood. The animal studies from the NIH have very
19 old blood in very sick animals suggests that there
20 could be problems here. Dr. Hod and Spitalnik at
21 Columbia have shown that older blood and -- beyond
22 35 days with current anticoagulants has some

1 problems. So I think this lays unanswered, what
2 is the effect of PRT on this whole issue? Are we
3 going to have to do another recess study? We're
4 going to have to get -- Nancy had a lot of
5 retirement to do another in-forum study. The -- I
6 don't know how we will deal with this. Are we
7 going to just use the traditional markers of red
8 cell recovery, hemolysis, et cetera to say this is
9 all fine or are we going to need more clinical
10 data to resolve all of this issue and I think
11 that's something we have to think about.
12 So other unanswered questions. Do we
13 really need blood storage for 42 days or could the
14 blood system in the U.S. handle shorter storage
15 periods? We heard from Dr. AuBuchon and other
16 people that the 21 day, you know, time would be a
17 -- problematic but maybe we could get better. And
18 we do know that for longer -- from distant
19 hospitals and certainly for the military use,
20 longer periods of storage are required. We
21 understand that if we shorten the storage period,
22 perhaps, due to the adoption of PRT for red cells,

1 outdating might increase, cost might increase, and
2 -- but perhaps, some of these products' problems
3 could be mitigated by the adoption of newer
4 technology and advanced transport systems are a --
5 commonly used in other industries but don't
6 necessarily get applied to transfusion.
7 So then, sort of, the final, sort of,
8 summary is will FDA or can FDA adopt guidelines
9 for industry that will allow the enhancements in
10 blood storage or pathogen-reductions solutions to
11 be licensed and implemented such that they will be
12 cost sensitive? I think this is a big issue. I
13 think the FDA here by having this meeting is
14 saying they want to work with all of us to advance
15 these goals. So I think this is a terrific start
16 and we haven't heard much of a discussion of what
17 they will do with these issues going forward, but
18 hopefully we'll -- we will hear in printed word or
19 word even here about other steps that they want to
20 take.
21 But one of the, you know, questions will
22 come up and come up to me, like, how much of the

1 new knowledge about red cell storage would need to
2 be applied to applications and for licensure of
3 PRT red cells? I mean -- we -- Simone Glynn at
4 NIH funded a whole series of studies in vitro and
5 clinical trials on red cell storage. We know a
6 whole lot more about the mechanisms of red cell
7 storage. Are these all going to have to be
8 incorporated into regulatory review or will we
9 just do the same review in the past? Will FDA
10 continue to work with blood centers to increase
11 efficiencies with modified procedure and
12 elimination of redundant testing? We've seen that
13 as an important issue to try to lower the cost.
14 And then will these cooperative efforts result in
15 PRT components that hospitals view as cost
16 effective and worthy of the increased expense? So
17 this is a real issue and I know one we'll deal
18 with because I'm concerned that if guidelines and
19 requirements become too burdensome, the clinical
20 advantage is of -- some of the better solutions
21 we're talking about that would help patients may
22 never be realized. So I think these are obviously

1 the goal of us all in this room today working
2 towards.
3 I think we've heard some wonderful
4 presentations of the state of the art. We've
5 heard some encouraging things about what might go
6 forward. It would be nice to combine some of
7 these events. For instance, I hadn't thought in
8 the past of combining pathogen-reduction with cold
9 storage even though I'm very interested in both.
10 So I think this really puts together a wonderful
11 opportunity for citizens of these ideas and
12 hopefully bringing forward to our patients.
13 I thank you for the attention you have
14 given me and my -- the permission to -- here to
15 be, sort of, the final rambler. Thank you.
16 (Applause)
17 DR. VERDUN: So wow, I just want to say
18 thank you to everyone. This has been, I think, a
19 wonderful workshop and quite successful because of
20 all of you. I, in particular, wanted to just
21 thank Jennifer Scharpf and CD Atreya who did a lot
22 of the -- not only the logistics but also some

1 behind the scenes things that really made this
2 happen and come together today, so I wanted to
3 especially thank them. In addition, I would like
4 to thank our federal partners that have worked
5 with us and our presenters today, and also all of
6 the participants both in phone -- on the phone and
7 in person.
8 And, you know, stopping short of
9 summarizing the summaries, I'm not going to do
10 that actually, but I just wanted to really say
11 that FDA really is truly committed to moving
12 pathogen reduction technologies forward. And
13 really moving the needle forward is going to
14 require collaboration among everyone here and we
15 really do appreciate all of you being here. That
16 definitely means a lot. And I really -- we really
17 do look forward to working with everyone to
18 advance the field. We take all of the
19 considerations that have been brought up today
20 quite seriously, including the concluding remarks
21 from Paul Ness. I appreciate those and the
22 questions -- the compelling questions that he had

1 for FDA. But I think this really truly is a
2 partnership and we do look forward to working with
3 all of you. So come to us early, come to us
4 often. We're here for you and, again, thank you
5 everyone for coming and for participating. Thank
6 you. (Applause)
7 (Whereupon, at 12:42 p.m., the
8 PROCEEDINGS were adjourned.)
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1 CERTIFICATE OF NOTARY PUBLIC
2 DISTRICT OF COLUMBIA
3 I, Carleton J. Anderson, III, notary
4 public in and for the District of Columbia, do
5 hereby certify that the forgoing PROCEEDING was
6 duly recorded and thereafter reduced to print under
7 my direction; that the witnesses were sworn to tell
8 the truth under penalty of perjury; that said
9 transcript is a true record of the testimony given
10 by witnesses; that I am neither counsel for,
11 related to, nor employed by any of the parties to
12 the action in which this proceeding was called;
13 and, furthermore, that I am not a relative or
14 employee of any attorney or counsel employed by the
15 parties hereto, nor financially or otherwise
16 interested in the outcome of this action.
17
18
19 (Signature and Seal on File)
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21 Notary Public, in and for the District of Columbia
22 My Commission Expires: March 31, 2021