1 FOOD AND DRUG ADMINISTRATION (FDA)

2 Public Workshop

3 Advancing Animal Models for Antibacterial Drug

4 Development

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6 MEETING

7 DATE: March 5, 2020

8 TIME: 8:30 a.m.

9 LOCATION: FDA White Oak Campus

10 10903 New Hampshire Avenue

11 Bldg. 31 Conference Center

12 the Great Room

13 Silver Spring, MD, 20993

14 REPORTED BY: KeVon Congo, Notary Public

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1 A P P E A R A N C E S

2 John Farley, FDA

3 Ursula Waack, FDA (ORISE Fellow)

4 Abhay Joshi, FDA

5 Judith Hewitt, NIH/NIAID

6 Tina Guina, BARDA

7 Yuliya Yasinskaya (Chair)

8 Jennifer Hoover (Co-Chair)

9 Lynn Miesel, Eurofins Scientific

10 Brian Luna, University of Southern California

11 Jþrgen Bulitta, University of Florida

12 Matthew Lawrenz, University of Louisville

13 Alexander Lepak, University of Wisconsin

14 John Farley (Chair)

15 Marina Kozak (Co-Chair)

16 William Hope, University of Liverpool

17 Thomas Walsh, Weill Cornell Medicine of Cornell

18 University

19 Binh Diep, University of California . San Francisco

20 William Weiss, University of North Texas

21 Andrew Phipps, Tunnell Government Services - BARDA

22 Edward Weinstein, FDA

1 External:

2 Tina Guina BARDA

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11 Alexander Lepak University of Wisconsin

12 Brian Luna University of Southern California

13 Eric Nuermberger Johns Hopkins University

14 Bradley Spellberg University of Southern California

15 Thomas Walsh Weill Cornell Medicine of Cornell

16 University

17 William Weiss University of North Texas

18 Cara Cassino ContraFect

19 Jennifer Hoover GlaxoSmithKline

20 Lynn Miesel Eurofins Scientific

21 Achim Wach Polyphor

22

1 DR. JOHN FARLEY: Good morning,
2 everyone. I.m John Farley. I.m acting director of
3 the Office of Infectious Diseases at the Center for
4 Drugs at FDA and I want to welcome you to the workshop
5 this morning. It.s our second workshop focusing on
6 animal models. Title this morning is Advancing Animal
7 Models for Antibacterial Drug Development. So I think
8 what we.re going to do is begin with asking our
9 panelists to introduce themselves and any disclosures
10 they may wish to share, and then I.ll make some
11 introductory remarks, so I.ll start with Dr. Joshi.
12 DR. ABHAY JOSHI: Good morning. My
13 name is Abhay Joshi. I.m serving as the clinical
14 pharmacology reviewer with Division of Infectious
15 Disease Pharmacology at Office of Clinical
16 Pharmacology with FDA.
17 WILLIAM WEISS: Bill Weiss, director of
18 preclinical services at University of North Texas
19 College of Pharmacy and working with Binh Diep on
20 ventilator-associated rabbit model.
21 DR. BINH DIEP: I.m Binh Diep from the
22 University of California San Francisco and I.m an

1 associate professor in the Division of Infectious
2 Diseases. My area of research is in microbial
3 pathogenesis, so we develop lots of rabbit models for
4 that purpose.
5 DR. CARA CASSINO: Good morning. I.m
6 Cara Cassino. I.m chief medical officer and head of
7 research and development at ContraFect. ContraFect is
8 working on direct lytic agents as novel antibacterial
9 therapies and our lead compound, exebacase, is just
10 entered Phase 3. Thanks.
11 DR. TINA GUINA: Hi. I.m Tina Guina.
12 I.m program manager at Biomedical Advanced Research
13 Development Authority, BARDA. I have experience in
14 vaccine and therapeutics development, development of
15 animal models.
16 DR. ALEXANDER LEPAK: Hello. I am Alex
17 Lepak. I am from University of Wisconsin. My
18 research area is in using animal models in
19 particularly pharmacokinetics and pharmacodynamics for
20 drug optimization and drug development.
21 DR. MATTHEW LAWRENZ: My name is Matt
22 Lawrenz. I.m from the University of Louisville. We

1 do a lot of work there on biodefense and drug-
2 resistant pathogens and I.m going to tell you guys
3 today about some of the work we.re doing on a
4 pulmonary model for pseudomonas.
5 DR. LYNN MIESEL: I.m Lynn Miesel from
6 Pharmacology Discovery Services and we conduct
7 preclinical testing services for drug discovery and
8 we.re conducting model development and preclinical
9 testing services for NIAID.
10 DR. URSULA WAACK: I.m Ursula Waack.
11 I.m an ORISE post-doctorate fellow in the Office of
12 Infectious Diseases here at the FDA.
13 JENNIFER HOOVER: Jennifer Hoover. I
14 am the director of Preclinical Pharmacology Group at
15 GlaxoSmithKline Pharmaceuticals and I.ve been working
16 with animal models and PKPD in industry for over 25
17 years. Thanks.
18 YULIYA YASINSKAYA: Good morning. My
19 name is Yuliya Yasinskaya. I.m clinical team leader
20 in the Division of Anti-Infectives here at the FDA.
21 DR. SUMATHI NAMBIAR: Good morning.
22 Sumathi Nambiar, director, Division of Anti-

1 Infectives.

2 DR. MARINA KOZAK: Marina Kozak,

3 project officer in BARDA.s antibacterial program.

4 DR. ERIC NUERMBERGER: My name is Eric

5 Nuermberger. I.m a professor of medicine at Johns

6 Hopkins University in the Division of Infectious

7 Diseases. My research interests are largely in anti-

8 mycobacterial agents in drug development in animal

9 models.

10 DR. EDWARD WEINSTEIN: Good morning.

11 My name is Ed Weinstein. I.m a clinical team leader

12 in the Division of Anti-Infectives.

13 DR. BRADLEY SPELLBERG: Brad Spellberg,

14 LA County, USC Medical Center. I.m honestly a

15 recovering mycologist, but like a decade ago or so

16 moved into the gram-negative space, so we do a lot of

17 gram-negative research.

18 DR. JUDY HEWITT: Judy Hewitt, NIAID.

19 Lot of experience with animal models, mostly in

20 biodefense, but also anti-microbial resistance.

21 DR. BRIAN LUNA: Brian Luna, USC. I.m

22 part of the group that.s going to be sharing about a

1 mouse model for setting Acinetobacter.
2 DR. JURGEN BULITTA: Jurgen Bulitta,
3 University of Florida Antibiotic PK-PD (inaudible)
4 inhibition and (inaudible).
5 DR. KELLIE REYNOLDS: I.m Kellie
6 Reynolds, the director of Division of Infectious
7 Disease Pharmacology in the Office of Clinical
8 Pharmacology at FDA.
9 DR. ANDREW PHIPPS: Good morning.
10 Andrew Phipps. I.m a contractor supporting BARDA in
11 the areas of nonclinical development and animal
12 models.
13 DR. ACHIM WACH: Achim Wach, head of
14 drug metabolism and pharmacokinetics at Polyphor, a
15 Swiss biotech company and we are using cyclic peptide
16 derived structures to -- as antimicrobial agents.
17 DR. SIMONE SHURLAND: Simone Shurland,
18 Clinical Microbiology Review at the Division of Anti-
19 Infectives. Thank you.
20 DR. JOHN FARLEY: Great, thanks.
21 Thanks very much, everyone, and thanks so much for
22 taking time out of your schedules to come together. I

1 think most of us would appreciate having about six
2 hours to not be thinking about COVID-19, so that would
3 be -- it.s actually sort of a little vacation.
4 I want to also introduce James Byrne.
5 James, if you could stand up. Would that be okay,
6 just so folks who -- know who you are. James has done
7 most of the heavy lifting for us organizing this
8 workshop and if you have a question, he would be more
9 than happy to try and answer that today. and then
10 he.s sitting next to Thushi Amini, who.s our associate
11 director for research and she can also help out. So
12 thanks very much.
13 So animal models are used in
14 antibacterial drug development for a number of
15 purposes. They.re used early in drug development, of
16 course, but increasingly animals have played an
17 important role in later drug development. So we.re
18 here today to discuss scientific progress since our
19 last workshop, which was almost exactly three years
20 ago and talk about ideas for future work and continued
21 progress.
22 In that time, we.ve come together at

1 FDA, NIAID, and BARDA to get a number of edgy projects
2 up and going. It turns out that science is hard and
3 you.ll get to hear a lot of that progress today. For
4 models used early in drug development, we.ll have an
5 opportunity to discuss variability and consider
6 harmonization efforts. We.ll also hear about various
7 resources that have been developed through the support
8 of our HHS partner agencies.
9 We.ll then have a chance to hear about
10 progress on the development of a number of animal
11 models, generally intended for use in later drug
12 development, talk about ideas to address a range of
13 challenges as well as thoughts from you about where we
14 ought to go from here. In terms of the regulatory
15 role for these models, FDA.s hope is that they may one
16 day be useful as supportive data to accompany a human
17 clinical trial.
18 That human clinical trial would be
19 anticipated to have a number of uncertainties
20 including prior and concomitant antibacterial drug
21 use. We.re hoping that the data from those models
22 might help address some of those uncertainties.

1 While we have much to learn from the
2 development of animal models used in animal rule
3 applications, such as the African green monkey model
4 in plague -- and a number of folks sitting around the
5 table played a big role in that -- the models that
6 we.re working toward today would be expected to be
7 part of a standard new drug application that would be
8 anchored by a human clinical trial would not be
9 expected to meet all of the animal rule regulatory
10 standards, and as you.ll sort of figure out today, the
11 science has a ways to go, even if we thought that that
12 was an appropriate path to follow.
13 I think you.ll be very impressed by the
14 work that has been done, but realize there.s much work
15 ahead, so we.re very grateful for you taking the time
16 to be here today. I.m going to begin by introducing
17 our first couple of speakers who will lay the
18 foundation for us. Our first speaker, if I.m correct,
19 yeah, I am, is Ursula Waack. Dr. Waack received her
20 PhD in micro and immunology from University of
21 Michigan.
22 We.ve had the pleasure of having her as

1 a post-doctoral ORISE fellow here in the Office of
2 Infectious Diseases at the FDA, and previously she
3 completed a fellowship at USDA and she.s going to talk
4 about some work she.s done assessing animal models of
5 bacterial pneumonia that have been used in
6 investigational new drug applications or IND
7 submissions to the FDA, focusing on bacterial
8 pneumonia. So I think, Ursula, do you want to do the
9 podium? I think that might be easier. Okay, great.
10 Thanks so much.
11 DR. URSULA WAACK: Good morning, and
12 thank you, Dr. Farley. I.ll just wait for that to
13 get... As John said, I.m excited to talk to you about
14 some of the research that I have conducted lately at
15 the FDA, looking at animal models and IND
16 applications. I have no disclosures. So animal
17 models play an important bridge between nonclinical
18 development and clinical development, and very
19 broadly, they can be put into three categories: Kind
20 of PKPD studies, safety or toxicology, and kind of
21 proof of concept.
22 So my goal and the research question I

1 sought to answer was, is there a way to really
2 understand the models that were used for proof of
3 concept and are there ways to improve or harmonize
4 these models. To do -- to answer this question, I
5 made two different databases. So the first one, here
6 on the left, was an IND database. So this is made
7 from submissions -- for IND submissions to the FDA and
8 we looked at those submitted to the Division of Anti-
9 Infectives since January 1st, 2000.
10 This date was picked because that was
11 pretty much the dawn of digitization here at the FDA
12 and IND submitted after that time, we would have
13 access to the records. And then using the search
14 terms for pneumonia or bacterial infection, I looked
15 through all the study reports to see and gather all of
16 those that were pneumonia models, and we categorized
17 those as any that were -- had inoculations into the
18 respiratory tract.
19 I excluded studies that were specific
20 for tuberculosis, cystic fibrosis, or biothreats,
21 because we felt this was very specific models and we
22 were looking at general models. So that left us with

1 27 unique INDs with 180 unique studies. For
2 comparison, I also made a published studies database
3 and we wanted this database to mirror the same
4 conditions as our IND database.
5 So we -- I searched PubMed using the
6 terms animal model, pneumonia, and antibacterial,
7 using the same timeframe as the IND database. As with
8 the IND database, we looked for literature that had
9 pneumonia models and excluded tuberculosis, cystic
10 fibrosis, or biothreats. As all of the study reports
11 in the IND database looked at treatment after
12 bacterial inoculation, we did the same for our
13 published studies and I removed those manuscripts that
14 were coinfections with viruses such as influenza
15 strains.
16 When you compare the two databases,
17 there were 22 studies that overlapped and were in both
18 databases, so to prevent duplication, I removed those
19 from the published study database, but kept them in
20 the IND. So that left us with 137 papers and 377
21 studies. So what did I find? Well, we first looked
22 at the bacterial side of things, so here I.m showing

1 on this graph the bacterial strain -- species that
2 were used in the IND database. On the X axis, we have
3 the time, and this was -- the study report was
4 completed, and on the Y axis is the number of studies.
5 So we did notice those gram-negatives
6 and gram-positives we used throughout, but gram-
7 positives shown in the black and the gray bars were
8 more prevalent toward the beginning of our time
9 period, and as you can see towards the end, we don.t
10 have any gram-positive in our submissions, and we
11 think the rise of the gram-negative may be due to the
12 rise of antimicrobial resistance.
13 We did try to look to see if there were
14 common strains within our bacterial species, but we
15 believe that because companies use either internal
16 numbering or unique clinical strains, we couldn.t find
17 a common strain among our species. Now, when you
18 compare that to what we found in the published
19 studies, we see a much greater variety of bacterial
20 species including some of the more uncommon, like
21 legionella, but we don.t see that trend of more gram-
22 positives.

1 You can see the black and the gray bar
2 are throughout the whole time period and just like
3 with the IND figure, we have time on the X axis, and
4 this was the year the manuscript was published, and
5 then studies on the Y. So now, I then looked at the
6 animal side of the models, so here I am showing on the
7 Y axis the species and that.s further subdivided
8 through the inoculation route and number of studies on
9 the Y.
10 So if you look at the IND specific
11 database here on the left, you can see that there were
12 three bacterial -- animal species used, so mouse,
13 rabbit, and rat, and predominantly mouse models are
14 the most commonly used, and the majority of them are
15 intranasal inoculation. Now, rats were also used, but
16 they were mostly intrabronchial and intratracheal.
17 Now compare that to the published database on the
18 right, we have once again more variety.
19 So we had guinea pigs and pigs;
20 although, mice are the predominant animal species.
21 And we see more variety in inoculation route.
22 Although intranasal does make up the majority of the

1 inoculation route, we do see more along the
2 intratracheal and the oral, but we see the same trend
3 with the larger animals using the intratracheal and
4 the intrabronchial inoculations.
5 Interestingly, when I was looking
6 through the IND database, we had no studies that had
7 ventilator-associated pneumonia. We do see a few in
8 the literature; those are mostly the pig models. So
9 that is an avenue where we.re lacking some animal
10 models here at the FDA.
11 Then, we wanted to ask, is there
12 another reason why we would use one animal species
13 over the other, so we looked at time for the studies.
14 So here in this graph, I.m showing the animal species
15 on the X axis and the number of studies on the Y, and
16 the animal species are then subdivided into the length
17 of studies. This is all hours post-infection and if
18 you concentrate here with the IND models on the left,
19 with our mouse model, you can see that the predominant
20 time is that 24 to 27 hour post-infection.
21 And this tends to correlate with about
22 24 to 26 hours past the start of treatment, so these

1 are much shorter, more acute pneumonia models. With
2 the rat and the rabbit, we see those tend to go for
3 the longer studies, especially with the rat we have a
4 large amount of 96 to 119, so more the four days.
5 Compared to the literature model, we see the same
6 trend. Within the mice, the largest amount of studies
7 are within that 24 to 47, but as we.ve seen before
8 with other variables, there.s a lot more variety, so
9 we know that it.s possible to have mice models that go
10 longer; although, that.s not the most commonly used.
11 And once again, with the larger
12 animals, we see that it goes for longer amount of time
13 periods. Another part of study design that we looked
14 at was what endpoint was commonly used. So here, if
15 we have IND database once again on the left and
16 published literature on the right, and in the blue we
17 have bacterial load and you can see for both databases
18 bacterial load was the most commonly used endpoint.
19 And then the IND database, we had equal
20 amounts of use of dose for 50 percent survival or
21 survival, and that could be percent survival or time
22 for survival. Compare that to the published

1 literature, once again, the bacterial load is the most
2 common, but we do see a few more percentage of this
3 survival, which may be a more clinical relevant
4 endpoint.
5 Our last question that we were
6 wondering was the use of neutropenic or
7 immunocompetent models. So here on the left, we have
8 the IND database and that.s divided into whether the
9 animal was neutropenic or immunocompetent and the
10 first thing we notice is the numbers of studies in
11 general were very similar.
12 However, when you look at the
13 distribution when compared to the inoculation group,
14 you see that in the neutropenic animals, the
15 predominant model is intranasal. And if you recall
16 from previous slides, this corresponds with mice, so
17 our most common model for the IND database was mice
18 that were neutropenic, inoculated intranasally. The
19 immunocompetent animals within the IND database
20 encompassed -- there was really no trend for any
21 particular one and they were evenly used.
22 We saw similar trends and once again,

1 just a little bit more variety in the published
2 literature database with the neutropenic model being -
3 - the most common being intranasal, but you can see
4 here from the graph on the right that the
5 intratracheal and the oral weren.t that far behind in
6 numbers of studies. But the overall numbers comparing
7 the neutropenic and the immunocompetent were, once
8 again, very similar, so without taking into account
9 any other reason for wanting neutropenic or
10 immunocompetent, there seems to be standard amounts of
11 neutropenic and immunocompetent models used in both
12 databases.
13 So my work has brought up a few main
14 conclusions and one thing that we found is the study
15 design was highly variable. We were hoping to find a
16 way to use these models to maybe help predict, but the
17 problem we ran into is that there.s so many different
18 design choices and everyone makes very different
19 design choices that it.s impossible to compare across
20 drug programs.
21 So this is really an opportunity for
22 harmonization. Is there a way that we can harmonize

1 these models to help compare across programs, for
2 example, with the bacterial strains, having everyone
3 either report or use common bacterial strains like ATC
4 strains or banked strains? Another thing that we were
5 actually surprised is looking at the differences
6 between the IND database and the published literature
7 database.
8 Now, these are distinct datasets.
9 There.s very little overlap, only 22 studies. So the
10 trends were very similar, despite being distinct, but
11 if you think about it, there.s only 22 studies that
12 were in both, so that means when reviewers get these
13 reports, the majority of these reports have not yet
14 been published and so the populace will also not see
15 some of those reports unless that drug is approved.
16 So that just gives you an idea that not everyone is
17 seeing the same data.
18 A few more conclusions that we can draw
19 is that both neutropenic and immunocompetent animals
20 were used in the models and that studies with the
21 neutropenic mice inoculated intranasally were the most
22 common. And in general, mice were utilized for the

1 short-term studies, so less than 48 hours, so that
2 corresponds to about 24 hours of treatment and larger
3 animals for the longer term studies, so the greater
4 than 48 hours, and then also bacterial load is the
5 most popular endpoint.
6 I.d like to acknowledge by colleagues
7 here at the FDA and the ORISE Institute for my funding
8 and I have two minutes for questions if there...
9 DR. JOHN FARLEY: Any questions from
10 the panel?
11 DR. URSULA WAACK: All right.
12 DR. JOHN FARLEY: So I think two of the
13 things that we could probably talk about as we hear
14 from presenters down -- the rest of the morning is,
15 you know, I think -- I do want to thank Dave Schlaze
16 for actually suggesting a critical tweak to this
17 project that I think produced at least some
18 interesting observations for sure.
19 The one thing that.s apparent to me is
20 that the models that support the development of the
21 drugs that ultimately getting approved, those models
22 don.t get published and I think that that.s something

1 we can -- that companies can be thinking about because
2 getting those out into peer-reviewed publications
3 early, I think, would be in the public good.
4 And I think the other piece that we can
5 talk about down the road is efforts toward harmonizing
6 these models, not just from sort of a reviewer
7 perspective, but from an ability to kind of look at
8 your molecule and compare it to others, perhaps, that
9 are either already developed or in development as
10 well. So just some things to think about. Any other
11 thoughts from the panel before we move on?
12 WILLIAM WEISS: I get a little worried
13 about harmonization. If you look at these models,
14 neutropenic versus non-neutropenic, a lot of that is
15 dictated by the strain themselves, in particular the
16 endpoints also. Klebsiella and pseudomonas are easy
17 to get a survival endpoint as well as CFU.
18 Acinetobacter is a bit of an issue for that, getting a
19 CFU endpoint. Harmonizing for ATCC strains, I know
20 that.s been discussed before.
21 If we.re looking to treat multidrug
22 resistance, I mean, that really is what you want to be

1 looking at, and this day and age, I mean, we work with
2 a lot of companies that have basically no funding to
3 look at just ATCC strains, you go right for the
4 multidrug resistant strains.
5 Animals, again, a lot of companies need
6 to work with larger animals. A lot of that is
7 dictated by their formulations, their solubilities of
8 their test articles. I think it.s going to be very
9 hard to do that across labs. I don.t know the
10 mechanism, how we could actually do that because
11 there.s just so much variability in this business.
12 DR. BRADLEY SPELLBERG: John, could I -
13 - I was going to reserve comments until the panel
14 discussion, but since you raised the issue, when we
15 first moved into Acinetobacter research, I was kind of
16 shocked by the limited state of knowledge of actual
17 virulence factors and actual pathogenesis, and one of
18 the crippling aspects of acineto specifically, I think
19 less so pseudomonas, is the reliance upon strains that
20 are essentially nonvirulent, the reliance upon use of
21 microbiological endpoints that cause no physiological
22 significance in mice, and in order to get relevant

1 physiological clinical endpoints, you have to cripple
2 the immune systems of the mice in a way that is not
3 relevant to the vast majority of patients who develop
4 these infections.
5 So I would reiterate, actually, your
6 statement, John. There needs to be, if we.re going to
7 advance understanding at a molecular, basic level that
8 is relevant to patients, we need to be using models
9 that mimic the clinical environment and not simply
10 rely on, well, I.m going to drop the CFUs and -- by a
11 log or two in 24 hours in mice that have normal pH,
12 don.t experience leukocytosis, don.t experience
13 illness behavior, and have no physiological or
14 clinical signs or symptoms of infection, and aren.t
15 crippled immunologically in a way that is distinct
16 from how 90 percent of patients who get the infections
17 are.
18 DR. JOHN FARLEY: Great. And we.ll be
19 hearing -- I.m sorry, go ahead Jurgen.
20 DR. JURGEN BULITTA: It.s a similar --
21 for your analysis, did you see any trend towards,
22 perhaps, better behaved drugs, like if you.re do a new

1 cephalosporin or a new quinolone, to be used
2 predominantly in the mouse model and perhaps the
3 peptide antibiotics or new mechanism of action drugs,
4 leveraging some the more advanced, larger animal
5 species? Any trend like this in your database?
6 DR. URSULA WAACK: So you.re asking if,
7 in the mouse, if there were for newer ones and the
8 larger for...
9 DR. JURGEN BULITTA: I did -- was there
10 any trend towards one drug class being more or less
11 used in different elements, because you really want to
12 look at more, whatever toxicity, perhaps, for peptide
13 antibiotics in the kidneys, so which...
14 DR. URSULA WAACK: No we looked at a
15 lot of variables. One of them was class and then the
16 bacterial load. A lot of variables I didn.t point
17 out, so we didn.t see a trend, so -- and we aren.t
18 suggesting that there.s going to be one model for
19 everything. There might be something specifically for
20 Acinetobacter, something specifically for pseudomonas,
21 but if you.re trying to compare two drugs and they.re
22 essentially treating the same bacterial species on the

1 same time, there.s still a lot of variability even
2 across that, so it.s kind of hard to compare. And we
3 don.t know what the best model is going to be. We
4 don.t have any data that says, using black 6 mice is
5 better than using BALB/c mice or anything like that.
6 DR. JOHN FARLEY: Great. Thanks. I.m
7 going to go ahead and move on to our next speaker, so
8 that.s Abhay Joshi. Dr. Joshi is a -- in our Office
9 of Clinical Pharmacology and is -- I had the pleasure
10 of working with him serving both divisions in the
11 Office of Infectious Diseases as well as working
12 providing subject matter expertise for us on a number
13 of these animal model contracts. So he.s got some
14 kind of global observation to get started with and get
15 people thinking and he.s going to talk about the PK
16 considerations in animal models for antibacterial drug
17 development.
18 DR. ABHAY JOSHI: Thank you, Dr.
19 Farley. This is my disclaimer for my talk. So the
20 objective and scope of today.s talk is to discuss
21 pharmacokinetic consideration -- still closer? Is it
22 better? Okay. So objective and scope of my talk is

1 to discuss pharmacokinetic considerations for animal
2 infection model experiments that are conducted during
3 the late stages of antibacterial drug development.
4 For the purposes of my talk, late stage
5 is defined as at or after the point in a drug
6 development program when a dosage regimen for clinical
7 efficacy study has been determined. So the potential
8 value of conducting animal model experiment in late
9 stages is that it allows you to compare or screen
10 activity of a drug under development against hard to
11 treat pathogens which are not always being used during
12 the early stages of drug development. And for this
13 late stages, the key consideration is what dosing is
14 being evaluated in these animal model experiments.
15 So based on the literature and
16 experiences we have with this type of models, there
17 are mainly two types of approaches that are used to
18 select a dosing regimen. One is based on bacterial
19 killing and the second is based on drug exposure. So
20 first, based on bacterial killing or Approach A, our
21 dosing is selected for animal infection model that
22 will give the same extent of bacterial killing

1 expected in human in a patient who receives the
2 clinical dosage regimen.
3 And this is achieved by giving -- by
4 matching or exceeding the PKPD targets, known PKPD
5 targets for drug, or selecting a dosing that would
6 give drug concentration time profile that will achieve
7 desirable bacterial killing. So it.s -- the dosing is
8 given to match the bacterial killing, not necessarily
9 the same extent of drug exposure. In the Approach B,
10 based on drug exposures, a dosing is selected in
11 animal model which would give three drug exposures in
12 a selected animal infection model that is comparable
13 to exposure we might see in a patient who receive a
14 clinical dosage regimen. For the purposes of my talk,
15 I will call this approach as a humanized dosing.
16 For late stages animal model
17 experiments, it appears that humanized dosing is a
18 preferred approach because it is a more comprehensive
19 approach than both of those approach. The rationale
20 is that it avoids any uncertainties associated with
21 the use of PKPD target estimates and also it mimics
22 the overall drug exposure cycles anticipated in

1 humans, so by that, if a novel drug has any known or
2 unknown mechanistic or dynamic relationship with
3 bacterial killing, this approach would still cover
4 that scenario.
5 Now, there are differences in drug
6 elimination rate between animal and human, and mostly
7 the drug gets cleared faster than animal models, so
8 it.s little bit challenging to come up with the dosing
9 strategy that would give us humanized dosing. The
10 potential dosing strategy that can be considered is a
11 staggered continuous infusion and/or intermittent
12 dosing. In next few slides, I will go over briefly
13 about these approaches and give one example how it
14 might look like in animal infection models.
15 To start with staggered continuous
16 infusion, the figure here on the left provides an
17 hypothetical example how a humanized dosing would look
18 like from staggered continuous infusion. The Y axis
19 represents the free drug concentrations. X axis
20 represents the clinical dosing interval in time. The
21 black lines represents the free drug concentration
22 range anticipated in human from a clinical dosage

1 regimen and the red line represents the drug
2 concentration in animal model from humanized dosing
3 using continuous infusion.
4 There are advantages and disadvantages
5 of this approach. Advantage is that it provides
6 flexible dosing options and it provides more
7 opportunity to match the human-equivalent drug
8 exposures. However, disadvantage is that infusion may
9 not be suitable throughout for all animal infection
10 models, and also, it requires relatively complex
11 experiment setup and dosing calculations.
12 So I.ll give one example of meropenem.
13 Figure on the left shows unpublished data which --
14 preliminary data of ongoing work in ventilator-
15 associated pneumonia rabbit model. Again, same, Y
16 axis is meropenem concentration and X axis is time.
17 The line in green represents concentrate -- meropenem
18 concentration in rat patients receiving 2 gram dose
19 every eight hours via three-hour infusion.
20 And on the red line represents the
21 meropenem concentration data in a rat -- uninfected
22 rabbit model. So the researchers reached to this

1 humanized dosing after multiple PK experiments which
2 informed how to achieve humanized dosing with
3 staggered continuous infusion and it used a complex
4 experiment setup using programmable infusion pumps.
5 You will hear more specific details
6 about this example in future -- in afternoon
7 presentation or in -- during the panel discussion.
8 The second approach via intermittent dosing is a
9 hypothetical example on the left in the figure. The
10 red line represents the three drug concentrations when
11 multiple IV bolus or subcutaneous dosing is given over
12 the time interval. The advantage of this strategy is
13 that it.s related to the simple experiment setup, it.s
14 feasible for most type of animal models.
15 However, disadvantage is that this
16 strategy might not always possible to get the
17 humanized exposure. It depends on the drug properties
18 and it provides relatively coarse drug concentration
19 time profile and because it uses multiple doing, there
20 might be high peak of variability.
21 So if you look at example for the
22 intermittent dosing, figure on the left represents

1 data from murine pneumonia model, the line, blue,
2 black, and purple, represents the drug concentration
3 from a -- in critically ill patients who receives 2
4 gram meropenem dose every eight hours via 30-minutes
5 infusion and the green line represents that dosing --
6 drug exposures in animal model when we use
7 intermittent dosing.
8 You will hear more details about this
9 example as well as the other drugs in the morning
10 session presentation. It should be noted that for
11 this example, the level of refinement dependent on how
12 many doses you can administer in a day and there are
13 additional experiments are still being considered to
14 see if meropenem clearance can be slowed down with
15 cilastatin or probenecid so then it is more comparable
16 to human exposures.
17 So regardless of what dosing strategy
18 is being used, the key component is to match the human
19 exposure. And for that, it is critical to have
20 confidence in a drug exposure estimates that.s coming
21 out of this animal model. And for that, it is
22 important to perform supportive assessments. This

1 supportive assessment should include bioanalytical
2 method of validation for all the relevant matrices,
3 such as determining assessment of sensitivity,
4 selectivity, accuracy, precision, as well as sample
5 stability.
6 Also, since we are attempting to match
7 three drug exposures, it is important to have protein
8 binding information for both in animal and in humans.
9 And since these are late stages of -- late-stage
10 experiments, it.s preferred that for both
11 bioanalytical methods and protein binding methods uses
12 the same methods that are used for clinical studies.
13 Also, to determine humanized dosing, some prior dose
14 ranging peak experiments would be needed.
15 And also, it is preferred that
16 confirmatory peak assessments are done in the selected
17 animal model so that it gives the confidence that
18 indeed, humanized exposures were achieved. So I would
19 like to summarize by saying that the humanized dosing
20 appears advantageous to select for late-stage of
21 animal infection model experiments and it is important
22 to perform thorough supportive PK assessments.

1 Due to time constraints, I won.t be
2 able to discuss all the PK considerations, but we are
3 hoping to discuss this topic as well as additional
4 topics such as drug exposure at site of infection and
5 are there any disadvantages of humanized dosing in
6 addition to logistics and feasibility issues in
7 certain situations during -- we are hoping to get
8 feedback during the panel discussion and as we move
9 along with workshop.
10 With that, I would like to thank all
11 the individuals who have contributed on this topic as
12 well as attendees for their time and constant
13 attention. Thank you.
14 DR. JOHN FARLEY: Great, thanks very
15 much. I think I.m going to postpone panel discussion
16 until we.ve got to sink our teeth into a little bit
17 more data and talk further. So thanks very much for
18 laying that groundwork. I think next up we have Dr.
19 Judy Hewitt who has worked in this field for quite a
20 long time. She.s currently deputy director of the
21 Office of Biodefense Research, Resources, and
22 Translational Resources at NIAID and she.s going to

1 tell us about preclinical services at NIAID.
2 DR. JUDITH HEWITT: Thanks, John. I
3 appreciate the opportunity to be here. It.s been nice
4 to collaborate with FDA and BARDA over the years on
5 these models, so we.re happy to participate again. I
6 also have no conflicts as a federal employee.
7 So this slide is taken from the NIAID
8 website. Really just kind of tells you what our
9 mission is to lead research to understand, treat, and
10 prevent infectious immunologic and allergic diseases
11 and so this topic really plays into that very nicely.
12 We are really more in the early research stages and I
13 will show you that in the next slide where I.m showing
14 all of the various funding mechanisms that we use to
15 support these areas of research.
16 Our real goal is to reduce product
17 development risk and so in the background you have the
18 typical drug development pipeline. Across the top in
19 the orange box, I have grants shown and these go
20 everywhere from hit to lead basic research all the way
21 through Phase 1. That really should be a series of
22 orange boxes, because there.s not one grant that.s

1 going to get you the whole way, but we do fund some
2 clinical research through the grant mechanism.
3 We also have product development
4 contracts through -- which we award through broad
5 agency announcements or BAAs, and that.s where we.re
6 giving the sponsor money to directly support their
7 development of their own product. I.m going to spend
8 a little more time -- and we have one on the street
9 right now and the applications are due April 9th. I.m
10 going to spend a little bit more time talking about
11 preclinical services, but I do also want to mention
12 that we have some Phase 1 capabilities, so all of
13 these green boxes are contracts, and so they.re -- you
14 know, we.re giving money to accomplish a particular
15 task and get some return on that, some deliverables
16 back to the government.
17 This Phase 1 VTU, IDCRC, ARLG box
18 really describes all of our clinical activities. The
19 ARLG being the Antimicrobial Resistance Leadership
20 Group and we have some NIAID folks here representing
21 that group as well. I also want to mention the
22 Concept Acceleration Program where we are mining our

1 grant portfolio, looking for promising new concepts
2 and trying to move them forward, whether it.s through
3 preclinical services or helping them to get additional
4 data so that they can move further along, perhaps get
5 a grant or a contract.
6 And of course, then the goal is to, you
7 know, this dotted line is sort of the end of the
8 pipeline that NIAID can fund, and the goal is really
9 to pass things over that hurdle to BARDA, back to
10 industry, whoever the advanced development partner may
11 be. So what do our preclinical services provide?
12 I.ll show you in more detail what the preclinical
13 services are on the next slide, but here, I.m showing
14 you some of the features of it.
15 So the first one is that we.re lowering
16 risk with our activities. We have a lot of expertise
17 and capability within our office and our division
18 based on experience through these grants and
19 contracts, and so we want to bring that expertise and
20 capability to support others as they.re developing
21 their products. As I mentioned before, we want to
22 move promising discoveries along the drug development

1 pipeline through our Concept Acceleration Program.
2 These preclinical services are intended
3 to be gap filling. They.re not intended to provide a
4 full development program. We want to get you a data
5 package that will help you in your next grant or
6 contract application. And of course, before we
7 provide these preclinical services, we sign an
8 agreement with you called a Nonclinical Evaluation
9 Agreement where we.re assuring you that you will
10 retain all the intellectual property and
11 confidentiality. We discuss publication rights and
12 things like that, so that.s all part of that
13 agreement.
14 So this slide shows the preclinical
15 services in a nutshell that we provide. We do this
16 for both therapeutic and vaccines. I.m going to
17 focus, really, on the therapeutic side which is the
18 blue circle on the left here. So we provide in vitro
19 screening, medicinal chemistry, lead identification,
20 and lead optimization, chemical synthesis and process
21 development, in vitro admit, and really this
22 pharmacokinetics should be its own separate bullet

1 because that also includes in vivo activities as well.
2 And then this center bullet or group
3 here are services that are really common to vaccine
4 and therapeutic development, so things like reagents.
5 We develop and distribute those through our BEI
6 Resources Repository. I.m going to show you that in a
7 moment. We do a lot of animal model development and
8 you.re going to hear quite a bit about that in this --
9 in the course of today.
10 We can also perform in vivo screening
11 and efficacy testing so the in vivo screening, really
12 being more proof of concept data, the efficacy testing
13 being more under GLP conditions. We do product
14 development planning, so many of the early promising
15 discoveries that are coming out of academic labs,
16 investigators don.t always have all of the knowledge
17 they need to get something into the product
18 development pipeline, and so we can help them with
19 planning how they can get -- move their activities
20 forward.
21 Safety and toxicology testing. Often,
22 we find that this is a critical missing element in

1 somebody being able to move their package forward, and
2 we.re happy to provide that. And, of course, we can
3 do manufacturing including, under GMP, we can do lot
4 release testing audits and CMC documentation.
5 So we.ve done a lot of work, in
6 particular at the -- as I mentioned, at the early end
7 of screening new candidate therapeutics, and so we.ve
8 worked on a lot of animal models of bacterial
9 infections and this slide at sort of high level
10 summarizes the animal models that we have available
11 for testing candidate therapeutics, and so these
12 little icons on the left here indicate whether it.s a
13 mouse or a hamster.
14 So for the escape pathogens, we have
15 quite a few animal models available. We have the 24-
16 hour thigh and lung infection and this is for all
17 escape pathogens and we are very much committed to
18 trying to use strains that are available to everyone.
19 We.re using the FDA/CDC strains. One thing of note
20 that we.ve done through some of these is we.ve done
21 some PKPD baselining in the thigh infection model and
22 so we have data on ceftazidime, levo, and colistin and

1 we can make that available.
2 We.re in the process of trying to get
3 that information publicly available, but I.ll come
4 back to how you can access that data at the end. We
5 have peritonitis models, also ascending UTI, and in
6 parenthesis, for all of these I.m showing you the
7 pathogens that we have available. A 120-hour lung
8 infection for pseudomonas. Chronic lung infections
9 for models representing CF using pseudomonas and
10 Staph. aureus, and chronic infections in CF.
11 Also Neisseria gonorrhoeae infections
12 and C. difficile. These are also important, maybe not
13 the focus of all the talks today, but they.re
14 important in antimicrobial resistant pathogens for us.
15 So this slide is our BEI Resources Repository website
16 and so you see this graphic when you get to the
17 website. There are a couple that scroll through that
18 are recent highlights, and so this one in particular
19 is that we now provide through this resource a
20 pseudomonas collection.
21 This was developed by Rare and so we.re
22 making that available through BEI Resources. It.s

1 really important that we make all of these strains
2 available to the research community and this is
3 another -- let me back up. There.s one other thing I
4 want to point out here. We also have links here to
5 the Antimicrobial Resistance Leadership Group as well
6 as -- I.m not sure if I.m pointing to the right place
7 -- the FDA/CDC isolate. So when you go to our BEI
8 website, you can connect to all of these important
9 resources.
10 This is another screenshot within the
11 BEI Resources, and what I want to point out here is
12 when you go to the antimicrobial, there.s a search
13 function and so you can pick the bacterial species.
14 You can pick a drug and you can pick whether it is --
15 whether you.re looking for sensitive or resistant
16 strains, and so we.re making it very easy to go
17 through our vast catalog and find the strains that you
18 might be interested in particular.
19 So please, if you.re interested in
20 using that, please register for that resource. You
21 know, we.re finding that some people -- we.re also
22 distributing coronavirus through this and you have to

1 get through the registration process, which is not
2 onerous, but you need to do that before you can
3 actually order new materials.
4 So we.re also a participant in the
5 CARB-X program that you.re going to hear more about
6 today. This is a global public-private partnership.
7 There.s a lot of funding dedicated to this and you can
8 see across the top here all of the partners in this
9 program.
10 NIAID is providing in-kind resources,
11 so not direct money, to the CARB-X funded programs,
12 but through our preclinical services we are accessing
13 some of the preclinical services that I mentioned
14 before to help candidates progress through the
15 pipeline and so we.re using our expertise as well as
16 our money to move things along, so this is a summary
17 of the many, many projects that have been helped
18 through that program, but this next slide shows a
19 little bit more detail what our division has provided
20 in the way of support for a lot of the CARB-X
21 projects.
22 So we.ve supported 59 projects and that

1 includes six of the graduate programs. One thing that
2 we have learned is that prior to the CARB-X award,
3 many of the successful CARB-X programs had some
4 support from NIAID in the way of grants or our
5 preclinical services or even our product development
6 contracts through BAA, so 32 of those projects have
7 been helped by our services post-award -- so this is
8 post-CARB-X award -- we.ve supported 36 projects and
9 obviously there.s some overlap between these and we.ve
10 conducted more than 180 studies to move these CARB-X
11 projects along the pipeline.
12 So in my last slide here, I.m just
13 giving you come contact information if you want to
14 contact us about any of these preclinical services.
15 So your program officer in all likelihood is going to
16 be someone in our bacteriology and mycology branch,
17 potentially also our office. I mentioned that we.re
18 very much in favor of standardizing animal models,
19 harmonizing, making strains and reagents available.
20 And so Ann Eakin in our office, she.s
21 actually the concept accelerator for DMID for
22 therapeutics and so if I can get Ann to wave her hand,

1 she.s in the audience, and her email is
2 Ann.Eakin@NIH.gov. she is the one that can get you
3 information about the standardization of the models
4 that we have performed through many of these
5 preclinical services and I.m only giving this talk
6 because she was originally supposed to be in Italy
7 right now.
8 So please contact us. You can contact
9 us directly for any of these services. The people who
10 run those services will get you to the right person if
11 they.re not the one, so thank you for your attention.
12 DR. JOHN FARLEY: Thanks very much,
13 Judy, and we.ll have time during the panel discussion
14 if folks have further questions. So we.re going to
15 move on and hear about CARB-X from Dr. Guina who.s
16 currently the CARB-X program manager at BARDA, has
17 about 25 years of experience in infectious disease
18 research, so thanks very much, tina.
19 DR. TINA GUINA: All right, thank you
20 very much, John. Good morning. I want to thank our
21 FDA colleagues for putting together this workshop. I
22 have been working this space in industry, in academia,

1 in government for many years and I think these are
2 absolutely critical questions to be addressed. I
3 think they.re also very important for our innovators
4 who are companies and everybody else who is trying to
5 get funding by CARB-X portfolio and getting funding
6 from different government agencies.
7 The reason why we are presenting today
8 and talking about CARB-X is because it sort of
9 provides really nice snapshot of what our current
10 global efforts in development of new solutions for
11 therapies, vaccines, and diagnostics or that are
12 addressed in drug resistant bacterial infections.
13 CARB-X is a global nonprofit
14 partnership that was put together by U.S. government
15 in collaboration with Wellcome Trust and Boston
16 University in 2016 to address drug-resistant infection
17 with the understanding that the preclinical global
18 pipeline of antibiotics was really dwindling and many
19 different reports by governments, by Pure Trust and by
20 WHO and many other organization have shown that there
21 is a serious lack of innovation and considering the
22 increased -- continuous increase in resistance, it was

1 pretty clear that new solutions are needed.
2 Since 2018, we were very fortunate to
3 also have partners from U.K. government, German
4 government, and Bill and Melinda Gates Foundation join
5 our team. All funders and Boston University
6 contribute significantly to funding and also to
7 strategic vision of CARB-X, which is continuously
8 adapting depending, you know, on all the findings that
9 we together collaboratively, as colleagues and
10 organizations and sponsors, arrived to, based on our
11 studies, research, and product development challenges.
12 In addition to funders and Boston
13 University, we also joined by various global
14 accelerators that provide (inaudible) technical and
15 business support to CARB-X companies and, of course,
16 the most important component of this partnership are
17 our innovators and product developers and I.ll talk
18 about it little bit in full in slides.
19 So I mentioned CARB-X funds candidates
20 that address serious bacterial threats. Our current
21 strategy is that projects must address specific
22 bacterial infections that are on antibiotic resistant

1 threats list issued by the CDC or the Priority
2 Bacterial Pathogens List published by WHO which
3 actually overlap significantly. In terms of our
4 vaccine strategy recently, we have asked all
5 applicants to consider recommendations that are
6 provided in vaccines to Tackle Drug-Resistant
7 Infections Report by Wellcome Trust.
8 Our current portfolio includes
9 therapeutics, both traditional and nontraditional
10 approaches, preventives such as vaccines, microbiome
11 antibodies, and other and rapid diagnostics for
12 pathogen identification and antibacterial
13 susceptibility testing.
14 Therapeutics and preventatives are
15 funded from hit to lead stage through the first in
16 human clinical studies and diagnostics are funded at
17 the development stage of feasibility demonstration
18 through systems integration and testing just before
19 they commence clinical development.
20 As I mentioned previously, in addition
21 to funding CARB-X provides significant scientific,
22 regulatory, and business expertise and support. This

1 may not be so important for some more established
2 companies, but for some of our companies which are
3 literally virtual companies with maybe three medicinal
4 cabinets which have maybe 20, 30 years of experience
5 in drug development but they don.t have the know-how
6 in absolutely all aspects of product development.
7 This is very, very important aspect of CARB-X.
8 Depending on company needs and sort of
9 the potential regulatory and technical challenges for
10 their product development, CARB-X puts together
11 company support teams that includes representatives
12 from different global accelerators and also it is
13 really important to mention that they also pull in
14 many people from CARB-X Scientific Advisory Board,
15 some of which are people who worked in industry or in
16 academia on research in this space in animal models
17 for over 20 years.
18 Many of them have come back from
19 retirement because they.re very enthusiastic about
20 this program. They really want to help. They want to
21 make sure that we move forward as quickly, as
22 efficiently as possible and that we support our

1 innovators. So all these services are of no cost to
2 product developers and they.re sort of in-kind and all
3 of our companies, as Dr. Judy Hewitt mentioned, have
4 streamlined access to NIAID preclinical services, so
5 they benefit from CARB-X ecosystem.
6 There are also many seminars, webinars,
7 educational opportunities, and different conferences
8 where our CARB-X innovators can interact with all the
9 funders, with other members of CARB-X ecosystem and
10 also interact with each other, and we.re actually
11 improving that as we go along.
12 So this slide shows our portfolio as of
13 February 1st, 2020 and it includes both current
14 companies, current programs in the portfolio as well
15 as six programs that graduated, five of which have
16 actually completed first in human Phase 1 clinical
17 trials. As you can see, there has been really
18 excellent progress considering the fact that many of
19 these companies and many product developers are really
20 working on very innovative and very challenging
21 programs, so I really commend them for that.
22 We are excited to say that one

1 diagnostic program that graduated recently for CARB-X
2 Portfolio has received a contract award by BARDA for
3 advanced research and development, and we definitely
4 look forward to supporting more of our CARB-X
5 graduates. So what is in a CARB-X Portfolio?
6 Therapeutics, really, represent about
7 70 percent of our portfolio and because today.s
8 workshop is focused on therapeutics, I.ll talk a
9 little bit more about that. In terms of direct acting
10 therapeutics, vast majority of which are small
11 molecules, you can see that current portfolio
12 addresses various biosynthetic pathways and bacterial
13 cell including cell wall synthesis, DNA synthesis,
14 protein synthesis, and we have couple of really
15 interesting, very novel approaches to inhibiting fatty
16 acid biosynthesis, and there are a couple of others.
17 Several of these have very new
18 mechanism of action and when I talk about novel
19 mechanism of action, I.m talking about what is
20 currently available as approved drug and many of these
21 who actually are addressed in -- previously addressed
22 therapeutics and approved -- sorry, targets in

1 approved drugs, they actually are, in most cases,
2 target another site in same, and same with protein.
3 So there is a high level of innovation.
4 We are really very excited and proud to
5 say that almost one half of our current therapeutics
6 portfolio includes nontraditional therapeutics which -
7 - with very wide away of approaches to address
8 bacterial infections and create new therapeutic
9 solutions. These include antivirulence factors. For
10 example, here Antabio is working on an inhibitor of
11 pseudomonas toxin. Microbiotix is working on type 3
12 secretion inhibitor in pseudomonas. BioVersys is
13 working on Staph. aureus inhibitor virulence factors,
14 and (inaudible), our new member of portfolio, is
15 developing an antibody therapeutic that addresses
16 biofilm and other -- it's a broad spectrum bacterial
17 infection potential therapeutic.
18 Then we have several potential areas
19 which address membrane permeability, (inaudible) is
20 working on an inhibitor of bacterial reflux pump.
21 ContraFect has two products in our portfolio with
22 phage lysing and also broad-spectrum antibacterial

1 peptides. We have couple of other peptides and very
2 interesting amino acid polymer being developed by
3 Amicrobe and then several microbiome candidates.
4 In other category, we have interesting
5 immune therapeutics, antibodies that actually inhibit
6 certain aspects of bacterial surface and attachment to
7 the host and then several peptide nucleic acid fusion
8 candidates that either inhibit essential enzyme in
9 bacterial cell or potentially will inhibit virulence
10 regulators. So you can see that this level of
11 innovation is well beyond what we expected and what
12 our partners expected when we started this program, so
13 really excited to continue working with innovators and
14 help them the best we can.
15 So obviously, we.re coming back to the
16 aspect of talking about the animal models. They.re
17 absolutely essential tools for us to -- for all of our
18 innovators to establish the proof of concept in
19 product development, but also they.re really
20 increasingly used as our colleagues talked about this
21 morning, as tools to actually evaluate PKPD and
22 probability of target -- probability of target

1 attainment in clinical studies, so they.re
2 increasingly used even in the later stage development,
3 so CARB-X is committed to help innovators and
4 collaborate with all of you here in the room and more
5 broadly to establish best practices and guide
6 developers in utilizing these animal models to
7 mitigate development risk and to support their product
8 clinical pharmacology dossier.
9 So obviously, there are a number of
10 animal models that are of interest and indications
11 that may be challenging, so we.ve been talking a lot
12 today about pneumonia and that is definitely something
13 that.s very challenging to us. We also interested in
14 understanding how animal models can actually
15 contribute to MDR pathogen studies and our
16 understanding of efficacy in MDR pathogen area.
17 And then also we have number of
18 candidates that are nontraditionals and there are
19 spectrum indications in animal model efficacy and
20 animal models and PKPD studies can be really essential
21 to enhance the dossiers and hopefully provide
22 additional evidence then in support of efficacy plane.

1 Of course, this is just tip of the iceberg because we
2 have number of antivirulence candidates. I hope that
3 future workshops and discussions will talk about how,
4 actually, what are the critical studies to show that
5 these antivirulence candidates could be efficacious
6 and predict their clinical efficacies and what is the
7 regulatory pathway.
8 And CARB-X and many others in this room
9 are committed to evaluating different animal
10 nephrotoxicity model and their translation to clinic,
11 because they.re really important safety aspect for a
12 number of our therapeutic candidates, especially for
13 peptides.
14 So here.s some questions that our
15 colleagues for CARB-X R&D team have put forth here for
16 this audience and panel -- esteemed panelists to
17 consider. So obviously, we have -- we.re going to
18 discuss a lot today. What are the best models that
19 translate in vitro activity for direct and indirect
20 acting agents for Acinetobacter and pseudomonas
21 pneumonias? In addition to that, our questions are,
22 when we.re considering nontraditional agents, are the

1 best predicted models the same as those used for
2 direct acting agents?
3 I.m thrilled that actually here on the
4 panel we have several members and several developers
5 who are working on some of these nontraditional agents
6 and I look forward to hearing from them about their
7 experiences and hopefully we can have quite a robust
8 discussion on that. And for peptides and other
9 nontraditional agents that actually do have pretty
10 good broad spectrum activity but perhaps have higher
11 activity for pseudomonas and Acinetobacter, what is
12 the best demonstration of efficacy to justify in our
13 clinical focus?
14 And I don.t know if this workshop will
15 address that, but this is a continuous question and
16 it.s really important for developers who are working
17 in this really difficult space and trying to position
18 their products. So -- and I think, I believe that may
19 be a topic for some additional workshops in the
20 future, will be what are the best models to translate
21 in vitro activity for Neisseria gonorrhoeae
22 infections.

1 So in addition to CARB-X and efforts of
2 NIAID preclinical services, just wanted to say that
3 BARDA also has nonclinical development effort which
4 has been stood up primarily to support biodefense
5 indications in animal models that actually support
6 approval of drugs and vaccines for under animal rule;
7 however, several of our task partners and contracts
8 have also been awarded to support some work in this
9 space and Dr. Andrew Phipps will talking later today
10 about person model of ventilator-acquired bacterial
11 pneumonia caused by Pseudomonas aeruginosa.
12 And in the end, I want to acknowledge
13 all our partners, especially CARB-X R&D team and CARB-
14 X core at Boston University and again first -- and
15 really most importantly our product sponsors which
16 have dedicated significant resources, time, expertise,
17 and enthusiasm to working this pretty challenging
18 space. I want to thank also my colleagues at BARDA
19 and NIAID who are supporting antibacterial research
20 and development and have been excellent collaborators
21 and have been supporting the companies and CARB-X in
22 the past years. Thank you so much.

1 DR. JOHN FARLEY: Thanks. Thanks, both
2 Judy and Tina. Lots of important efforts to de-risk
3 development and work to enrich the pipeline. So at
4 this point, we.re going to take a 15-minute break.
5 We.re running just a teeny bit behind schedule and I
6 think what we.ll do is take a break and reconvene
7 right at 9:55. There.s coffee available -- for sale,
8 of course; this is the government -- outside. Thanks.
9 (Break)
10 DR. JOHN FARLEY: Great, and the
11 session, I.m going to turn over the session
12 chairmanship to Yuliya Yasinskaya who actually headed
13 for the FDA many of the reviews for animal models of
14 Yersinia pestis and Jennifer Hoover who is with us
15 from GSK. So thanks very much.
16 DR. YULIYA YASINSKAYA: All right.
17 Welcome to our Session 1 with the presentations of the
18 specific animal models and we.re actually going to be
19 discussing murine models in the first session and our
20 fist speaker is Lynn Miesel. Dr. Miesel leads the
21 infectious disease services for Pharmacology Discovery
22 Services, a preclinical CRO owned by Eurofins. She

1 serves as a PI on NIAID projects for developing rodent
2 infection models, PKPD analysis, and the NIAID
3 preclinical testing services. Lynn had worked on
4 antimicrobial drug discovery for over 20 years.
5 Welcome.
6 DR. LYNN MIESEL: Thank you very much.
7 So today, I.m going to present an ongoing project at
8 Pharmacology Discovery Services and this project is to
9 develop a murine model for pseudomonas lung infection
10 and it.s conducted with MDR clinical isolates.
11 So the Pharmacology Discovery Services
12 is conducting this project for NIAID and NIAID.s
13 overall mission is to facilitate and streamline the
14 discovery of therapeutics for Pseudomonas aeruginosa
15 and we all can appreciate the significance of this
16 mission. Pseudomonas is a leading pathogen for
17 hospital-acquired and ventilator-associated pneumonia,
18 and PDS is proud to support NIAID.s effort on related
19 projects to this mission and that includes conducting
20 testing services to evaluate therapeutic candidates,
21 developing mouse thigh and lung infection models with
22 MDR isolates.

1 And generating PKPD tutorials with
2 example studies of standard drugs and the protocols
3 and the example data from the model development and
4 PKPD studies are available to the drug discovery
5 community. So for the lung infection model, there.s
6 generally two types of models. There.s the bacterial
7 load model that many investigators use and there.s the
8 host survival models that are often used to evaluate
9 therapeutics.
10 And the goal of this pseudomonas lung
11 infection model that we.re trying to put in place is
12 to sort of make a hybrid of the two, and that is to
13 correlate the mortality from the onset of mortality
14 with the pathogen burden, the pathogen dissemination,
15 and the tissue pathology. And we.re striving to
16 optimize this model so that it has an extended
17 infection period, hopefully up to 48 hours. That.s
18 pretty challenging.
19 And then we.re also comparing infection
20 by intranasal and intratracheal routes of infection.
21 The studies are being conducted with MDR clinical
22 isolates that are available to the research community

1 and from the CDC and FDA AR bank. So our overall
2 approach involves use of persistently neutropenic
3 mice. We came to that as we were going along in this
4 project.
5 The development steps were first to
6 optimize the inoculum, then characterize the natural
7 history of infection, and then benchmark the models
8 with approved antibiotics. And I want to give credit
9 to the overall approach of this model and that.s to
10 Dr. Lawrenz and his team at University of Louisville.
11 We.re general -- following the general approach in
12 these studies.
13 Model development has been conducted
14 with two AR bank clinical isolates, AR0246 which is an
15 NDM1 producing strain and AR bank 0266 which does not
16 have a defined or characterized mechanism for
17 carbapenem resistance. Both strains are resistant to
18 carbipenems and AR bank 0246 is generally resistant to
19 most antibiotics with the exception of colistin. It.s
20 susceptible to colistin. AR bank 0266 is resistant to
21 carbipenems and ceftazidimes and cephalosporins but
22 it.s susceptible to many other drugs.

1 We.re going to focus on, in this
2 presentation on AR bank 0246. The AR bank 0266
3 studies are ongoing but we -- just for lack of time,
4 I.m not going to cover both. So the first step in
5 model development is optimization of the inoculum, and
6 this study was initially conducted with neutropenic
7 mice in which animals were rendered to neutropenic by
8 cyclophosphamide administration at day minus four
9 prior to infection and then day minus one. This is
10 the standard method for neutropenia.
11 Then animals were infected at day zero
12 by the intratracheal or by the intranasal inoculation
13 routes. Then animals were observed at six-hour
14 intervals for body temperature change and cage-front
15 check for health. So six-hour intervals from day --
16 time zero through the end of the study at day five.
17 Animals were sacrificed if they achieved at four
18 degree body temperature change or a 20 percent loss of
19 weight or were found moribund. The inoculum was
20 titrated. Yeah.
21 So three iterations of the inoculum
22 titration were conducted, because this was actually

1 kind of tricky to get it right. In the first round,
2 the inoculum was too high. The strains ended up being
3 rather virulent and so with the higher inoculums of 10
4 to the 5th to 10 to the 7th, all of the animals
5 succumbed to infection within -- before 18 hours. So
6 the second round of studies were conducted with an
7 inoculum ranging from 10 to the 5th to 10 to the 3rd
8 CFU per mouse.
9 Again, intratracheal and intranasal
10 routes of inoculation I.m showing here at you, the
11 intranasal inoculation routes. And so on the vertical
12 axis you have the body temperature and then as a
13 function of time. And animals that are below the four
14 degree temperature are -- have succumbed to the
15 infection -- zero degree temperature succumbed to
16 infection. Right.
17 So what you see is that the time of
18 mortality onset varies as a function of the inoculum
19 and the lower inoculum counts have longer animal
20 survival. We selected the 10 to the 3rd inoculum
21 count for model development because the other inoculum
22 counts resulted in earlier animals. mortalities were -

1 - which was not desired. There was the problem,
2 though, that about 30 percent of the animals survived
3 the infection and interestingly at sacrifice, the
4 bacteria were completely cleared from the lungs in
5 those animal groups.
6 So what we gathered from that is that
7 the animals -- the neutropenia lasts, persists for 48
8 hours, so what.s probably happening is that the immune
9 system is rebounding and then completely clearing the
10 infection. So we switched from the standard method
11 for inducing neutropenia to a persistent neutropenia
12 model in order to have the prolonged infection period.
13 We simplified the model. In these
14 studies that are presented in this slide, we used male
15 and female mice and we switched to using male mice
16 only for subsequent studies simply to minimize the
17 variability. Right, so upon optimizing the inoculum,
18 we then did a natural history of infection study
19 looking at a larger number of animals per group,
20 looking at animal survival out to five days after
21 infection, and then bacterial burden in tissues and
22 histopathology/pathology of the infected tissues.

1 Animal groups were added to the study
2 to look at earlier time points at four hours and 28
3 hours after infection, so these were scheduled
4 timepoints. And again, body temperature and body
5 weight were used for endpoints -- humane endpoints.
6 So this slide shows the animals. survival as a
7 function of hours and with intranasally inoculated
8 animals -- solid lines are for Study 1; dashed lines
9 are Study 2; purple is intranasal; and blue is
10 intratracheal.
11 There.s not a large difference between
12 the intranasally and intratracheally inoculated
13 animals. And the results are reasonably consistent
14 between the different days, but do note that there is
15 a rather broad span in the onset, of the time of onset
16 of mortality. And the median survival time is 46
17 hours for intranasal, 40 to 46 hours; 39 to 50 hours
18 for intratracheal inoculation.
19 All right. So this slide shows on the
20 top panels the bacterial burden at time points or at
21 sacrifice, so you see that this is time points, four
22 hours after infection, 20 hours after infection, or at

1 the humane endpoint when the animals succumb to an
2 infection. So you see that the bacterial counts in
3 lung tissue increase over time as expected, and that
4 the bacterial burden is very similar between the
5 intranasally and intratracheally inoculated animals.
6 The infection does disseminate to the
7 spleen and counts are observed at the 28-hour
8 timepoint. Substantial counts in spleen tissue are
9 observed at the humane sacrifice timepoints. The
10 histopathology also correlates with infection time;
11 although the histopathology score is generally very
12 low, below two, on a range from zero to five, and the
13 pathology scores are very similar between
14 intratracheally and intranasally inoculated animals.
15 Pathology also increases over time as -- that.s the
16 gross pathology, as expected in this model.
17 So then the next step was to benchmark
18 the models with a standard of drug. This is an MDR
19 pathogen and it.s the only drug that was -- the only
20 approved drug for susceptibility was colistin, so this
21 study was conducted with the persistently neutropenic
22 male mice that I just described. Inoculation was both

1 intratracheal and intranasally and animals were
2 infected at day zero. Colistin dosing was initiated
3 12 hours after infection and dosing was -- two dose
4 administrations were conducted at 12-hour intervals.
5 Again, time points were taken every six
6 hours for humane sacrifice. We also sacrificed
7 animals at baseline 12 hours of the first dose and
8 after 24 hours after the first dose, so 36 hours after
9 infection. The inoculation here is with 10 to the 3rd
10 CFU per mouse. And so there.s a few points on how did
11 we come to the dosing. So we dosed primarily with
12 colistin either at 30 milligrams per kilogram twice
13 daily or with a titration, and the colistin dosing was
14 based on published literature, both from the Roger
15 Nation.s Lab and then also in-house data.
16 The duration of colistin administration
17 was based on tolerability. We found that colistin --
18 we did a tolerability assessment and found that in
19 persistently neutropenic mouse, colistin was tolerated
20 up to 24 to 48 hours but not longer, so we limited our
21 dosing to 24-hour period. And then, the question was
22 well, how do we choose a time for dosage and we chose

1 -- when to start colistin dosing in that the time for
2 dosing was based on experimental data.
3 We did a study in which we varied the
4 time to dose by four hours, six hours, or 12 hours or
5 16 hours after infection and the only parameter that
6 was -- that was the only parameter that was varied.
7 The dosing period on the twice-daily dosing was the
8 same in all of the animal groups. And what we found
9 was that the baseline counts increased with -- between
10 the four, six, eight, and 12 and 18-hours dose --
11 baseline time points as expected and that colistin
12 resulted in a reduction in counts between baseline and
13 also relative to vehicle treatment up to 12 hours
14 after infection.
15 However, with 18 hours after infection,
16 colistin was no longer efficacious and so we presume
17 that it just -- after 18 hours is the point of no
18 return, that colistin cannot be efficacious, either
19 because the animals are too sick or because the drug
20 is -- because of an inoculum effect. All right.
21 So then with two colistin
22 administrations, one at 12 hours after infection and

1 one at 24 hours after infection, resulted in an
2 increase in animal survival compared to the vehicle,
3 which is in orange, results in an increase in survival
4 both with intranasally inoculated animals and
5 intratracheally. The 30 mg per kg dose group was
6 protested in both intranasal and intratracheal
7 inoculation. And this survival also correlated with
8 an increase in the mean survival time, as expected.
9 This slide.s a little harder to get
10 especially with the difficult pointer. So this slide
11 shows the bacterial counts following colistin
12 administration and I.m going to direct you here. This
13 is the baseline counts in black in the lung,
14 intranasal and intratracheal inoculation, baseline.
15 This is at 12 hours at the time of dosing. The
16 bacterial counts increase by two -- three logs
17 compared to baseline between -- at 36 hours after
18 infection.
19 And then colistin causes a very
20 significant reduction in counts at 30 milligrams per
21 kilogram. And in looking at counts at the humane
22 endpoint, the first one was initial -- the time point,

1 the selected time point. In looking at the animals at
2 humane endpoints, colistin does cause a reduction in
3 end counts; although, there is a broad spread. The
4 animals the succumbed to the infection generally had a
5 larger number of counts in lung tissue.
6 The colistin also reduced bacterial
7 dissemination to spleen. This is most notable at the
8 36-hour time point. There is some reduction;
9 although, it.s not significant and there is a very
10 broad spread in counts in spleen tissue. The general
11 observations are observed both with intranasally and
12 intratracheally administered infection routes.
13 So to compare, then, intranasally
14 inoculated and intratracheally inoculated animals, we
15 looked -- we pooled all of the data from the multiple
16 studies and found that general intranasal and
17 intratracheal inoculated very similar results, with
18 only significance found with the mean survival time
19 and very small difference, 42 hours versus 54 hours
20 for intratracheal to intranasal. And the
21 histopathology score, which is very low in general,
22 histopathology score of 1, is significantly larger for

1 intratracheally inoculated; although, again, the
2 effects are very small.
3 But overall, I would say that
4 intratracheally and intranasally inoculated animals in
5 these models under these experimental conditions are
6 similar. So to summarize, the body temperature
7 monitoring has really facilitated the correlation of
8 mortality onset with the pathogen burden, the pathogen
9 dissemination to other tissues, spleen, and the tissue
10 pathology.
11 This approach of frequently monitoring
12 the animals and sacrificing them at humane endpoints
13 prior to natural mortality enables the selection of
14 time points for dosing and sacrifice and it helps to
15 gather relevant data for, again, the tissue burden and
16 tissue pathology. The isolates that we.re working
17 with are very virulent in neutropenic mice.
18 The approved antibiotics, colistin in
19 this particular study, amikacin for the other strain
20 that we are working with, were efficacious and
21 intranasal and intratracheal inoculation results --
22 yield similar results. The general limitation of

1 these models, well one is that it seems to -- the
2 longer duration of infection with sacrificing animals
3 at the humane endpoints results in more data scatter.
4 In the colistin study, that.s expected
5 because the animals had a long period of time between
6 the last dose and the sacrifice. But in general,
7 there.s a bit more variability than we.re accustomed
8 to seeing in terms of the survival time and the
9 percent mortality. And we.re taking a close analysis
10 of this. Again, this is work that.s ongoing and so
11 far it.s acceptable but it is a lot more variability
12 than we.re accustomed to seeing.
13 So for next step and future directions,
14 I think it would be fantastic to be able to use these
15 types of models to ultimately correlate PKPD -- to
16 conduct PKPD analysis to be able to correlate drug
17 exposure with multiple treatment outcomes in mouse.
18 And I hope the community really seriously considers
19 this as a approach. The other future direction is to
20 establish this type of lung infection model with other
21 pathogens and other strains and to take this approach
22 with immune competent mice, perhaps considering an

1 assessment of different mouse lineages.
2 So I.m going to close, then, with
3 pointing out that there.s other drug -- other
4 resources for drug discovery at NIAID and these are a
5 list of the contracts that are ongoing and I want to
6 acknowledge the FDA, CDC AR bank for the strains and
7 funding from NIAID and the contributors at NIAID and
8 Pharmacology Discovery Services for these studies.
9 DR. YULIYA YASINSKAYA: Thank you,
10 Lynn. I think we.re going to continue on with the
11 presentation and we will have a panel discussion right
12 after. I think we.ll hold the questions to the
13 presenter to the panel discussion as well. So our
14 next presentation is going to be given by two
15 speakers. It.s going to be Dr. Brian Luna and Jurgen
16 Bulitta. Dr. Luna received his PhD from the Johns
17 Hopkins University School of Medicine. He.s currently
18 an assistant professor in Molecular Microbiology and
19 Immunology Department at University of Southern
20 California.
21 JENNIFER HOOVER: Dr. Bulitta is an
22 associate professor at the University of Florida

1 College of Pharmacy. He is supported by the
2 University of Florida.s Preeminence Program in drug
3 discovery and development and by the Perry E. Foote
4 Eminent Scholar Chair endowed professorship. Dr.
5 Bulitta has won NIH, FDA, and industry grants of over
6 $35 million, published 142 peer-reviewed papers, and
7 contributed to over 97 Phase 1 to Phase 4 clinical
8 trials since 1998, so thank you for your presentation.
9 DR. BRIAN LUNA: Thank you guys very
10 much for the introduction. We.re really happy to be
11 here and share on behalf of the group. I.d like to
12 start by saying that this is certainly a team effort
13 that we.re going to be talking about, so I just want
14 to acknowledge that this was an effort by a number of
15 different labs, and we.re happy to be sharing our
16 progress on behalf of everyone.
17 So we are trying to develop a mouse
18 model or characterize a mouse model for the study of
19 Acinetobacter infections. The reason that we decided
20 to go with a mouse model is historically it.s been
21 shown to be a very valuable tool for preclinical
22 studies, so that.s how we kind of decided to go

1 forward with the mouse in particular. The study
2 design for what we did was very similar to the last
3 presentation, so what we started with was a natural
4 history study. We then characterized the PK in
5 infected mice, so Jurgen is going to talk more about
6 that later.
7 And then the last outcome or the last
8 thing that we.re trying to do is to show therapeutic
9 success in these infected mice. So the basic idea is
10 we would infect mice. We would look at different
11 outcomes including clinical measures, so temperature,
12 activity scores, microbiological measures such as
13 CFUs, blood chemistry, and then cytokines as well.
14 The central hypothesis for our work is
15 if the mouse is going to actually be reflective of
16 therapeutic outcomes, what we can envision happening
17 is if we infect mice with a particular strain of
18 bacteria and we treat with a given antibiotic, so if
19 that mouse was infected with a bacteria that is
20 sensitive to that antibiotic, we should see
21 improvement of the mouse and treatment success.
22 However, if we infect with a particular

1 strain of bacteria that is resistant to that given
2 antibiotic, the antibiotic should not improve the
3 mouse and we should end up seeing treatment failure.
4 The antibiotics that we.re going to be looking at are
5 already FDA approved antibiotics, so again, this is
6 just characterizing that the outcomes that we received
7 in our mouse model should reflect what we would expect
8 from clinical outcomes.
9 So how does acineto cause disease?
10 What we.ve characterized thus far, the main virulence
11 mechanism seems to be the ability of acineto to escape
12 uptake and clearance by the host immune system.
13 Because the bacteria is able to escape clearance, it.s
14 able to continue to grow and to replicate. As it
15 replicates, it continues to shed LPS and causes a
16 massive amount of inflammation through an LPS TLR4
17 mediated signaling cascade.
18 So the first thing that we needed to do
19 was to identify what bacteria we.re actually going to
20 be using in the mouse model, so there.s a couple
21 criteria that these bacteria had to satisfy. So for
22 our efficacy studies, we.re going to look at three

1 drugs. We.re going to look at amikacin, meropenem,
2 and polymyxin B.
3 So our panel of isolates needed to be -
4 - to constitute a bacteria that are going to be both
5 sensitive to these antibiotics and also constitute
6 bacteria that are going to be resistant. The other
7 thing that we wanted to do with our mouse model is we
8 wanted to use an immune competent mouse model. So
9 additionally, the bacteria that we.re going to look at
10 have to be virulent and cause a lethal infection in
11 immune competent mice.
12 The strains that are asterisked and in
13 bold are the strains of bacteria that we ended up
14 going forward with. This is only a subset of the
15 strains that we characterized. The biggest hurdle was
16 trying to identify strains that were virulent in both
17 our IV bacteremia model and then also in our oral
18 aspiration pneumonia model, so we.re also going to
19 looking at two infection models here as well.
20 For the natural history part of the
21 study, we wanted to see how the mice responded to
22 infection by the different isolates and so this work

1 was published, I believe, last year in Plus One, so
2 what we generally see is a consistent -- a relatively
3 consistent response from the host regardless of which
4 strain of acineto we.re using for the infection. So
5 on the left is looking at our bacteremia model. On
6 the right is our oral aspiration pneumonia model. The
7 top two graphs are looking at body temperature and the
8 bottom two are looking at activity scores, so how
9 mobile and how active the mice are.
10 As I mentioned before, the disease
11 progression seems to be a LPS TLR4 mediated sepsis
12 kind of response. We have two models, our blood model
13 and our oral aspiration pneumonia model. It.s
14 important to point out that the disease response is
15 different in our two different models. So in our oral
16 aspiration pneumonia model -- so in both models, we
17 see a decrease in pH, so the mice are becoming
18 acidotic. In our oral aspiration pneumonia model, we
19 see increase in bicarbonate which is indicative of
20 respiratory failure, so it.s a good control for our
21 oral aspiration pneumonia model that they are actually
22 suffering from some sort of respiratory problem as

1 well.

2 So next, what I want to highlight is

3 the cytokines. So as described earlier, we.re

4 thinking that there.s this LPS TLR4 mediated

5 proinflammatory response. Regardless of which strain

6 is being used, we see an increase in our

7 proinflammatory cytokines, so TNF and IL6, again,

8 consistent across the different strains that we.re

9 using for infections. So for the specific isolates

10 that we.re using, those isolates are available upon

11 request. We.re also in the process of working to get

12 them deposited.

13 This slide needs to be updated. We.re

14 actually looking to deposit them to the BEI Repository

15 to make them easily and publicly accessible. In

16 regard to the trigger to treat criteria, so in our

17 model we are treating the mice two hours post

18 infection. That roughly correlated with decrease in

19 activity score. The activity score is more pronounced

20 -- is more consistently decreased in the oral

21 aspiration pneumonia model as compared to the blood

22 model, so there are some differences between.

1 There.s also the increase in the
2 proinflammatory cytokines at that time point as well.
3 And again, the overall goal of our study is to be able
4 to recapitulate what we think should be the expected
5 clinical outcomes, based on the sensitivity of the
6 strains used for infection. Okay, so who do we think
7 is -- this model.s going to be appropriate for? Who
8 do we think is actually going to be using it?
9 We think it.s going to be useful for
10 both academic and also for industry settings.
11 Currently, there is no well validated mouse model for
12 the study of therapeutics in acineto, so we think that
13 this model is going to be able to fill that niche.
14 Some important characteristics about our model is that
15 we are using immune competent mice, so there.s
16 definitely a lot of leg work that went into
17 identifying strains that are going to be able to cause
18 disease in immune competent mice, and that part
19 definitely is not trivial.
20 We.re also looking at humanizing the PK
21 regimens that are going to be used for amikacin,
22 meropenem, and polymyxin in acineto-infected mice and

1 Jurgen.s going to be talking about those specifics
2 more later. So what about the limitations? So one of
3 the obvious limitations is that mice are not humans.
4 As Brad Spellberg has pointed out in the past, very
5 few of the patients in his hospitals actually have
6 tails, so that.s just one way that our mouse model is
7 certainly a model.
8 That being said, there.s still a lot of
9 value that we think we can gain from this model and it
10 is still useful and important. Jurgen will talk a
11 little bit later about some of the PK issues in
12 particular and some of the hurdles in developing these
13 humanized dosing regimens.
14 Okay, lastly, I want to conclude with -
15 - the first part which is talking a little bit about
16 the efficacy. Again, as I mentioned, we.re infecting
17 mice with different strains of bacteria, so the
18 bacteria are going to be either, in this case, either
19 sensitive or resistant to amikacin. The mice are
20 being dosed with a humanized dosing regimen of
21 amikacin. Those details you.re going to -- we.ll
22 describe shortly. So if we look at the slides, the

1 top two panels up here are from mice that are infected
2 with our resistant -- are showing as resistant to
3 amikacin based on MICs.
4 The bottom two panels are mice that
5 were infected with a strain that is sensitive to
6 amikacin. So if we look at the top panel, at both the
7 four and 18 hours post-infection, we really don.t see
8 any decrease in CFUs in response to treatment. If we
9 look at the bottom two panels, we see a significant
10 decrease in CFUs in response to treatment at both four
11 and at the 18-hour time points.
12 So this is in our IV bacteremia model,
13 the clinical endpoints seem to be reflected by our
14 mouse model. So as I mentioned, we.re looking at two
15 infection models, so the next slide is looking at our
16 oral aspiration pneumonia model. The same kind of
17 outline as the previous slide, so the four panels on
18 the left are mice that were infected with our amikacin
19 resistant isolate. The four panels on the right are
20 the mice that were infected with our amikacin
21 sensitive isolate.
22 The top panels up here are CFUs in the

1 blood. The bottom two panels are CFUs in the bowel
2 fluid. For our resistant isolate, we really don.t see
3 much of a difference in the reduction of CFUs in
4 either the blood or the bowel compartments. On the
5 righthand side, we do see a significant reduction in
6 CFUs in both the blood and also the bowel compartment
7 in this model.
8 So again, in both our bacteremia and
9 our oral aspiration pneumonia model, the response to
10 amikacin seems to be predictive of what we would
11 expect based on the sensitivity. And with that, I.ll
12 turn it over to Jurgen.
13 DR. JURGEN BULITTA: Thank you so much,
14 Brian, for kicking this presentation of with all of
15 the efficacy part. So I.m going to talk about the
16 pharmacokinetic aspects. Now, this slide is a visual
17 predictive check for the single dose range study on
18 amikacin for the intravenous, so the bacteremia
19 challenge model with three different doses from 1.37
20 to 100 per gram. Please remember that this is a
21 destructive sampling mouse dataset, so you should not
22 look at this with the same eyes compared to a human

1 Phase 1 PK study with a quinolone or so.
2 So overall, we were quite happy. This
3 is the same dataset for the OA, so the oral aspiration
4 challenge model with the top half being the plasma
5 concentrations and the bottom half after three
6 different doses being the lung epithelial lung fluid
7 concentrations mentioned in Dr. Louie.s laboratory.
8 So here, it.s not perfect, but it was actually really
9 quite acceptable and we were overall happy.
10 The ELF penetration of amikacin was
11 relatively high, somewhere around 70 percent. Good.
12 Vis-þ-vis population PK parameter estimates, so we.re
13 using important sampling for estimating these
14 destructive sampling datasets and that is working very
15 well. On the middle of the slide, you see the
16 parameters for the IV model and on the right side, the
17 oral aspiration model. Okay.
18 So the clearance here after a single
19 dose was the same, but volume of distribution was
20 slightly larger for the intravenous dosing model
21 giving rise to slightly longer half-life of 48 minutes
22 for the IV compared to 36 minutes for the OA model.

1 Now, I would like to remind people that the ELF
2 penetration of aminoglycosides is actually not that
3 bad, 73 percent, and that would match Dr. Rosewald.s
4 review from a couple of years ago on ELF penetration
5 in patients.
6 So, so far, so good. Yes. Now, the
7 clinical concentrations of amikacin as one of the
8 clinical relevant aminoglycosides are depicted on this
9 slide for ventilator-associated bacterial pneumonia
10 patients on the left and critically ill patients on
11 the right. So this is for doses of a median of 20
12 milligrams per kilogram on the left side and 25
13 milligrams per kilogram on the right side.
14 So the significant variability and, of
15 course aminoglycosides, you would dose once daily in
16 humans, so your peak concentrations are somewhere
17 around 50 to 100 and your trough concentrations
18 between 5 and 10 in this patient population, and with
19 -- we use this guideline to humanize our humanize our
20 drug concentration regimens.
21 Apologies that the blue curve got
22 swallowed on the left side so we have to use the right

1 on the near-scape, so after -- this is for the
2 intravenous challenge model. We evaluated a couple of
3 different options and eventually settled on four times
4 daily dosing, so doses -- a large dose of 62 percent
5 at zero hours and 18 percent at six hours, 11 percent
6 at 12 hours, and 8 percent at 18 hours.
7 So this is why you see the four
8 different peaks here at the X axis. We could.ve gone
9 more complex to optimize the timing of the doses, but
10 we kept it relatively simple. And so the model
11 predicted area under the curve here is about 200 --
12 300 milligrams time hour divide by liter and this is
13 well within range of the clinical AUCs observed in
14 critically ill patients. Good.
15 This is the same dosing algorithm for
16 the OA method, so now you see plasma concentrations on
17 the left side and epithelial lining concentrations on
18 the right side, so we of course matched the plasma
19 against the plasma. We went for a slightly different
20 algorithm here with these percentages differing a
21 little bit. The criterion was we did not exceed with
22 the peak concentrations in mice the 90th percentile of

1 the human concentrations so this is why what you see
2 here is a little bit lower in plasma.
3 Had we gone for higher concentrations,
4 we would have had a better approximation, but then we
5 would have exceeded the human concentration profiles.
6 In the next slide, this is ELF concentrations in blue
7 versus plasma concentrations in pink and green. ELF
8 is a little bit delayed, but at least the peaks are
9 quite nicely in this range of human concentrations.
10 Good. Now comes, unfortunately, real
11 life. So on the left side, we have the IV challenge
12 models, so bacteremia model and for the first and
13 second dose the PK was quite similar to what we had
14 expected. You do see at later time points, with
15 concentrations in plasma increase, actually, despite
16 those doses being only about 11 and 8 percent here.
17 So what we attributed this to is a decrease -- a
18 systematic decrease in clearance and you.ll shortly
19 see also in volume of distribution during the later
20 parts of a dosing intervals where my post-doc mentor,
21 Dr. Alan Forest would.ve always said, sometimes you
22 have the highest concentrations of drugs in the mice

1 who die because we.re dead and when organs fail.
2 So in the first two dosing intervals,
3 the concentrations behave quite reasonably nicely, but
4 then later on you see a substantial variability. For
5 the oral aspiration model on the top here in plasma
6 and on the bottom in ELF, the same phenomenon also
7 occurs but the variability and the extent of the
8 change of PK over time is certainly much less.
9 Now, this is the individual curve
10 that.s pulled out from a population PK analysis. So
11 here, during the first and second dosing interval, the
12 concentrations are quite what you would expect, but
13 when during those later dosing intervals in order to
14 come up with a concentration of this around 120
15 milligrams per liter or so, at this time point, you
16 would.ve more or less have to have more or less no
17 clearance here at that time point and when, if you
18 look on logarithmic scale, one very nice thing when
19 you compare this slope here which is very, very steep,
20 it.s actually steeper in this initial slope when the
21 mice were probably not yet quite that sick or very
22 much affected by the infection.

1 You can see where you could argue these
2 possibly are hyperclearance mice. Now, there.s of
3 course a lot of research which still needs to go into
4 this but certainly very substantially increase in
5 animal variability of PK during the later dosing
6 intervals in this intravenous challenge model. On the
7 right side, it is the same profiles for the oral
8 aspiration. There, the variability is much less.
9 Clearance also changes, but this model is -- the mice
10 are a little bit less affected by the infection.
11 Now, of course, you may question
12 whether aminoglycoside may essentially cause
13 nephrotoxicity and that is the case, but you would not
14 expect that one to occur within 24 hours in a mouse
15 model. So if this happens, it would be later. Good.
16 So here are the population PK parameter
17 estimates for the IV model on the left and the OA
18 model on the right side. So clearance changes
19 systematically with dosing interval and also the
20 variability and clearance is dramatically high after
21 12 hours. The same thing happens to volume of
22 distribution for the IV model but not for the OA

1 model. And surprisingly to me, the ELF penetration
2 ratio was actually rock solid no matter what happened
3 to clearance.
4 So for the OA model, clearance also
5 decreased but the effect was much smaller compared to
6 the IV. So the conclusions here, we tried to target
7 the human-like concentrations in the mouse model to
8 simulate, not exceed the 90th percentile of plasma
9 concentrations in VABP patients. The AUC was in the
10 range of those experienced in humans and (inaudible)
11 for amikacin.
12 However, it became clear that during
13 the later dosing intervals, variability and -- was
14 higher and with clearance decreased over time.
15 Now, to polymyxin B. So here, a huge
16 credit goes to Dr. Arnold Louie and his LCMS
17 bioanalyst, (inaudible) who really measured all of the
18 four individual components of polymyxin B.
19 So the components, B1, B1 isoleucine,
20 B2, and B3, and then the last column on the right side
21 is the sum of all four. So this was very nice. Dr.
22 Luna performed the study at three different doses, 8,

1 12, and 16 milligrams per kilogram and that worked
2 very nice in collaboration and with discussions with
3 our FDA colleagues, we developed a population PK model
4 for mice with the four different components and
5 significant work has been done to corroborate this
6 model by additional analysis and that was greatly
7 appreciated.
8 So in essence, we fit all of those four
9 components and the sum of them simultaneously to come
10 up with a population PK model for destructive sampling
11 in mice. Suffice it to say, 20 years ago, nobody
12 would have done this because the estimation algorithm
13 were just not yet robust enough to do something like
14 this, in my opinion.
15 So this is a visual predictive check at
16 the 16 mg/kg dose level for the IV challenge model
17 where it.s perhaps not perfect, but all of the four
18 components were very reasonably captured and I would
19 like to point out that the half-life in mice is quite
20 long, so much longer -- so you would perhaps expect
21 the half-life in mice to be significantly shorter, but
22 here it is not incomparable compared to that in

1 humans.
2 The population PK parameter estimates
3 are here. One thing we get out is the relative
4 variabilities of those four components of polymyxin B
5 which was very nice. First component, B1, is a
6 predominant. B1 isoleucine and B2 are about 12 to 13
7 percent. And then B3 is the smallest abundance
8 component, so that worked very nice. I highlighted
9 here the clearance and I.m not showing the estimates
10 for the OA model, but it differed significantly
11 between IV and OA.
12 So then, we made two proposals to FDA
13 colleagues about humanizing polymyxin B dosage
14 regiments. One was zero hour and 12-hour dosing. The
15 other one had dosing every six hours. We eventually
16 settled on the twice-daily dosing, so zero and 12
17 hours for the IV model at 11 mg/kg and 10 mg/kg.
18 This is the observed PK data and the
19 visual predictive check for the IV challenge model for
20 polymyxin B components where you can see the predicted
21 PK -- human PK-like profiles were quite reasonably met
22 for the animals and the mathematical model is working.

1 On the bottom right, this is the clinically achieved
2 concentrations for total polymyxin B by Sandri, et al.
3 from a CID paper in 2013.
4 So we appreciate the variability in
5 patients so overall this validation was reasonably
6 successful in my opinion. So here -- so we came up
7 eventually with two humanized dosage regimen for
8 polymyxin B, 11 and 10 mg/kg for the IV model and
9 substantially lower doses of 7 and 6 mg/kg for the OA
10 model because it was very different between IV and OA,
11 about twofold.
12 So it seems here very important to take
13 home the lesson that one has to validate for PK in the
14 animal -- so with the bacterial pathogen and with the
15 bacterial strain which is used for the efficacy
16 studies. Since we saw consistently real differences
17 in the PK parameters and studying noninfected animals
18 probably would result in considerably different PK
19 compared to what one would get in an efficacy study.
20 Now, meropenem that Dr. Joshi very
21 kindly introduced this morning. Meropenem has a very
22 short half-life, both in humans but even more so in

1 mice. So we targeted the highest clinical dose of 2
2 grams every eight hours as a short-term infusion in
3 critically ill patients. And we tried to achieve peak
4 concentrations in mice between 60 and 100 in trough or
5 average concentrations of 1 to 10 milligram per liter.
6 Good. So these are the human profile
7 on the left on the near scale and on the right on
8 logarithmic scale for the median, the 10th, and the
9 90th percentile for short-term infusion in critically
10 ill patients.
11 Now, if you could dose 12 doses
12 individually in mice per day, so four doses per eight-
13 hour dosing interval, four times three is 12, be 50
14 milligram, 30, 18, and 11 mg/kg, you can reasonably
15 approximate, not perfectly, but you can reasonably
16 approximate the human PK profile in critically ill
17 patients.
18 Some (inaudible) will not let you do
19 because it.s too cumbersome or too invasive for the
20 mice, and I see a couple of nods in front of me, so,
21 yes. So it.s not perfect. This situation is
22 certainly much worse, where we only dose two

1 individual doses per eight-hour dosing interval for a
2 short half-life drug certainly puts us into a very
3 different spot when compared to amikacin and
4 polymyxin.
5 Now, in order to figure out what would
6 be the impact of doing one or the other, we simulated
7 the time of MIC of (inaudible) meropenem in plasma and
8 in ELF for different MIC values for four doses
9 individually per eight-hour dosing interval in two
10 doses and we predicted the highest MICs which could be
11 reasonably covered assuming the 20 and 40 percent peak
12 time of MIC targets for meropenem.
13 It.s not perfect, so we certainly would
14 love to explore cilastatin or probenecid as means to
15 prolong the renal elimination, so decrease renal
16 clearance and therefore prolong the half-life, both
17 with Dr. Luna and with Dr. Miesel. We discussed the
18 use of uranyl nitrate, which of course, Dr. Craig has
19 used abundantly. This will be challenging nowadays
20 because you may not be able to buy it and so this
21 challenges (inaudible).
22 So in summary, this is an immune

1 competent mouse model which Dr. Luna.s lab has
2 developed. We have humanized the pharmacokinetics of
3 amikacin and poly B and ongoing work is therefore
4 meropenem. The therapeutic outcomes for amikacin and
5 for polymyxin nicely reflect those which one would
6 expect for a susceptible and a resistant strain and we
7 would like to highlight that despite those drugs being
8 well behaved and very long on the market already,
9 there is unique challenges which one has to address
10 when humanizing dosing regimens.
11 Thank you very much for your attention
12 and this is a large team of collaborators.
13 DR. YULIYA YASINSKAYA: Thank you so
14 much, Brian and Jurgen. That.s excellent
15 presentation, lot of information there. Because we
16 are running kind of very late, we.re going to continue
17 with our presentations and again, we.ll take questions
18 to the presenters at the time of the panel discussion.
19 Our next presentation is also given by
20 two speakers. It.s about the murine model of testing
21 therapeutics against pulmonary pseudomonas infection
22 as presented by Matthew Lawrenz and Alexander Lepak.

1 Matt Lawrenz is associate professor in the Department
2 of Microbiology and Immunology and a member of Center
3 for Preventive Medicine in Biodefense and Emerging
4 Infectious Diseases at the University of Louisville.
5 His laboratory has extensive experience
6 using small animal models to study pathogenesis and in
7 the testing of vaccine candidates against plague.
8 Since 2013, he has worked with NIAID and the FDA on
9 the development and use of the clinical models for the
10 screening of the novel antimicrobials against
11 bacterial pathogens including MDR, Pseudomonas
12 aeruginosa.
13 JENNIFER HOOVER: Dr. Lepak is an
14 assistant professor at the University of Wisconsin in
15 the Department of Medicine, Division of Infectious
16 Diseases. He is an active physician, educator,
17 researcher, and leader within the UW Antimicrobial
18 Stewardship Group. His research pursuits are in
19 performing and translating murine animal models,
20 animal model antimicrobial pharmacodynamic studies to
21 optimize therapy against numerous pathogens. Thank
22 you for your presentation.

1 DR. MATTHEW LAWRENZ: All right. I
2 just want to start off by saying that everything that
3 I.m going to show you guys today is a collaborative
4 team work between three different universities, so
5 most of the hands-on animal work is performed at the
6 University of Louisville and that.s under the guidance
7 of myself and my collaborator, John Warawa. We.ve
8 been working on this project for a long time together.
9 And then we work with Dr. Lepak and Dr.
10 Andes at University of Wisconsin for some of our PKPD
11 studies. And finally, we have a team of statisticians
12 that we work with down the road from us at the
13 University of Kentucky and that group.s led by Arnie
14 Stromberg.
15 So what I.m going to tell you guys
16 about today is our efforts to validate a platform that
17 we hope will be useful for preclinical screening of
18 novel drugs against multidrug resistant pseudomonas.
19 This is funded through the FDA and we have two goals
20 in this validation process. The first was to take an
21 existing model that we developed with NIAID and
22 validate that against a panel of different pseudomonas

1 strains that we hope would represent some of the
2 potential isolates that might be seen in the clinic
3 downstream.
4 Our second goal was to develop a couple
5 of benchmark antibiotics that we could use in this
6 model and that.s where Dr. Lepak will come in and tell
7 us about the work that we.ve been doing on PKPD to try
8 to get towards a humanized dose on these benchmark
9 antibiotics.
10 So the model that I.m going to tell you
11 guys about today a transient neutropenic mouse model
12 for pulmonary infection. As this audience is well
13 aware, pseudomonas is really kind of an opportunistic
14 pathogen where we see most of the problems occur in
15 immunocompromised patients such as cystic fibrosis,
16 cancer, or in certain cases severe injuries, for
17 example, soldiers that we see in the battlefront.
18 Just like humans, mice are relatively
19 resistant to pulmonary infection with Pseudomonas
20 aeruginosa. It.s not that we can.t establish an
21 infection in these animals; it.s that it requires a
22 relatively high number of organisms to establish that

1 pulmonary infection and there.s complications that
2 come along with that in drug therapy that I.m happy to
3 talk about in the panel discussion that we.ve seen in
4 some of our previous work with immunocompetent models.
5 So to overcome this barrier, with NIAID
6 we developed this transient neutropenic model and Lynn
7 kind of introduced it a little bit at the beginning.
8 We induce neutropenia in these animals through
9 cyclophosphamide administration and I.m showing you
10 kind of the workflow here for that administration.
11 It.s two doses of cyclophosphamide and we administer
12 those five and one day before installation. You.re
13 not hearing me?
14 And what I.m trying to highlight on
15 this slide here on the righthand side is looking at
16 the number of circulating neutrophils in these animals
17 after this dosage, and we see on average about a 94
18 percent reduction, transient reduction, in these
19 neutrophils at the time of infection.
20 The other aspect that I want to point
21 out in this model is the mechanism that we use for
22 instilling the bacteria into the animals. We use a

1 method of intratracheal instillation where we actually
2 intubate the animals, so we put a catheter into the
3 animals and then we can instill the bacteria,
4 bypassing the upper respiratory tract, and instill it
5 directly into the lungs.
6 What I.m showing you here is in the
7 center is just to show you guys that when we use this
8 method and we instill a 5 microliter bolus of material
9 into the lungs -- in this case, it.s Evans blue and
10 you can see the distribution of that dye through all
11 the lobes of the lungs -- we get broad distribution
12 within the lungs.
13 And the other point that I want to make
14 that.s shown on the righthand side is that this is a
15 highly reproducible and efficient mechanism for
16 instillation of the bacteria. This is a graph that.s
17 just showing three different doses that were
18 administered to the animals on the X axis, and on the
19 Y axis is the number of organisms that were recovered
20 30 minutes post-installation. We see that we get
21 about 98 percent of the bacteria instilled directly
22 into the lungs and hopefully you can see that there

1 are three animals at each one of those doses and you
2 can see that this is highly reproducible.
3 An individual that.s trained in this
4 IMIT instillation procedure can, in our workflow,
5 instill this into an animal about one animal per
6 minute, so we can do a high number of animals through
7 this mechanism.
8 So as I said, the main goal that we had
9 with the FDA in this project was to take this existing
10 model that we had developed against a single strain of
11 pseudomonas, the CUNCD strain at the top of the table,
12 and apply this towards or validate it against a
13 variety of pathogens, pseudomonas pathogens, that,
14 again, we hope reflects what.s in the clinic. I.m
15 shoring you the organisms that we chose for this.
16 This came from the FDA/CDC resistance bank and we
17 chose these organisms for a couple different reasons.
18 One of them is they are multidrug
19 resistant, but they have different resistance profiles
20 to a couple antibiotics and those are the antibiotics
21 that we.re going to use as our benchmark antibiotics.
22 And secondly, we tried to choose strains that had

1 different known resistance mechanisms based on the
2 genomes of these organisms.
3 Now, the one problem with the FDA/CDC
4 panel is that while this is very good for in vitro
5 screening of antibiotics, there.s almost no data
6 available on the virulence of these isolates. So we
7 had to really start from the ground floor to establish
8 and validate these organisms.
9 So this is the workflow for our initial
10 studies and really all we.re doing here is to
11 determine the LD50 of these strains. Again, this is in
12 a neutropenic model. The strain that we.re using here
13 are BALB/c mice. We use male and female mice through
14 all of our studies, and I.ll tell you right now, we
15 see no sex bias in anything, so I.m not going to
16 discuss that later on. And in this case, it was just
17 a simple LD50 where we infected the animals with
18 escalating doses of each strain.
19 These are the survival curves for our
20 four strains, and there.s two points that I want to
21 make on this data. The first is that we see a
22 difference in the virulence of these organisms, so you

1 can see on the lefthand side the 230 and 231 strains
2 are highly virulent in this model where the LD50 is
3 less than 100 CFU by this installation model; 246
4 falls in an intermediate range, and then the 241
5 strain is actually fairly attenuated compared to the
6 others.
7 The other thing that I want to point
8 out here is that in this transient neutropenic model,
9 depending on the strains, we tend to see most of the
10 mice succumbing to the infection within 48 hours post-
11 infection. The other thing that we looked at during
12 these LD50 studies is we looked at the bacterial loads
13 within the lungs of these animals, and the only thing
14 I want to point out in this graph -- these graphs here
15 is that in the animals that succumb to disease, we see
16 proliferation of the bacteria.
17 So the black symbols are all the
18 animals that were euthanized during the course of the
19 infection and the red are the animals that made it out
20 seven days post-infection. So in general, what we see
21 is that we.re reaching somewhere around 10 to the 8th
22 bacteria in animals that meet moribund criteria.

1 So with that data in hand, then we
2 wanted to move and do a natural history study again to
3 allow us to have part of the model being to look at
4 the log reduction within the lungs as a parameter that
5 we could use for monitoring efficacy of drugs. So for
6 this natural history we chose a timespan of about 21
7 hours and that was based, again, on our LD50 at --
8 after 21 hours our animals begin to succumb to this
9 infection, and so for this type of study, if we stop
10 at 21 hours, we were confident that we.d have power in
11 our sample size to get good bacterial counts within
12 the lungs consistent, a large number of animals.
13 So in this case, what we.re using is
14 the same neutropenic model but we.re now instilling 10
15 times the LD50 or each of the strains, so each strain
16 has a different instillation based on its LD50. So
17 what I.m going to show you first is some of the
18 parameters that we look at in this model, so we
19 monitor temperature every eight hours on these animals
20 and what I want to highlight here is you can see now
21 the temperature of these animals over that 21-hour
22 period and you can see at least for the strains on the

1 righthand, the last three strains, that we start to
2 see drops in temperature with these animals and, in
3 fact, the 241 strain, those animals would be
4 euthanized based on this criteria.
5 Of course, the whole point here is to
6 determine the bacterial burden within the lungs so
7 that we can do, hopefully, log reduction analysis.
8 And so what I.m showing you here are the bacterial
9 burdens at three hours and 21 hours post-infection and
10 you can see at three hours, essentially what we have
11 there are the number of bacteria that we put in there.
12 If you look at 2:30, we put 1,000 bacteria in there;
13 we get about 1,000 bacteria at three hours post-
14 infection.
15 But importantly, what we see is
16 proliferation of all of these strains within the lungs
17 over that 21-hour period. On average, this is about a
18 two log increased numbers, so we think that gives us a
19 good dynamic range if we.re going to look at log
20 reduction in downstream applications.
21 The last thing that I want to show you
22 is pathology, so in the same animals we harvest tissue

1 and look at pathology within the lungs. And you can
2 see that at three hours post-infection, regardless of
3 the dose that we give these animals, we are not seeing
4 pathology yet within the lungs. But by 21 hours post-
5 infection, now, we.re beginning to see significant
6 increase in the development of inflammation and
7 pathology within those tissues.
8 So we can go back now and I can expand
9 on that table that we have and add the virulence data
10 to those strains. So again, I want to highlight that
11 we have a panel that represents different resistance
12 profiles and has different resistance mechanism. We
13 now know the LD50, the bacterial loads at those time
14 points, and also the pathology.
15 Now, one of the items that came up in
16 discussion with the FDA when we started generating
17 this data was this idea of trigger to treat, and we.ve
18 already kind of discussed this at panel today.
19 Trigger to treat, when we think about it in the
20 clinic, is usually going to be an individual with a
21 pulmonary infection where they.re going to show
22 symptoms, potentially of pneumonia, et cetera.

1 And hopefully it was obvious in the
2 data that I showed you that we don.t see pathology at
3 three hours post-installation. So the next step that
4 we.re going -- we.re moving forward with now on this
5 model is to see if we can see the development of
6 pathology at later time points and can use that then
7 as a potential for trigger to treat for this model.
8 And so when we get back to Louisville, we.re going to
9 begin looking at this and add in some time points, six
10 hours and 12 hours post-instillation, to see if we can
11 find those trigger to treat criteria.
12 All right, so I.m going to step away
13 now and I.ll let Alex come up and talk to you about
14 what we.re doing for our benchmark antibiotics.
15 DR. ALEXANDER LEPAK: Okay. So what
16 I.m going to talk to you about is aztreonam plasma
17 pharmacokinetics in the mice and you.ll probably
18 notice a lot of similarities with some of the
19 difficulties in modeling that we ran into in terms of
20 some of the earlier speakers today.
21 So here are the plasma pharmacokinetics
22 from infected mice. There.s four different doses

1 listed here and I think what.s important is, one, it.s
2 quite linear and quite dose proportional when you look
3 at the exposures, and secondly is that the half-life,
4 perhaps not surprising, is quite short. It varies
5 between 0.4 and 0.8 hours, depending on the dose.
6 So what does aztreonam look like in
7 humans? There are a variety of doses for which there
8 is published human pharmacokinetic data and that.s
9 shown in the table. Two grams q. eight hours is
10 perhaps the more often used clinical does and that is
11 shown in the lefthand side and what I.m showing you
12 here is the concentration time curves that you would
13 expect for total drug concentrations which are the
14 solid symbols and then free drug concentration. For
15 humans, the protein binding is approximately 50
16 percent.
17 So the challenge here is how do we pick
18 a dosing regimen that is meaningful? And by
19 meaningful, what I mean is we want to have a dosing
20 regimen that accomplishes the goals of the study, but
21 we also want to have dosing regimens and exposures
22 that are translatable as we think about the studies

1 from mice to humans. And so as you.ve heard multiple
2 times, matching PK concentration time curves and PKPD
3 exposures depends on a lot of moving parts.
4 It certainly depends on the
5 pharmacokinetics and specifically half-life often
6 plays a major role. It can depend on the MIC of the
7 organisms for which you.re treating. And then
8 finally, frequency of the drug administration can play
9 a major role. And so due to differences in
10 metabolism, which is extremely common and was noted in
11 this study where the half-life in mice was between 0.4
12 and 0.8 hours and the human half-life is about two
13 hours, it is impossible to exactly match the
14 concentration time curve.
15 When that happens, there are two major
16 approaches, so one approach, which is the approach we
17 used, and the approach that you saw Jurgen present
18 with meropenem in the previous discussion, is to
19 prioritize a dosing regimen in mice to mimic a human
20 dosing regimen based on what the PKPD driver is. And
21 so for aztreonam, that.s time above MIC.
22 Now, another way you can do it is that

1 you can try to match the shape of the curve using
2 complex dosing regimens, and you saw some of that
3 already today where you can vary the timing of the
4 dose so the interval is not necessarily consistent or
5 even vary initial dose and subsequent doses to try to
6 really mimic that concentration time curve. And this
7 is very challenging and within those challenges are
8 the risk for dosing errors and iatrogenic events to
9 the mice because you are dosing them so frequently.
10 And I think the real question, which
11 I.m sure we will get into when we have the panel is
12 this, how close is close enough? I mean, how close do
13 you really need to match these concentrations time
14 curves when you are looking at a mouse versus a human?
15 So here are two figures. We.ll start on the left.
16 So the aztreonam plasma concentration
17 is shown on the Y axis and time along the X axis, and
18 so for the meropenem -- sorry, for the aztreonam 2
19 gram IV q. eight hour dosing, that is the black
20 symbols and this is total drug concentration. And
21 then shown is the total drug concentration that you
22 would expect for the 320 mg/kg mouse dose or the 640

1 mg/kg mouse dose.
2 And so I.m sure you can appreciate on
3 the lefthand side total drug concentrations will be
4 much higher in the mice at these doses versus what the
5 human exposure is. However, when we take into account
6 protein binding, because protein binding is different
7 between mice and humans -- in the mouse, the protein
8 binding is estimated somewhere around 84 percent --
9 you can see that the two lowest doses that were
10 studied in the PK study, the 320 and 640, actually
11 bracket pretty nicely what the human free drug
12 exposure would be in terms of a Cmax.
13 But what we.re, obviously, really
14 interested here is what are the time above MICs that
15 we might see? And so this is a large table, so I.m
16 going to kind of walk you through it. The different
17 doses are in the first column. The dosing interval is
18 in the second column, and so we have dosing intervals
19 that vary from q. 4 hour, q. 6, q. 8, q. 12. And then
20 we are representing the free drug percent time above
21 MIC that you would expect to see against an organism
22 that had an MIC of 4, an organism that has an MIC of

1 32, and then a quite resistant organism that is
2 greater than 64.
3 And so for those that may not be aware,
4 the aztreonam PKPD targets are somewhere between 40
5 and 50 percent time above MIC for stasis, so you can
6 see highlighted in orange against the susceptible
7 strain you get a nice splay of time above MIC
8 exposures over all the different doses from 320 all
9 the way up to 2560. But to focus you a little more
10 what I included here on this slide is how well the q.
11 6 hours, 640 SUBQ matches the human time above MIC
12 above MIC exposure that you would expect for 2 grams
13 IV q. 8. And so for a susceptible organism, MIC of 4,
14 you would get 70 percent time above MIC in the mice.
15 For a human at the human exposure, it
16 would be close to 100 percent. For a moderately
17 resistant organism, you get a marginal time above MIC
18 somewhere between 30 and 40 percent for both the mouse
19 and the human. And then, obviously, for a very
20 resistant organism you.re going to get a very low free
21 drug time above MIC, close to zero percent.
22 And just shown here is to also

1 highlight that the Cmax will not be, in terms of free
2 drug, will not be all that different between the mouse
3 for the 640 dose and the human 2 gram dose. ELF
4 pharmacokinetic were carried out as well. I.m not
5 going to spend a lot of time on this, mostly because
6 in the published literature there is essentially no
7 human ELF pharmacokinetic data. So while we have some
8 ELF data here for mice, how that relates to humans is
9 really up in the air at this point.
10 It was much flatter. There were not as
11 high of peaks, but when you look at AUC exposures,
12 which is a common way to look at ELF penetration, it
13 was between 19 and 42 percent and that is consistent
14 with at least a few of the other murine aztreonam ELF
15 studies that are out there. And with that, I will
16 end.
17 DR. YULIYA YASINSKAYA: Thank you very
18 much. Thank you.
19 DR. JOHN FARLEY: Yuliya, let me just
20 jump in for one second --
21 DR. YULIYA YASINSKAYA: Sure.
22 DR. JOHN FARLEY: -- before you guys

1 take off. So we have had two folks who haven.t been
2 able to travel and that.s William Hope from University
3 of Liverpool and Tom Walsh from Cornell. They should
4 be on the phone and maybe we.ll check right now and
5 ask you to introduce yourselves. William, are you
6 there? How about Tom? They may be muted. You may
7 hear them jump into the panel discussions, because I
8 heard that they were listening in, so thanks very
9 much.
10 DR. YULIYA YASINSKAYA: Right. Well,
11 thank you very much, the presenters for the Session 1.
12 We had a very interesting presentation, a lot have
13 been done in recent years in terms of the development
14 and understanding of the murine models of lung
15 infection as well as the sepsis, so again, the
16 presentations were very data driven. There.s a lot of
17 information there. We understood that there are lots
18 of challenges in developing and understanding these
19 models, so I just want to make sure if the panel
20 member have any questions to the presenters, we have a
21 little bit of time to address those before we go on
22 into the panel discussion questions.

1 DR. BRADLEY SPELLBERG: I really
2 enjoyed the pseudomonas presentation and it seems like
3 you guys encountered many of the same issues that the
4 poor people who I work with encountered, the -- as
5 George calls them, the poor longsuffering people. You
6 do have two really virulent strains of pseudomonas and
7 I wonder if it would be worth looking at how those
8 strains perform in immune-normal mice.
9 DR. MATTHEW LAWRENZ: Yeah, I actually
10 wasn.t expecting them to be that virulent. Typically,
11 and I don.t remember if I said this in the talk or
12 now, when we go from, at least in the strains that
13 we.ve worked with before, from a immunocompetent to
14 the neutropenia, it.s about a three log difference in
15 infectious dose, so we still would be -- we.re going
16 to be up around 10 to the 5th, 10 to the 6th as an
17 estimate, but it might be worth running them through
18 to see if it.d be lower than that.
19 DR. BRADLEY SPELLBERG: Yeah, and I do
20 not know. In some ways, pseudomonas is a more complex
21 pathogen that Acinetobacter is. Acineto is an
22 accidental pathogen. It.s an environmental organism

1 and it really doesn.t, in my opinion, utilize things
2 like invasings and adhesings and extracellular toxins
3 like many other pathogens do.
4 If it is true as for pseudomonas -- as
5 for acineto in your pseudomonas hypervirulent strains,
6 a very small percentage of the -- we.ve put more than
7 100 Acinetobacter clinical isolates in the mice. A
8 very small percentage are hypervirulent. They differ
9 in their ability to avoid immune clearance and if that
10 is the mechanism of hypervirulence for pseudomonas,
11 you might actually find that it.s not a 3 log
12 difference. I might be a smaller increase.
13 DR. YULIYA YASINSKAYA: Any more
14 questions? Lynn, you had a comment on the previous
15 question? No?
16 DR. LYNN MIESEL: No...
17 DR. YULIYA YASINSKAYA: Okay. All
18 right, so we.ll go on into the panel discussion
19 questions then. So again, you had heard a lot of very
20 interesting data and a lot of challenges that murine
21 model of gram-negative infections pose to the drug
22 development as well, so we would like to discuss or

1 for you to discuss what do you think about the
2 perspective on the utility of the murine models of --
3 in the anti-infective drug development and what the
4 challenges and successes that we have in the
5 development of those models.
6 DR. BRADLEY SPELLBERG: They.re good.
7 JENNIFER HOOVER: Maybe I.ll start with
8 a comment. Jen Hoover from GSK. So in industry, you
9 know, we.re always trying to make sure that we are
10 developing packages of data that are acceptable for
11 regulatory submission, break points, et cetera, et
12 cetera. And I had, before today, at least, felt that
13 we were fairly well served in terms of just straight-
14 up pneumonia models for evaluating PKPD, for example.
15 But I hear a lot of the work going on
16 around there and just from the presentations we.ve
17 heard today, it look like there are quite a few
18 differences between what folks are looking at and so
19 I.m left sitting here a little bit going -- scratching
20 my head, what.s a sponsor to do. So if you guys could
21 maybe give some feedback on that, that would be great.
22 DR. BRADLEY SPELLBERG: It.s a quiet

1 group, so I.ll go first, but y.all need to start
2 speaking so I stop speaking. I think that.s why John
3 and his team and the FDA wanted this work to be done,
4 to validate models to get standard packages for drug
5 developers that would both ease the question that
6 you.re asking and give reassurance to FDA that the
7 data coming out the back end would be likely to
8 translate to something meaningful during clinical
9 trials.
10 DR. LYNN MIESEL: So many of the
11 benefits of these models that we.ve been talking about
12 will be helpful for addressing nonclassical
13 therapeutics, nonstandard. So with a standard
14 antibiotic, probably the 24-hour bacterial load models
15 are fine for PKPD assessment and then in translation
16 to the clinic, but it really becomes challenging for
17 groups that are developing a virulence inhibitor or
18 immune therapeutic on how do you do those models and
19 so we are striving for something that had a longer
20 duration of efficacy, something that had an
21 alternative endpoint other than just bacterial burden.
22 JENNIFER HOOVER: Actually, I think

1 that.s a great point, Lynn, because for small molecule
2 antibiotics they usually work fairly well and fairly
3 rapidly and so I think you can use models that require
4 higher inoculant where the animals get sick pretty
5 fact, but certainly -- and we.ve only, sort of,
6 dabbled in sort of nontraditional approaches, but we
7 struggle to show efficacy with things that aren.t
8 small molecules using our traditional animal models,
9 again, because I think usually have to give a very
10 high burden to make the animals sick and it happens
11 very quickly and you don.t have a window in which to
12 intervene. So thank you for that.
13 DR. CARA CASSINO: Yeah, I can comment
14 further on that. Cara Cassino from ContraFect. So
15 first of all, great work on the murine model. The
16 presentations were great and a lot of work has been
17 done and I think in general, the notion of
18 standardizing models in a way that they can be used,
19 reproducibly, et cetera is obviously, would be greatly
20 beneficial and would be an important step.
21 The challenge in my mind, so for small
22 molecules for which -- well, we.ve seen, small

1 molecules for which we.re familiar with and think we
2 understand are still difficult to make them behave in
3 these models; although, you.ve made a lot of progress
4 and I really congratulate you. We.re working on novel
5 biologic therapy, direct lytic agents. These are cell
6 wall hydrolase enzymes derived from clones, from
7 lysins from bacteriophage.
8 And what we found in the discovery end
9 of the spectrum is that although it.s very attractive
10 to be able to use the murine models for profiling, for
11 screening, for PKPD, for all the practical reasons
12 that I think everybody in this room knows, the
13 biologic agents don.t always behave that way and it.s
14 not even just because they.re fast or slow. I mean,
15 our lysins are pretty rapidly acting.
16 There are differences among species,
17 and so some of the species don.t translate as well.
18 So from our perspective, it.s an even more complicated
19 arena so for our lead anti-staphylococcal lysin, we
20 were able to use rodent models to do screening,
21 determine PK driver. Looking at exposure, though, we
22 realized higher order animal models would probably

1 better translatable to the human.

2 We have other compounds in our

3 portfolio where we.re realizing that the murine models

4 can be completely misleading and we might be

5 overlooking compounds that have a lot of promise just

6 because we don.t have the right model and I guess, to

7 throw it out to the group, you.re the experts. I.m a

8 simple pulmonary critical care doctor from New York.

9 How can we bridge that? You know, how do we bridge

10 that in the discovery end. Any thoughts?

11 DR. JOHN FARLEY: I --

12 DR. THOMAS WALSH: This is --

13 DR. JOHN FARLEY: Oh, sorry. Go ahead,

14 Tom.

15 DR. THOMAS WALSH: I was going to say,

16 I think you really bring out some really excellent

17 points. Our model systems are really complimentary.

18 I think it.s paramount that we understand that this

19 complimentarity can provide us with insight, sometimes

20 with small molecules, sometimes with larger agents and

21 biologic. And in that regard, even if we have

22 optimization in a murine model, complimenting that de-

1 risking and going into clinical trials with a larger
2 animal species is really helpful, but we have seen in
3 the rabbit model systems is a much closer similarity
4 in many of the immunological, many of the
5 pharmacokinetic and dynamic properties including for
6 biologics, for example in cytokine studies, GCSF, for
7 example, interferon gamma, strikingly effective in
8 that regard.
9 And so I would advocate that when one
10 comes up against these conundrums of not being -- of
11 finding a sense of incompatibility or inconsistency
12 within the murine model, then to have a smooth
13 transition to, say, well we.ll move to another model
14 system. And I would advocate that I think there.s
15 ever expanding use of rabbit model systems both for
16 systemic infections, pulmonary, as we.ll hear from Dr.
17 Hope, CNS infections, osteoarticular, where we found
18 going back to the original (inaudible) rabbit model to
19 be highly predictive.
20 So I would really encourage that and
21 since we.re readily willing to help in this vital
22 mission through FDA, BARDA, NIAID, and our great

1 collaborations with industry, please reach out to us.
2 DR. BRADLEY SPELLBERG: It.s unwise to
3 ever disagree with Dr. Walsh, and so I agree with
4 everything Dr. Walsh said. I would add to it, in our
5 studies with monoclonal antibodies, actually, the
6 mouse model works pretty well. Surprisingly, even
7 when you humanize the monoclonal, it still works just
8 fine in the mouse, and that many of the antivirulent
9 strategies will be used adjunctively with antibiotics.
10 And so when you use a subtherapeutic antibiotic dose,
11 it.ll smooth out the timeline to add the biological
12 in.
13 And then the last point I.ll make is
14 just the lesson I think we all learned with the anti-
15 CV28 immunotherapeutic that I think the primate target
16 is one amino acid off the human target, but the
17 antibody activates the primate target, killing the
18 animal -- sorry, was effective in the primates but in
19 the humans, it activated CV28 and caused cytokine
20 storm.
21 The only animal model that really
22 matters at the end of the day is the homo sapiens

1 model and so the question is, how do you bridge from
2 mouse to the homo sapiens, and I think Tom makes a
3 good point. Some model -- for some agents, you.re
4 going to have to use a different model.
5 DR. CARA CASSINO: Yeah, in our
6 experience, the rabbit has been a bit more reflective
7 of the, what we see as what we.re seeing in our
8 clinical program which is now in Phage 3, but it.s a
9 challenge for drug development because the rabbit
10 studies are -- you know this very well, they.re big,
11 they.re expensive, they.re costly, they.re
12 challenging, and if you want to do PKPD, they.re --
13 which we do because we.re not an immunologic therapy.
14 We.re a direct lytic agent and we have
15 established MICs and we.ve been able to borrow much of
16 the standard antibiotic paradigm to determine dosing
17 for humans, but it is a conundrum. I.m just throwing
18 it out there. I don.t know that there.s a solution,
19 so, anyway, we continue to be -- look at the rodent
20 models but there are compounds that, for a variety of
21 reasons, may not be the appropriate model to do the
22 work.

1 JENNIFER HOOVER: I want to go back to
2 this notion that different models are fit for
3 different purposes, which I think we could probably
4 all agree upon. So my wishful thinking is that
5 perhaps from today, we could have maybe not guidance,
6 maybe that.s a strong word, but recommendations or at
7 least something to suggest which models may be best
8 for which purposes or for which types of agents, for
9 example. That would be really helpful for us, I
10 think.
11 DR. JURGEN BULITTA: Maybe a little bit
12 of a historic perspective. So the mouse model has
13 been used for over 70 years throughout the entire
14 planet on different laboratories, so we have an
15 experience base with the mouse model which is
16 uncomparable to what we have for what we have for
17 research in other agents, so I believe it.s important
18 to keep in mind what the expectation to go through
19 (inaudible) of drug development is just unlikely to
20 happen in a normal therapeutic area scenario.
21 What I do believe, though, is that it
22 will be critical to assess pharmacokinetics and

1 perhaps even site-specific pharmacokinetics in other
2 animal models because it would just be foolish to
3 acknowledge, but these technologies exist. These very
4 advanced scanning methodologies for lungs in
5 tuberculosis, for example, and so we can learn from
6 what we already have succeeded in the animal, in the
7 mouse model system.
8 Now, despite several of the academics
9 including myself having pointed out some of the issues
10 with the, perhaps more well-behaved mouse model, I
11 certainly believe that these are very valuable models
12 which work very well. But if you get a bunch of
13 academics and want them to point out the difficulties,
14 this is of course what you get.
15 DR. THOMAS WALSH: Jurgen, this is Tom.
16 Do you think when one is contemplating the investment
17 of massive resources as well as the treatment of
18 individual patients that having the robustness of
19 preclinical data of complimentary systems may decrease
20 the risk, may ensure potentially a more optimal
21 outcome, and to that regard, even at the level we
22 find, for example, in informed consent, we -- our

1 patient population can be very, very sophisticated and
2 they.ll want to know with a new antimicrobial what has
3 been done.
4 And when we talk with them and we say,
5 well, we.ve studied these in different animal model
6 systems and they.ve worked very effectively even
7 though we have very little information and patience,
8 we think this may be more beneficial for you
9 especially with a live, threatening infection; there
10 is a sense of security that these have been vastly
11 studied in the laboratory and so in that regard, while
12 we recognize the limitations of larger animals in
13 terms of being able to have the number of strains and
14 the number of robust sampling, that explicitly you and
15 some of your other outstanding colleagues have
16 demonstrated, can we envision a more focused, not only
17 PKPD approach, we.re using fewer samples and using
18 fewer organisms, fewer animals, using the prior murine
19 data, for example, to build and reinforce a predictor
20 of models going into patient populations.
21 DR. JURGEN BULITTA: Undoubtedly, Dr.
22 Walsh, you.re correct. I would like to highlight for

1 any such modelling has to be done in close
2 collaboration with the immunologist and colleagues who
3 provide this expertise. A pure mathematician would be
4 lost in such arena.
5 DR. THOMAS WALSH: Very good. Thank
6 you.
7 DR. ACHIM WACH: This is Achim Wach
8 from Polyphor. Maybe I can add a little bit
9 perspective from the small biotech. So our problem is
10 basically that we miss a couple of data points
11 sometimes, so for example, it.s like cheap wines that
12 you have, when you look at PK. If their two-
13 compartment model is their one-compartment model, this
14 is one question. The other one is, do we really see
15 the peak if you do a subcut and for me, like a future
16 model would not be taking a humanized PK, but rather
17 having a kind of time resolved PK and PD readout in
18 the murine model which would give us a much better
19 idea of time over MIC and the correct estimation of
20 AUC and Cmax.
21 MAN 1: Dr. Joshi will agree these
22 technologies are available and very well working for

1 my opinion and depending on your drug trials which is
2 what we have discussed so -- earlier today, it depends
3 heavily on the drug trials how important it is to fit
4 the peak precisely or a trough concentration or when
5 also under on the permeability. Dr. Lepak showed a
6 (inaudible) which is kind of the world.s slowest
7 penetrating (inaudible) and then which we showed
8 meropenem is one of the fastest. Of course, these
9 types of things need to be considered.
10 DR. ABHAY JOSHI: I think consideration
11 also should be given for what purpose models are being
12 used. Either they will inform the dosing regimen or
13 we want model to screen which is dosing regimen which
14 is already established. So if it.s just -- dosing is
15 not yet established, then we can think about various
16 approaches and see what correlates with bacterial
17 killing, but if the intention is to already known
18 dosing regimen would work under hard to treat pathogen
19 or not, then probably humanized exposures would be a
20 less risky approach.
21 MAN 1: well, I only partially agree
22 because we have seen from Jurgen.s presentation that

1 you induce other problems like maybe an acute kidney
2 effect that was giving rise to the higher exposure to
3 amikacin in that fourth or -- third or fourth dosing
4 and I wonder if we.re not complicating the system by
5 doing this.
6 DR. ABHAY JOSHI: No, I completely
7 agree. So that that was one of the hope that from
8 this workshop we.ll get that feedback. But then that
9 comes to Dr. Walsh.s point that maybe for that
10 particular drug, that particular model is not
11 suitable.
12 DR. THOMAS WALSH: This is Tom. I have
13 a question for the panel in general. When we
14 encounter very short half-life compounds, meropenem
15 being an example, but sometimes peptides also can be
16 cleared, small antimicrobial peptides can be cleared
17 very quickly, in order to maintain a time -- a
18 prolonged half-life with normal renal function, what
19 do you consider the role of potentially Alzet pumps or
20 continuous infusion systems in subcutaneous
21 (inaudible)?
22 DR. ABHAY JOSHI: So I don.t think I

1 got the complete question, but what I understood is
2 for --
3 DR. THOMAS WALSH: I.m happy to repeat;
4 forgive me. When we encounter short half-life
5 compounds in murine or rabbit systems, if one has
6 short half-life compounds, we.re often left with
7 either intent as Dr. Lepak showed with his q. 3 hour
8 dosing or as Jurgen showed with, essentially q. 3 hour
9 dosing, obviously that.s not tolerable to the animal
10 and it also is relatively impractical for workflow.
11 What, then, is the possibility or your
12 thoughts on the possibility in murine models or other
13 model systems of using the Alzet, A-L-Z-E-T, type pump
14 systems for release of a continuous infusion, assuming
15 that you.d want to see a continuous infusion?
16 DR. ABHAY JOSHI: So I.m not much
17 familiar with the mouse model and that system, so I.ll
18 give it some general answers. So for murine model, my
19 understanding is that continuous infusion wouldn.t be
20 feasible, so in that case, I think we.ll take a
21 similar approach. What we.re doing is try to get the
22 TCs as similar to as in human in mice, so I guess for

1 PK, we should do the same approach that we get close
2 to as possible as in mice with human PK. Now,
3 regarding rabbits, I think you will see in afternoon
4 session there will be one presentation we.ll be
5 showing some continuous infusion how they approached
6 going for humanized dosing, so I think that will
7 provide different perspective or different strategy.
8 DR. WILLIAM HOPE: In terms of Alzet
9 pumps in murine models, we have some experience with
10 them and I think they.re extremely limited in what you
11 can do. The pumps are very small. In most cases, in
12 a mouse you have 100 microliters. You need fairly
13 equally as soluble compounds to go into those. It.s
14 not IV. You still have to be absorbed from a SUBQ
15 site, so we.ve seen limited utility and if you need to
16 increase exposure, it.s my opinion, like it or not,
17 you have to do the repeat dosing in order to that that
18 type of exposure.
19 DR. BRADLEY SPELLBERG: I think one of
20 the things we.re dancing around is the balance between
21 not having the perfect be the enemy of the good. If
22 we achieve perfect matching of human dosing requiring,

1 what was it, 12 administrations over eight hours, all
2 of our staff will quit. All of the biotech companies
3 trying to do it will go bankrupt and so efficacy will
4 not translate to effectiveness.
5 I think the FDA has expressed to us
6 great interest in what was alluded to in prior talks,
7 the use of adjunctive agents that prolong half-lifes
8 of some of the beta-lactams and we.re very interested
9 in exploring that. If we could use an adjunct like a
10 probenecid and make the dosing humane to the lab tech
11 and to the mouse and to the bottom line for the
12 companies paying for the work, and achieve 80 to 90
13 percent accuracy, that probably is a better efficacy
14 to effectiveness translation.
15 DR. JOHN FARLEY: Yeah. This is John
16 Farley, so thanks for that, Brad, and I think -- so I
17 kind of am somebody who knows a little about a lot and
18 so I surround myself with people like you. So sort of
19 the naþve notion I had going into this was that that a
20 long-term goal would be to develop an
21 Enterobacteriaceae model that could be used in the
22 development of a CR reactive agent in the future and

1 sort of one of the things I.ve learned from you all
2 and your work, particularly in the murine space, is
3 how difficult that is how difficult that is.
4 So the thought would be that of course
5 the carbapenem would be the control of the future and
6 the future model. So that was kind of the thinking
7 behind that and I still think that this is definitely
8 worth pursuing, but it.s obviously going to be a
9 challenge in the murine space, at least for that
10 particular goal, so...
11 JENNIFER HOOVER: Can I ask a point of
12 clarity, then, around -- there.s been a lot of talk
13 about humanized dosing and we do it, so I.m a fan, so
14 don.t take this as a criticism. Just wondering what
15 you see as the goal there, right, because normally you
16 would already have a PKPD target and so given your
17 humanized dose isn.t really going to get you any
18 farther with that, so is it just to, for a novel
19 agent, confirm that you.re going into the clinic with
20 the right dose or is it for supporting break points or
21 is it more about doing it for those control compounds
22 to benchmark the model and to know what you.re

1 actually comparing against?
2 DR. JOHN FARLEY: From the FDA
3 perspective, it.s all three. It.s also the
4 recognition that our clinical programs nowadays are
5 very streamlined and has been -- has sort of been
6 alluded to, this data is important in terms of the
7 investigative brochure, in terms of thinking about the
8 clinical trial. It.s also why, from our perspective,
9 and this also may be naþve, when Ursula did her work,
10 she.s noticing tons of models used in the IND space
11 where the drug is administered immediately after
12 inoculation, right.
13 And that seems to really be a missed
14 opportunity and so one of the things that we.ve pushed
15 and we.ve learned a lot from the three murine models
16 that are presented today, that it really is feasible
17 to at least establish that the animal has disease
18 before you administer the drug. And so that.s an
19 incremental step, but an important one to actually
20 demonstrate that in some living organism, your drug
21 has some benefit before we start randomizing patients,
22 so...

1 DR. WILLIAM HOPE: John, can I make a
2 comment? Can you hear me?
3 DR. JOHN FARLEY: Absolutely, William.
4 DR. WILLIAM HOPE: One thing I didn.t
5 hear mentioned in any of the discussion this morning
6 and something I guess I.ve been increasingly aware of
7 is that most beta-lactams, as we said these models are
8 -- this is a half-life question -- can the half-life,
9 which often you don.t see because it approaches the
10 limit of detection of the assay, and as is often at or
11 around the MIC, so I think that that is also a problem
12 that.s easy to match the easy stuff, where
13 concentrations are 100 milligrams per liter but the
14 gamma phase, I.m sure, accounts for a lot of biology
15 and pharmacology that we.d skate over and I.m aware
16 that that back end is really there. We need to pay
17 more attention. I don.t think humanization or pumps
18 or any of those measures can help that problem.
19 DR. JURGEN BULITTA: William,
20 completely agree to this. I believe one of the huge
21 values of humanization is if you do combination
22 therapies. So let.s say if you have two agents at the

1 same time at the right place, in a human-like
2 concentration, I would propose predictive performance
3 of such a modal is vastly improved, I have missed -- I
4 only saw the tail end of the (inaudible) situation
5 back in (inaudible), but my understanding is that yes,
6 you had (inaudible) in vitro, but only for 10 minutes
7 in vivo so that is one of -- so predictive performance
8 for combination therapy is a huge benefit under
9 humanized conditions.
10 The other part while I personally am a
11 strong proponent of mathematical models, is actually
12 when we humanize and discuss humanization, we have an
13 active discussion of that is reasonable, what is
14 clinically or in vitro laboratory-wise achievable.
15 And that, in itself, has value because when you can
16 discuss how do we want to move forward in which areas
17 or corners do we have to cut for variety of reasons,
18 and legitimately so.
19 DR. JOHN FARLEY: Just to go back to
20 another point and sort of talk a little bit more about
21 question one. So -- which was the sort of, I guess,
22 sort of regulatory relevance and development

1 perspective. So I think Brad and others brought up
2 that we need to sort of stay a little bit ahead of
3 where the science is going and we.re moving toward
4 combination therapies, right.
5 And so from a regulatory perspective,
6 what everyone ought to care about and what the FDA
7 definitely cares about is what is the contribution of
8 each element. Because I think with the pretomanid
9 approval for XDRTB, you actually had an approval of a
10 regimen and that was, I think, and important step and
11 a step where we need to be headed. That.s a disease
12 where you certainly can.t do a factorial clinical
13 trial.
14 And so a murine model in drug
15 susceptible TB was used so understand the contribution
16 of the components of each element. And that ended up
17 being quite central to the regulatory review. We need
18 to understand that. And so part of the -- the sort of
19 niche for more advanced murine models is contributing
20 to that particular regulatory need and that does mean
21 more well -- PK, that people are comfortable with and
22 sort of exposures in the model, understanding that the

1 mouse has the disease before you administer the drug,
2 understanding end points, et cetera, so we.re sort of
3 -- that.s sort of the niche from our perspective where
4 we.re seeing murine models but -- and underscores, I
5 think, the importance of the work.
6 DR. TINA GUINA: So to follow on this
7 discussion, I was hoping that maybe we can discuss
8 little bit of the role of different strains in
9 multidrug resistant strains, because as we know, some
10 of these strains are not virulent in mice and as we.ve
11 seen in earlier presentations, there.s white a
12 different LD50, so really talking about what would
13 really support regulatory dossiers, so I would like to
14 hear from presenters who talked about this today and
15 then also from others who want to contribute. Thank
16 you.
17 DR. BRADLEY SPELLBERG: Yeah, that.s t
18 really important point. And I alluded to earlier, if
19 we put strains into mice that achieve detectible CFUs
20 but don.t cause physiological stress to the animal,
21 don.t cause clinical disease, that at some level at
22 least mimics the clinical illness the patients

1 experience, then by definition we can.t use the feels,
2 functions, and survive translation to clinical trials.
3 And we.ve actually published this in Acinetobacter.
4 You can make mice completely normal physiologically
5 and clinically with high densities of bacteria if you
6 eliminate LPS from the bacteria.
7 And so what does that mean? Okay, so
8 I.ve reduced the CFUs. The mouse was fine either way.
9 I think that we really need in these models to have
10 not just bacterial density as the endpoint, but
11 clinical endpoints. Mortality is an important one.
12 You should be able to make the mouse live. But you
13 also should be able to normalize other functions like
14 temperature and pH, and I think it was very reassuring
15 for us to know that in the pneumonia model, the mice
16 are hypercapnic. They.re hypo-ventilating even though
17 they.re tachypneic.
18 Their respiratory rate is sky high, but
19 because they have extensive clinical pneumonia,
20 they.re not exchanging CO2 effectively. They die of
21 respiratory acidosis. The bacteremia mice die of
22 metabolic acidosis from septic shock and they.re

1 hypoglycemic and it.s a really good match to the
2 clinical disease that patients get.
3 Those kinds of parameters, adding into
4 the model, I think give validity to the FDA that
5 there.s a clinical benefit of the drug before it gets
6 into patients.
7 DR. YULIYA YASINSKAYA: Are there
8 differences between the different -- the isolates that
9 they.re virulent and not so virulent in murine models
10 compared -- and the clinical isolates that we isolated
11 from humans with the actual infection, you know, those
12 are virulent in humans. Do we have the isolates that
13 are virulent in humans and not that virulent in mice?
14 DR. BRADLEY SPELLBERG: Virulence in
15 humans is very difficult to define because we.re now -
16 - we.re not dealing with pneumococcus. We.re dealing
17 with pathogens, at least thus far in this
18 conversation, that are in patients who are in the ICU
19 with central lines and have had surgery and on 15
20 antibiotics and have 27 comorbidities. And so when
21 someone dies, is it because that strain was virulent
22 or because of 27 other clinical factors that drove

1 their outcome?
2 In the mice, it.s completely
3 controllable, so I can.t answer the question of the
4 other direction, but what I can tell you is in
5 Acinetobacter, at least, there is enormous variations
6 in the virulence in the mice from clinical isolates.
7 We have clinical isolates that do not cause detectable
8 disease in immune normal mice. We have clinical
9 isolates that blow away in immune normal mice. And
10 the LD100s span four to five logs.
11 So I can.t go the other direction
12 because the clinical scenario is too complicated and
13 it.s hard to tease out what drive the outcome in any
14 individual patient. Since we can control the mice, we
15 actually can start teasing out what differentiates
16 hypervirulence in mice across these strains. And I
17 think that was what I was suggesting is that we should
18 be using strains that allow us to cause clinical
19 illness in relatively immune normal mice, unless we.re
20 looking at neutropenic patients.
21 If we want to develop a drug for
22 neutropenic patients or patients that are getting

1 specific forms of chemotherapy or CAR T-cells, then
2 studying a model relevant to that setting makes sense,
3 but otherwise, finding strains that can cause disease
4 in this similar patient population, to me, adds
5 validity as you start translating from bench to
6 bedside.
7 DR. TINA GUINA: So, Brad, in
8 principle, I agree with what you just said. I still
9 think that models that we.re typically using they are
10 typical dose ranging models and (inaudible) burden
11 models and PKPD models are really important in this
12 early stage of product development which is important
13 to many sponsors and many investigators because it is
14 that initial model after in vitro susceptibility has
15 been determined to actually show it and prove that
16 PK.s matching and I think that.s why so much work has
17 been done in these models and will continue doing
18 that, but I think humanized models in terms of
19 matching pathophysiology of human disease and then
20 matching appropriate strains is, I think, may be these
21 models could be used maybe later stage develop.
22 Curious what others think as well.

1 DR. BRADLEY SPELLBERG: Well, I would
2 just say, you and I are not in disagreement, per se,
3 that I don.t think picking strains that cause disease
4 in immune normal mice means that you can.t or
5 shouldn.t look at PK drivers of microbial clearance.
6 Not at all. What I.m saying is just because you drop
7 CFUs in an immune normal mouse doesn.t mean the drug
8 will work clinically in sick patients. And the
9 flipside is you may actually find drugs that work
10 clinically and don.t drop CFUs.
11 In the acineto world, my classic are
12 LpxC inhibitors which do not kill Acinetobacter, but
13 the de-fang the bug so it can.t cause disease. It
14 simply protects the mice immunologically, not by
15 killing. So you.re going to -- you have a selection
16 bias if the only tool you use to pick efficacy is
17 clearance of bug.
18 JENNIFER HOOVER: I think that.s a
19 great point, actually. I think it comes down to a
20 balance of what you.re trying to achieve in the
21 particular study that you.re doing. Certainly from a
22 PKPD perspective, we are always hunting for strains

1 that are unique to a given compound, right, you need
2 the right MICs. You may need a certain phenotype, et
3 cetera, et cetera, so usually for every compound, we
4 end up with a different set of bacterial strains that
5 we.re using to do our PKPD.
6 So while I agree it.s great to have
7 some really well-characterized strains and really
8 well-characterized models, I think we can.t have that
9 for every strain and so just like I think you -- I.m
10 kind of reiterating what you said, Brad, but
11 understanding that there needs to be flexibility so we
12 can look at other isolates that are maybe relevant for
13 other reasons.
14 DR. THOMAS WALSH: This is Tom. I
15 would just also like to underscore the points made
16 about hosts. What we may think about hosts as being
17 analogous to normal mice actually ever increasingly
18 we.re understanding in the ICU, even though patients
19 may not be neutropenic, they may not be
20 pharmacologically immunosuppressed. In a STEM cell
21 transplant recipients or solid organ transplant
22 recipients, there is a tremendous evolution and the

1 understanding of immune paralysis and that.s the
2 trauma patient.
3 That.s the medically complicated
4 patient, increasingly one sees, especially in the
5 setting of surgery and tissue injury, this striking
6 example of accounting for why patients will have
7 polymicrobial infections, severe recurrent persistent
8 bacterial infections that even though they.re not
9 pharmacally immunosuppressed, they do have an immune
10 paralysis.
11 So in developing predictive animal
12 model systems, having a sense of that, that we do not
13 necessarily need to just only have normal mice, normal
14 animals, but look toward other immune impaired model
15 systems that might have a more predictive outcome for
16 patients who do have -- enormous population that has
17 immune paralysis in the absence of pharmacologic
18 immunosuppression.
19 DR. MATTHEW LAWRENZ: I just want to
20 make one statement about the immunocompetent versus
21 the immunocompromised, and it comes back to how many
22 bugs you.re actually putting into the animal. And

1 we.ve run into problems with the immunocompetent model
2 if our -- the inoculum that we have to put into the
3 animals is so high that when we actually treat them
4 with antibiotics that are bactericidal, the animals
5 might reduce the number of bacteria but they actually
6 die because of the release of PAMPs and everything
7 else that happens and everything else that happens.
8 So that.s one of the reasons that we
9 originally were concerned about it. I appreciate the
10 fact that some of these more virulent strains might
11 overcome that problem, because we get into a mid-level
12 where now it might work in an immunocompetent where we
13 don.t have to worry about that confounder of
14 understanding if the drug.s protective or not.
15 DR. JURGEN BULITTA: There is a risk if
16 you go to hypervirulent strains. If you inoculate
17 with 28 bacteria CFUs I wonder how many resistant
18 mutants you will have in that initial inoculum? So if
19 your outcome is prevention of resistance, I love that
20 study, but you have -- one has to be clear that you.re
21 probably not going to study resistance prevention.
22 DR. THOMAS WALSH: And Jurgen, I would

1 echo that concern. The virulent organisms are
2 certainly important in recognizing some of the deadly
3 pathogens that we may see, but in term -- one of our
4 strategies, of course, is to try to prevent the
5 emergency of resistance.
6 What we.ve seen is helpful both in --
7 we have some murine models with KPC, but more
8 importantly in the rabbit model systems where we.re
9 able to go out for 12 to 14 days, is over time, the
10 expansion of the population particularly in the
11 untreated controls, the expansion of the population
12 and the very large burden of organisms that can be
13 achieved in an effective 40 gram lung were, over that
14 course of time with that massive amount of organism,
15 we believe that there is a sufficiently large
16 population, then, to test the hypothesis as to whether
17 one.s antimicrobial agent can prevent the emergency of
18 resistance over -- as a function of time of 12 to 14
19 days.
20 JENNIFER HOOVER: And you bring -- go
21 ahead.
22 DR. WILLIAM HOPE: the other problem

1 that we have debated amongst ourselves and I think the
2 agency has as well is not only go through a process of
3 selecting strains and having to discard strains that
4 are not fit in vivo or actually do something that we,
5 in terms of the (inaudible) expect, an NDM expressing
6 Enterobacteriaceae, the obvious example of that. with
7 a lot of uncertainty about that. So the other issue,
8 really, is the number of strains that get tackled
9 through these models.
10 I don.t think there.s been any sort of
11 agreement about what that should be and especially
12 when some strains like Acinetobacter and NDMs are so
13 hard to find and to be able to stud them in vivo, you
14 might only be able to get three or four and that
15 really doesn.t feel like enough when you.re making
16 complex dosing prediction from these models.
17 JENNIFER HOOVER: One of thee points,
18 maybe, I would go back to is time to treat. We talked
19 a little bit about that -- we, our presenters, so
20 kindly touched on that in their presentations. I
21 guess I worry a little when I see the inoculum being
22 fairly low or the baseline counts being fairly low

1 compared to what we would typically think of in a HAP
2 or VAP patient, so I.m wondering if, based on some of
3 the discussion this morning and then what we saw in
4 the presentations, is LD50 what we should be
5 targeting? Is 10 to the 6th at baseline, which is
6 what I kind of thought it was, sort of general
7 thinking, the right place to be before you start
8 treating?
9 Is there some clinical measure that
10 should be a trigger to treat? Just some general
11 discussion on that point from the panelists would be
12 great.
13 DR. BRADLEY SPELLBERG: I.m always
14 going to say it should be clinical. That doesn.t mean
15 that there shouldn.t be a microbial component to it,
16 but again, feels, functions, and survives, was chosen
17 for a reason. That.s what patients experience and the
18 trick is that the drugs, the small molecule
19 antibacterials, work by eliminating bacteria, and how
20 does that translate into feels, functions, and
21 survives.
22 DR. YULIYA YASINSKAYA: I think it.s

1 very important to do survivor models, specifically if
2 yo8u are planning on submitting a murine model as a
3 part of marketing application to support the clinical
4 trial to have this additional data that supports the
5 contribution of the components or in general, you.re
6 just bolstering the efficacy portion of the
7 application.
8 I mean, I supposed the bacterial load
9 reduction could be used in the murine model at the
10 earliest stage when we.re screening for the compounds,
11 trying to determine what potential dosing strategies
12 might be used and so on, but I think it.s very
13 important, too, to move towards the survival model
14 when we.re talking about the actually efficacy
15 support.
16 DR. BINH DIEP: I would like to make a
17 comment on the rabbit model of pneumonia, and there
18 the trigger to treat was of paramount concern to us
19 and, but in the end, how do you -- what is the trigger
20 to treat? Is it clinical? Initially, our plan was to
21 treat rabbits when they show signs of hypoxemia so put
22 bacteria into the lungs of the rabbits. We wait until

1 they have hypoxemia and this is using an i-STAT system
2 measuring PO2, measuring lactate, measuring a whole
3 variety of different parameters. Can we use this as a
4 trigger to treat? In the end, what we ended up doing
5 is that it takes time to run an i-STAT, to run a blood
6 gas, to determine whether the animal have overt sign
7 of pneumonia to treat, and that could delay treatment.
8 And in the rabbit model, we know that
9 treatment, if it.s delayed by just one hour, that we
10 don.t see efficacy of an antibiotic anymore. So we
11 ended up doing is the trigger to treat was determined
12 empirically so that, can we try treatment at three
13 hour post-infection, four hour post-infection, five
14 hour, six hours post-infection.
15 And we found that at five hours post-
16 infection, it.s about two-thirds of the rabbits
17 survive and it.s also at that particular time point
18 where we see two-thirds of the rabbits have hypoxemia
19 where the PO2 is less than 60 millimeter of mercury
20 and lactate is high at that point in. there are
21 neutrophilic infiltrate into the lungs.
22 So that was a way of justifying that

1 trigger to treat, but the trigger to treat was
2 determined empirically. I wasn.t, you know, a
3 clinical syndrome, a clinical diagnosis, when we start
4 treatment. We were able, however, in other animal
5 model validation that.s funded by the FDA to actually
6 treat septic shock, Pseudomonas aeruginosa septic
7 shock where we start treatment with the mean arterial
8 blood pressure is decreased by 20 percent.
9 That.s also at the time point when
10 cardiac output is also decreased and -- but in those
11 setting of treatment of septic shock, it requires ICU
12 supportive care that you may not be able to do in a
13 mouse model. So this requires fluid challenge. This
14 requires the use of vasopressors. And it makes the
15 model extremely complicated.
16 So it.s possible to do that to have a
17 trigger to treat that.s not time based, but it.s quite
18 complex.
19 DR. THOMAS WALSH: This is Tom and an
20 alternative that we.ve used in our pneumonia models
21 both fungal and bacterial, has been radiology. We.ve
22 been taking a very robust approach with CT scan, also

1 conventional chest radiography, but CT is relatively
2 more sensitive, and identifying at the different
3 points where we see pulmonary infiltrates that then
4 would be analogous to what one would see in an
5 intensive care unit. Being cautious not to let an
6 infiltrate accumulate massively because that.s
7 associated with high, almost intractable mortality,
8 but at the earliest signs of pulmonary infiltrate,
9 that.s also conserved in the rabbit model as a useful
10 and clinically relevant marker.
11 In murine models, there are little
12 mouse -- murine CT scans that potentially cold also be
13 employed. It depends upon the experimental radiology
14 department, but considering a radiology endpoint might
15 also provide both in murine and rabbit model systems
16 another clinical endpoint for triggering antibiotic
17 administration.
18 DR. BINH DIEP: So I agree that, you
19 know, the neutrophilic infiltrate into the lung is a
20 hallmark feature of human pneumonia and it.s very
21 important and you can diagnose that using an x-ray,
22 one way that you can get away from radiology is

1 instead of looking at what.s in the lung, you can look
2 at what.s disappeared in the peripheral blood. So
3 instead, you know, you can look at a neutrophil count,
4 the white blood cell count in blood.
5 And if -- just like in humans with
6 neutropenia due to the infection, these are not
7 neutropenic patients. But the state of neutropenia or
8 leukopenia that.s observed, is indicative of how much
9 neutrophil is in the lung, so you can do it that way
10 using a surrogate marker of white blood cell count and
11 that.s what we also use to justify our trigger to
12 treat because at three to four to five hour post
13 infection, we see a drip in neutrophil count in the
14 blood and where did the neutrophils go?
15 They go all into the lungs and this is
16 correlated with levels of plasma interleukin-8, the
17 chemokine attractant for neutrophils. And we see that
18 also, so radiology, it.s really difficult to use that
19 to diagnose treatment in the individual animal and the
20 reason is you need to anesthetize the animal to take
21 an x-ray and by the time that the animal wakes up, you
22 know, when do you start treatment and maybe the

1 anesthesia will also affect the clinical outcome. So
2 x-ray may be very difficult to do to diagnose,
3 treatment, and as a trigger to treat.
4 DR. THOMAS WALSH: So just for
5 clarification on that point, it would not be that one
6 would be treating -- one would be scanning every
7 animal, in that sense. One characterized the model
8 with given host response in the background, given
9 inoculum and a given pathogen.
10 We found that you characterize it
11 again, be it bacterial or fungal, characterize that
12 model system well and then from there, normally within
13 a relatively narrow timeframe, that treating those
14 models, treating those animals going forward does not
15 necessarily necessitate scanning every animal. We
16 have found, though, that what can also be helpful as a
17 parallel marker for therapeutic response is using
18 volume metrics on the animal.
19 We have been able to develop nice
20 algorithms that -- dosing algorithms such as gently
21 anesthetizing animals and over the course of treatment
22 -- again, this is over approximately 10 to 12 days in

1 a course of therapy, where you can see the diminution
2 in the pulmonary infiltrate and it yet gives you,
3 using the volumetric algorithms, another parameter for
4 therapeutic response, and that.s something that we
5 haven.t talked too much about.
6 We.ve talked about the, we talked about
7 the Log c (inaudible) gram and we.ve talked about that
8 being not necessarily the (inaudible), particularly
9 given the inflammatory markers that that is very
10 nicely articulated and survival is also a parameter,
11 but there are many other variables including, as we
12 saw, cytokine responses as well as potential
13 resolution of pulmonary infiltrates, so I think
14 capturing all of these markers on the therapeutic
15 monitoring side can also be very useful.
16 DR. BINH DIEP: But they.re -- Tom,
17 they.re not useful for trying to construct dose
18 exposure response relationships which is what the
19 whole field is based on and for that problem, you have
20 to control variants with an inch of its life. So all
21 these things that you.re talking about trying to make
22 things more clinically relevant or physiologically

1 relevant may be of interest and may have a role, but
2 when you.re trying to construct those relationships
3 you just get noise unless you control the system very
4 tightly and that.s why CFUs are so important now and
5 why they will continue to be.
6 DR. BRADLEY SPELLBERG: This is false
7 dichotomy to say it has to be clinically relevant
8 biomarker outcome driven or it has to be PKPD
9 microbial outcome driven. Both elements are
10 important. I think the point Tom was making, which is
11 what I agree with, is the field has largely ignored
12 the non-microbial PKPD component and we think it adds
13 value to look at that as well. So I don.t think it.s
14 either or. I think both are important. I think tom
15 agrees with that point, as do I.
16 DR. MATTHEW LAWRENZ: So I just want to
17 stress what Binh said at the beginning, too, of this
18 discussion was one of the things that we don.t
19 typically do in the mouse model is add supportive care
20 into this and so that.s something to take in mind when
21 we start to look at physiological trigger to treat, et
22 cetera. Patients are receiving other care that the

1 mice may not and so it gets hard to keep those mice
2 going without that type of supportive care and so it.s
3 just a consideration to take when you think about this
4 from a physiological standpoint.
5 DR. THOMAS WALSH: And on that note,
6 while there is massive -- extensive heterogeneity in
7 our critically ill patient population, in rabbit model
8 systems we can standard -- once we know the model
9 system well for a given organism, given the
10 background, we can standardize a background of
11 supportive care. For example, 10 mL of normal saline
12 per day may be just enough to enable that rabbit
13 population to go to course of a given therapeutic
14 outcome, in contrast if they died of third spacing or
15 intravascular volume depletion.
16 DR. YULIYA YASINSKAYA: We.re getting
17 late. I don.t want to keep you guys waiting for your
18 lunch. It.s about time. It.s 12:05. Speakers.
19 lunches will be in Room 1506. We.re breaking up for,
20 I suppose 45 minutes? Where is it? Hour? Yeah,
21 Session 2 starts at 1:00, so please enjoy your lunch.
22 Rest, think, and we.re looking forward to another

1 productive discussion in the afternoon.
2 (Break)
3 DR. JOHN FARLEY: If we could ask folks
4 to take their seat, we.ll be getting started in just a
5 minute and per William Hope, could we check audio?
6 Have we --
7 DR. WILLIAM HOPE: Can you hear me?
8 DR. JOHN FARLEY: We can hear you.
9 Good. So stand by. Thanks. So thanks for coming
10 back for the afternoon session. I.m John Farley and
11 my co-chair for this session is Dr. Marina Kozak from
12 BARDA and we.re going to move into larger animal
13 models beginning with a series of discussions on
14 rabbit models. First up is William Hope from the
15 University of Liverpool where he is the Dame Sally
16 Davies chair of AMR Research and director of the
17 Center of Excellence in Infectious Diseases Research.
18 So William, thanks so much for taking the time to join
19 us today, and we.ll invite you to get started with
20 your talk.
21 DR. WILLIAM HOPE: Thank you, John.
22 First of all, my apologies that I can.t be there in

1 person. I don.t need to explain the reason. So I.ll
2 just have to tell you to advance the slides, I think,
3 so we can move right along.
4 JOHN FARLEY: Can you see the screen?
5 So you.ve got up the principal problem right now.
6 DR. WILLIAM HOPE: Right, there was just a bit --
7 there.s a bit of a delay every now and then, John, so
8 I think that just to talk about some assumptions maybe
9 which we didn.t dissect in detail this morning, so a
10 fundamental assumption for PK and PD is that the
11 invading pathogens, the common pharmacological type in
12 any experimental system in patients.
13 But I think there.s a more profound
14 idea for bridging and translations that the -- that
15 assumption about the PK also assumes that the
16 pharmacodynamics are the same. That is, the drug is
17 allowed to interact with its target in the same way in
18 a hollow fiber model, or a mouse model, or a rabbit
19 model as in a patient.
20 And we as a community pay relatively
21 less attention to that than we do to issues about
22 human intervention, which was discussed extensively

1 this morning, and it.s a bit of -- I.ve always been
2 slightly puzzled by that.
3 So, for example, everybody is quite
4 happy to live use drugs for CU -- well, not live use
5 but to study drugs for CUTI patients based on fine
6 model data in the mouse. So, maybe this is a point
7 that we can come back and talk about later. So, the
8 next slide, please.
9 So, the model that we.re going to talk
10 about this afternoon mimics this disease, neonatal
11 meningoencephalitis. And I guess the point is that
12 neonates or neonatal -- babies with neonatal sepsis
13 often have occult central nervous system involvement.
14 Maybe because of an immature blood brain barrier.
15 Certainly involvement of the brain
16 results in poor neurodevelopmental outcomes no matter
17 what the pathogen. But clinically it.s very difficult
18 to know whether the brain.s been involved, and it.s
19 very difficult to definitively demonstrate that for
20 the purposes of clinical trials.
21 And here.s this point again, that
22 involvement of the central nervous system potentially

1 changes pharmacodynamics. So, it would not be
2 necessarily appropriate to use a sign model in any
3 species to predict what might happen in the brain of a
4 human baby.
5 And so, of course, all of us know that
6 some antimicrobial agents and classes are in effective
7 in the central nervous system, but more subtly perhaps
8 that there are also dose exposure response
9 relationships. And so, it may be that a certain type
10 of drug requires an alteration in dosage to achieve an
11 effect in the brain. So, next slide.
12 So, the purpose again today is to
13 establish predictive models, predictive experimental
14 models that explicitly define the pharmacodynamics of
15 the site of interest for new antimicrobials in the
16 neonatal brain and that these model and model systems
17 can be used to identify candidate regimens for
18 potential clinical use in human neonates. The next
19 slide.
20 So, and in keeping with the spirit of
21 the this afternoon, why the rabbit? So, the rabbit as
22 a larger animal model enables clinically relevant

1 central nervous system sub-compartments to be modeled.
2 So, distinguishing the cerebrum and the Cerberus
3 spinal fluid. And both pharmacokinetic and
4 pharmacodynamics relationships can be established
5 here. And in a sense it.s a more faithful anatomical
6 mimic of the human baby.
7 The other advantages I.m sure we.ll
8 hear this afternoon is that larger animals potentially
9 enable serial sampling, as might occur clinically,
10 although many babies can.t have more than one lumber
11 puncture but that might be feasible. And there.s also
12 a track record of using the rabbit model. This model
13 was first pioneered by Tom Walsh with a model of
14 Candida meningoencephalitis, and that model is being
15 used to characterize the dynamics of micafungin and
16 anidulafungin, and that.s both passed -- both of those
17 molecules are passed in front of both sets of
18 regulators in terms of licensing or potentially
19 licensing those agents for neonates. So, next slide.
20 So, these are the details of the model.
21 I.m not going to provide you with the preliminary data
22 that was used to establish model parameters or

1 performance, but this is an immunocompetent model, a
2 standard strain of Pseudomonas aeruginosa that.s
3 injected into the system under general anesthesia. We
4 employed a six-hour delay in initiation of
5 antimicrobial therapy. We had two indicator drugs or
6 benchmark drugs, Meropenem and Tobramycin, a 30-hour
7 model. We originally hoped to get this model out
8 longer but at 30 hours this model is almost
9 universally lethal. And we found that we couldn.t
10 serially sample CSF as we had hoped because rabbits
11 were too sick to tolerate repeated anesthesia to
12 enable that pap to occur.
13 And, again, following on the
14 conversation this morning, the endpoint in this study
15 was bacterial burden in the CSF and the cerebrum.
16 Although as I said, the model was lethal. So, next
17 slide, please.
18 So, just let me show you some of the
19 data for Meropenem. So, here.s the PKs from the
20 experiment, so there are approximately 36 rabbits.
21 The black is the profile in plasma -- you see a
22 similar profile through the course of this morning,

1 and the red is the time course of drug -- predicted
2 time course in the drug in the CSF.
3 The partition ratio, as calculated by
4 the AUC and CSF to that of plasma, is 14.3 percent,
5 which is not dissimilar to human estimates or humans,
6 at least that have meningitis. So, next slide,
7 please.
8 And here are the raw data. It may be
9 complex, but let me just say that the controls are in
10 black and they tend to be at the top. The high
11 dosages there in the yellow and the green tend to be
12 down at the bottom. So, it was clear, after a lot of
13 work and a lot of experiments, that there was a dose
14 exposure response relationship that we could see and,
15 of course, as you.ll appreciate after what I said,
16 that these are actually terminal CSF samples. They
17 weren.t repeated from live animals. So, each point
18 there represents a single animal. So, next slide,
19 please.
20 I won.t go through this but we did hear
21 this morning about using these models to construct
22 those exposure response relationships so there.s the

1 PK in the first three equations and we let the CSF
2 drive the effect. Sorry, next slide.
3 And so what we did -- and here was the
4 difficulty, and here is the difficulty, I think, with
5 larger animals, that you only get a single destructive
6 observation. So, we use the posteriors, the
7 (inaudible) posteriors from that mathematical model to
8 predict the time course of CFU changes in each rabbit.
9 We have two compartments, or two reads
10 -- we have the CSF and the brain. We decided just to
11 use the CSF or model the CSF data because we could
12 measure Meropenem in the CSF. It.s an interesting
13 idea or concept about what might be driving the
14 pharmacodynamics in the brain. Maybe the blood is a
15 better driver for that rather than CSF. That.s
16 another point for discussion. And we just measured
17 total, although we considered CSF in Meropenem
18 concentrations and CSF to be free. That.s probably
19 not true but that was how the data were handled. So,
20 next slide, please.
21 So, what I.m showing you now -- so,
22 these are the predicted densities of bacteria at the

1 end of the experimental period and here there are a
2 number of different exposures. So, here is the plasma
3 AUCMIC that.s been shown and a nice regression line.
4 The change in bacterial density is shown on the Y axis
5 there. And you see actually the data surprisingly
6 tight really for such a lethal model. So, next slide,
7 please.
8 I just -- I.m showing you this because
9 you.ll ask me. That is when you use the time above
10 plasma -- sorry, the time above the dosing integral --
11 the time the dosing -- the time the concentrations are
12 above the MIC and the dosing interval as the driver
13 time above MIC, you see a relationship. But it.s not
14 as tight, actually, as it was for AUC.
15 And if you go to the next slide and use
16 the CSF as a driver, you get this quite nice
17 relationship between the AUC that develops in the CSF
18 and the decrease in bacterial burden. And it.s what
19 the regression line is showing there. So, next slide.
20 So, that.s Meropenem. It.s an agent
21 which is widely used in the neonatal unit and has a
22 central role in the management of multidrug-resistant

1 neonatal sepsis. So, to compare that with Tobramycin,
2 which is obviously often given in combination but here
3 we.re showing or we have the ability to study
4 monotherapy. And in the same spirit here.s the PK.
5 And actually it was quite easy to -- the plasma PK
6 were very straightforward and it was easy to document
7 and quantify aminoglycoside in CSF. And the partition
8 ratio here was actually similar to Meropenem at 13.7
9 percent. So, next slide, please.
10 Now, here are the raw data and these
11 are more complex in the sense that the black are the
12 controls and you can see that, especially at the later
13 time points, that these are essentially overlaying
14 some -- the observations, the Tobramycin treated
15 rabbits. So, we were much less confident about
16 establishing dose exposure response relationships with
17 Tobramycin on the basis of the raw data only and when
18 you come to model it, which I.ll show you in the next
19 few slides.
20 So, here is the...sorry. Well, I can
21 say -- I can talk to both of these.
22 DR. JOHN FARLEY: You.re back one,

1 William. You.re good.
2 DR. WILLIAM HOPE: Yeah, okay. So,
3 here are the data from each rabbit again, and you can
4 see that there.s much less confidence about an
5 exposure response relationship here using plasma AUC
6 to MIC as the measure of drug exposure. So, there may
7 be something here but very, very variable and not
8 certain, and we chose not to put a regression line
9 through those data. So, the next slide then.
10 And here.s the CSF, and you can see
11 that this just looks like noise again. Maybe some
12 effect but not tight data and not convincing by any
13 means. So, next slide.
14 So, importantly, how can these models
15 in this approach be used in neonatal drug development?
16 So, next please. And so I.ve sort of several
17 observations and insights. And, of course, it may be
18 straightforward but it.s important to say that the
19 demonstration of drug in CSF does not necessarily mean
20 there.s meaningful clinical activity in that space. I
21 guess everybody knows that this is true but sometimes
22 we forget it because of our desire to bridge systems

1 on PK alone. And so you can see the completely
2 different responses from a dynamic perspective from
3 Meropenem versus Tobramycin.
4 The next point that I.d just like to
5 make is Meropenem does not have an FDA license for
6 babies under three months. I think you just skipped
7 forward a slide there. So, that if we.re going to use
8 these agents to benchmark, I heard that word this
9 morning, new agents, then I.m not sure what the
10 agency.s view is about using comparators, which they
11 don.t have -- haven.t granted a license to. So,
12 that.s another point of debate.
13 However, there.s sort of not much
14 choice in the matter. So, the dynamics of new agents,
15 and there are quite a few coming through now, could
16 potentially be assessed in this model. And at least
17 this model goes some way to de-risking subsequent
18 clinical development program by at least blocking
19 agents that don.t appear to have any central nervous
20 system activity. So, next slide.
21 So, here is the real difficulty -- and
22 I know that the FDA has struggled with this concept

1 and idea, and it.s a good point of debate, I think.
2 So, what do you do with this information? Because the
3 problem is -- I think as Brad said, that the law says
4 (telephone interference obscures) I think it says.
5 So, clinical efficacy data with proven or probably
6 disease is unlikely to be acquired, which is what the
7 license is ultimately based on.
8 And this disconnect between the
9 laboratory animal data and the clinical data that.s
10 never going to be able to be obtained is a difficult
11 one. And I know Laura Kovanda is going to talk about
12 this at the ASM meeting in Dublin in several months,
13 if we.re allowed to travel. And so it.s also worth
14 reviewing the agency.s recent assessment of micafungin
15 for neonatal meningoencephalitis, where micafungin was
16 not approved for -- specifically for neonatal
17 meningoencephalitis because of the absence of clinical
18 data, even though there was actually quite compelling
19 preclinical data that the drug was effective for that
20 disease.
21 And then there.s also the problem about
22 what do you do if a preclinical model predicts that

1 there should be dosage escalation, and that may be
2 higher than allometric scaling, for example, or the
3 initial PK studies. If there.s no opportunity for
4 clinical correlation, what do you do about it when a
5 PK and PD model is suggesting that a higher dosage
6 should be studied? Should you embark on more clinical
7 PK studies? And should you take the risk of dose
8 escalation and the intended safety risk? So, next
9 slide, please.
10 However, the experimental to clinical
11 bridge is the only realistic way new antimicrobials
12 can be developed for neonates, which is part of the
13 legal framework on both sides of the Atlantic. It
14 doesn.t solve the problem of having to acquire
15 definitive clinical data, although those data are
16 rarely, if ever, definitive. For sure, the current
17 experimental tools are limited, so this model.s only
18 been done with Pseudomonas rather than other bacterial
19 pathogens.
20 But I might consider that we -- I think
21 Tom used the word complementary systems if the PK and
22 PD approach is necessary but insufficient. But I

1 think that there is an advantage that this approach
2 can at least block the progressive -- progression of
3 compounds into neonates that are not safe for central
4 nervous system disease. For sure provide a foundation
5 for justification of doses into that -- into that
6 special population, and giving some reassurance that
7 underpin subsequent clinical studies, even if those
8 studies themselves are not likely to be definitive but
9 are still required legally. And I think that -- a few
10 more slides...take the next one.
11 The first is to acknowledge that this
12 work was supported by the FDA via a primary grant to
13 Duke University and a subcontract to Liverpool. So,
14 thank you for that support. And then the next slide
15 is a photograph of all the people that are involved.
16 And actually I won.t name them but I.ll just say, and
17 we.ll hear this this afternoon, that doing this work
18 is not easy. Especially learning how to anesthetize
19 large animals and to get into a space like the CSF
20 takes considerable skill and these are the people that
21 did that. So, with that I.ll stop and thank you.
22 JOHN FARLEY: Thanks very much,

1 William. And I think we.re going to move ahead to the
2 next talk.
3 DR. MARINA KOZAK: Next up we have Dr.
4 Thomas Walsh. He.s a professor of medicine
5 pediatrics, microbiology and immunology at Vale
6 Cornell Medicine of Cornell University and attending
7 physician of the New York Presbyterian Hospital. Dr.
8 Walsh, are you able to hear us?
9 DR. THOMAS WALSH: Yes, I am. Are you
10 able to hear me?
11 DR. MARINA KOZAK: Yes.
12 DR. THOMAS WALSH: Excellent. Very
13 good. To request that the standard of the time, I.m
14 sorry that I.m not able to attend. At 3:23 yesterday
15 afternoon, we received a ban on universal travel for
16 all Cornell clinical faculty. Anyone associated with
17 patient care to travel to any venue, domestic or
18 international. And so I.m very -- we had to make
19 adjustments, and I want to thank so much our FDA
20 staff, especially James, who was wonderful in
21 rearranging the venue in order to present this.
22 And at the same time I want to thank so

1 much our FDA colleagues for inviting me to present on
2 these important concepts of rapid model systems, large
3 animal systems, and understanding the ever-increasing
4 and emerging challenges of multidrug-resistant gram
5 negative pneumonia and all the other infections that
6 potentially we could address.
7 So, in that regard, if we think about
8 the challenges of multidrug-resistant gram negative
9 pneumonias in our critically ill patients, I think in
10 terms of the need for -- the problems of
11 therapeutically ineffective or toxic antimicrobial
12 agents, the immune impairment associated with
13 clinically ill patients, a delay in diagnosis and
14 detection, and then how we meet those challenges
15 through the bedside translational research. We train
16 and we work as physician scientists in this venue.
17 One moment, the slides are moving without my hitting
18 the button. And forgive me. I need to advance the
19 slides, is that correct?
20 MARINA KOZAK: Dr. Walsh, we.ll advance
21 the slides. Just let us know when.
22 DR. THOMAS WALSH: Okay, thank you.

1 Thank you so much. I appreciate it. And so if we go
2 to the next slide, in order to meet that challenge, we
3 then -- our response going from bench to bedside and
4 back to the laboratory and working intensely with our
5 laboratory staff and working ultimately through new
6 interventions, we address each of those with novel
7 antimicrobial compounds addressing the issues of PKPD
8 and safety. And then we have the augmentation of host
9 defenses. And then, finally, the development of early
10 biomarkers and therapeutic monitoring, which we work
11 through in in vitro systems, lab animal -- laboratory
12 animal models, Phase I, Phase II clinical trials,
13 Phase III, in which we are intensely involved at all
14 points -- especially understanding where we ultimately
15 want to target a given antimicrobial agent, and then
16 working through the laboratory toward that. This is
17 an endeavor that takes an enormous degree of team
18 effort and complementarity in multiple disciplines.
19 So, with that, if we go to the next
20 slide, please, and we address the question of novel
21 antimicrobial compounds, to the right you.ll see a
22 rabbit with a central silastic venous catheter. We

1 will investigate candidate compounds in one or more
2 rabbit models of multidrug-resistant gram negative
3 pneumonia. Next.
4 And with that, the central silastic
5 catheter provides atraumatic venous access. Next.
6 Just a little arrow that.s there, please. And in his
7 setting for multidrug-resistant gram negative, we
8 appreciate that host response can vary enormously.
9 But what we ultimately attempt to achieve is a
10 profound persistent neutropenia that basically
11 abrogates the neutrophilic host response and creates a
12 profound persistent neutropenia that we can achieve in
13 the rabbit model system through Ara-C induction; it.s
14 an S phase specific agent, reflecting that for -- that
15 we use in AML, for example. We can further modulate
16 the cyclosporine/methylprednisolone. But associated
17 with this intense immune suppression comes the daily
18 supportive care.
19 Our premises is that if we can achieve
20 success in these models, then when one does have
21 neutrophil response, one can also achieve a degree of
22 response in that setting, recognizing that neutrophils

1 can.t provide as much as 40 percent potentially of the
2 microbial activity but also recognizing, of course,
3 that they may contribute as well to the inflammatory
4 response.
5 So, in that regard, we are targeting
6 the most profoundly immunocompromised patients and in
7 that respect we then look toward organisms that are
8 going to replicate those infections.
9 So, if we go to the next slide we.ll
10 see that we have among the organisms studied within
11 pseudomonas aeruginosa, genetically defined pan-
12 susceptible organisms and OPRD porin loss, efflux
13 pump, expression and AmpC hyperexpression, and the
14 next with multidrug-resistant acinetobacter and for
15 KPC, where, unfortunately, New York City was the
16 epicenter for the U.S. epidemic of KPC, where we have
17 a large range of organisms from which to select. We
18 have our isolates in KPC and then also a visan isolate
19 at NDM-1, klebsiella pneumonia -- next -- and
20 strenotrophomonas maltophilia, an organism and
21 infection that is vastly underestimated in the
22 devastating complications that it has and, notably,

1 the most common metallo-beta-lactamase gram-negative
2 pathogen in the bloodstream.
3 On the next frame we have -- our
4 approach is a direct -- for establishing the gram
5 negative pneumonia -- a direct endotracheal
6 inoculation of a carefully quantified inoculant under
7 general anesthesia. With this we are able to colonize
8 the tracheal bronchial tree, and as immune suppression
9 progresses -- in what we see in our immunocompromised
10 patient population, colonization progresses then to
11 segmental or lobar pneumonia. And then from there,
12 one can then see within that timeframe that this
13 transition takes place within 24 hours, depending upon
14 the pathogen to trigger or treatment justification.
15 The duration can last out as long as 7-
16 14 days depending upon the untreated controls or the
17 treatment. Therapy will generally go 12-14 days and
18 allow, as I.ll mention later, the opportunity to also
19 be able to select or identify a potential emergence of
20 resistance.
21 If we undertake then the rationale and
22 benefits for selection of rabbit models in multidrug-

1 resistant gram negative pneumonia -- next slide -- and
2 compare it to conventional MIRING models where
3 duration is measured 24-48 hours, the rabbit model
4 reflects the human pattern of infection more
5 accurately over a 7-14 day period which animal serves
6 as a surrogate for patient care and closer to bedside
7 management, and the rabbit one is anatomically similar
8 to that of humans.
9 In the next frame we underscore that
10 the vascular catheter permits serial sampling for
11 blood cultures as well as antigenic molecular
12 proteomic markers over the course of time. And it can
13 reflect treatment durations of 5, 7, 10 or 14 days,
14 depending upon the questions being asked. As I
15 mentioned, we can also assess with the emergence of
16 antimicrobial resistance developing over the duration
17 of therapy. And this system can allow for the
18 accurate -- for the degree and duration of immune
19 suppression we.ve seen in our high-risk patients.
20 But there are limitations and there are
21 challenges for a selection of rabbit models in multi-
22 drug resistance. And that is labor intensity. There

1 is a necessity for support and monitoring of
2 immunocompromised large animals analogous of that of
3 intensity for immune impaired patients. Each rabbit
4 is the equivalent of a little patient. And they.re
5 monitored and cared for with the greatest degree of
6 humane -- and exceeding, well exceeding the standards
7 of humane care welfare.
8 There are also a limited number of
9 strains, unlike the multiple strains that can be
10 studied in MIRING models -- there.s a limited number,
11 but we endeavor to overcome that with well-
12 characterized representative strains chosen to address
13 the hypothesis being tested. Now, there are very high
14 standards for laboratory animal care and welfare under
15 IACUC, International AAALAC, and USDA. So, we have
16 three tiers of regulatory compliance.
17 But with that we exceed not only those
18 recommendations, we have contributed actively to the
19 animal husbandry of rabbits as well, addressing
20 various rabbit diseases, particularly the diarrheal
21 diseases, for example, and have established protocols.
22 And by obtaining these high levels of

1 standards or exceeding these high levels of standards,
2 it.s very clear and well known in laboratory animal
3 science, the better laboratory animal welfare equals
4 better science ultimately.
5 And then if we consider numbers of
6 animals, rabbit models do not replace but rather
7 complement the MIRING model system in taking this kind
8 of integrated approach -- strengthens the MIRING data,
9 the MIRING data strengthens the rabbit models, and
10 collectively going forward into critically ill
11 immunocompromised patients. And, again, the immune
12 impairment is a very broad one that we see ever-
13 increasingly in ICUs. It then de-risks the study and
14 also does justice to our patients in providing state
15 of the art clinical science before enrolling them into
16 clinical trials.
17 And then there.s the cost. Certainly
18 that has been mentioned this morning. But the large
19 animal systems, the risk of clinical trial strengthens
20 the predictability of outcome and ultimately proving
21 to be cost effective in, literally, multimillion
22 dollar drug development in clinical trial designs.

1 So, by way of illustration I wanted to
2 just illustrate two recent studies, one using
3 ceftolozane-tazobactam in our pseudomonas model. It.s
4 been spearheaded by Dr. (inaudible) Petraitis,
5 Associate Director, and Dr. Ruta Petraitiene, which
6 I.ll show you, our other associate director in the
7 Laboratory and Laboratory Animal Program in KPC and
8 ceftazidime-avibactam.
9 So far, the rabbit model for
10 pseudomonas aeruginosa, we have one pathology
11 persistent in neutropenic animals that is very
12 consistent with what we see clinically here to the
13 left. You see severe multifocal to coalescing
14 subacute necrotizing pneumonia with thrombosis
15 pruritus marked edema. It is of note that pseudomonas
16 is an anti-invasive organism. It has a wide range of
17 proteolytic activities, as you know, and one of them
18 is an elastase component that basically will elicit
19 thrombosis infarction, and that.s clinically seen
20 especially with aclima gangrenosum, but when can even
21 see by CT-scan even the presence of halo science
22 clinically and experimentally.

1 The tissue gram stains shows
2 intralesional gram-negative bacilli, large numbers of
3 intra and extracellular gram negative bacilli within
4 the untreated controls. With the strains of
5 pseudomonas, you genetically define these organisms --
6 were well defined in JMI Laboratories. They are
7 available to anyone who wants -- would like a wide
8 range of antimicrobials in which they.ve been studied.
9 In the particular experiment that I.ll show you, we.ve
10 studied ceftolozane/tazo and then as treatment
11 controls ceftazidime, piperacillin-tazobactam. It was
12 not our hypothesis to compare ceftolozane/tazo to
13 ceftazidime, to piperacillin-tazobactam. But more so
14 -- but they were more treatment controls -- but more
15 so to study the efficacy of ceftolozane/tazobactam
16 against an anticipated barrage that we will see
17 clinically of finally immunocompromised patients with
18 these different organisms.
19 And with that then we address the
20 question of plasma pharmacokinetics and humanized
21 dosing. Our approach basically using the background
22 of MIRING models and understanding, and if available,

1 Phase I, Phase II potentially in normal adult
2 volunteers depending on the availability of data to
3 characterize the plasma pharmacokinetics in this
4 situation over a range of dosing anticipated that
5 would cover the MIC within a reasonable dosing
6 interval.
7 Here, we show dose proportionality of
8 ceftolozane across the dosing range in calculation in
9 non-compartmental models we can show AUC that would be
10 comparable to that achieved, so we can further plot
11 that of flying above the MIC both with free drug and
12 total drug -- having defined the dosage that we would
13 use if we just elect one dosage, which in this case
14 we.ve done so, but we can also do a range of dosing
15 therapeutically, depending on the question being
16 asked.
17 Here, one can see if you look at the
18 little -- you can see untreated control on the black
19 bars with striking increase and the residual bacterial
20 burden of log CFU/g, and then one bar over. I.m
21 sorry, I don.t have a pointer here -- but one bar
22 over, and you can see C/T, that.s ceftolazane/tazo.

1 And across the pan susceptible, the OPRD porin loss in
2 the right panel, efflux pump expression in the left
3 lower panel, and AmpC hyperexpression virtually
4 complete eradication for the organism. If we then
5 harvest what remains of those organisms, those two
6 isolates, we.re not able to detect any resistance.
7 They still remained susceptible.
8 If we look at a panel of markers, we
9 realize also that a bronchoalveolar lavage may also be
10 a useful tool. Certainly it.s long going to be used
11 clinically in looking at responses and clinical trials
12 with repeat BAL, once can see then once again that
13 there is a significant decline of ceftolozane/tazo in
14 all of the organisms as measured by as much as a 10 to
15 6 log drop.
16 Or if we reflect for a moment on the
17 pathophysiology of gram negative pneumonia
18 particularly in a immunocompromised host and
19 specifically in profoundly neutropenic host, on one
20 hand there is the inflammatory component but on the
21 other hand there is direct organism mediated pulmonary
22 injury. And there are a number of ways in which to

1 measure that. Two very simple ways. Basically, one
2 way is the pulmonary lesion score. Normally, a normal
3 rabbit lung will weigh approximately1 5 grams. We can
4 however see the severe disease anywhere from 30 to 40
5 grams.
6 In this situation the ceftolozane/tazo,
7 the red bar, normalizes the lung weight literally back
8 to 15 grams. Whereas the untreated control still has
9 in contrast to the untreated control, which is 30
10 grams.
11 With that also we seek a relationship
12 to cumulative survival probability, where if one looks
13 then at the red -- enrooted red diamond,
14 ceftolozane/tazo is active against all of the
15 different strains. We see that ceft/tax does well,
16 except until it comes up against AmpC hyperexpression.
17 But our focus, nonetheless, is still on
18 ceftolozane/tazobactam, which improves survival
19 significantly in all of the animal groups.
20 If we then look at biomarkers, this is
21 also an important tool, there are a number of
22 cytokines which I won.t address that can be

1 exceptionally useful. I01 data, interleukin 8, as
2 well as IL6 and TNF alpha. But we also were
3 especially interested in a variety of other markers
4 that may not have been well-characterized.
5 So, in collaboration with Anthony
6 Suffredini in the initial development of the rabbit
7 model for pseudomonas aeruginosa where we were
8 comparing it in pathogenesis to pulmonary
9 aspergillosis, we were able to define nicely the
10 expression profile, proteomic expression profile of
11 one versus the other. And in the time course of
12 pseudomonas, we were able to find several key
13 molecules, 80a1, thymosin as well as C-reactive
14 protein through further selective analysis. C-
15 reactive protein actually correlated quite well with
16 therapeutic response. But the potential for host
17 biomarkers as both inflammatory and therapeutic
18 markers for host response and therapeutic response is
19 a very promising area. In addition, of course, the
20 system lending itself to molecular characterization
21 both from bronchoalveolar lavage and serial serum
22 sampling as a means of measuring therapeutic response.

1 If we look then at avibactam again in
2 the KPC model, here we see plasma pharmacokinetics
3 then such as avibactam across the dosage range --
4 we.re able to capture the AUC as well as prime above
5 the MIC with a properly dosing interval nearing that
6 of our immunocompromised patients. We can again show
7 the dose proportionality across the dosing interval.
8 And here we studied both a 7-day and a
9 14-day treatment course. We could see an impact, a
10 clearly significant impact at seven days. And this is
11 in the spirit where there has been a trend toward
12 decreasing the time course of pneumonia, the time
13 course of treatment of pneumonia. So, here in the
14 panel of markers you have pulmonary residual bacteria
15 burden, lung weights, pulmonary hemorrhage score and
16 BAL bactericidal burden. And you can see significant
17 impact of ceftaz-avibactam as well as polymyxin B
18 decreasing all of these markers.
19 Interestingly, if we go to a 14-day
20 course, although not -- it doesn.t reach statistical
21 significance if you compare 7 to 14 days, there is a
22 trend of further diminution in the pulmonary bacterial

1 burden, approximately the same in lung weight, and a
2 very subtle trend but still on there for BAL
3 bactericidal burden, raising the question insofar as
4 perhaps that we still might achieve more effect with
5 longer course of therapy, realizing that there.s
6 potential risk both clinically and experimentally for
7 emergence of resistance.
8 In this setting in days 7-14, we did
9 not see -- did not detect emergence of resistance to
10 ceftaz avibactam. This has been, of course, a great
11 concern in a number of settings including gram
12 negative pneumonia, hospital-acquired and ventilator-
13 associated pneumonia. But with the proper exposure
14 that were able to achieve with cefto/tavi we did not
15 see the emergence of resistance.
16 If one looks at survival versus --
17 ceftaz avibactam versus Polymyxin B, there clearly was
18 a difference between the two. Both were significantly
19 greater in survival compared to the red line indicated
20 here in untreated controls. I think it.s important
21 always to consider that when we.re evaluating agents,
22 particularly those with potential nephrotoxic endpoint

1 or even other organ site, that we try to incorporate
2 that into the model system.
3 Here, the mortality, though, is not
4 related to nephrotoxicity. No, we thought, well, of
5 course, this was nephrotoxic, but serum creatinine at
6 the doses of -- humanized doses of Polymyxin B that
7 we.re using were not nephrotoxic after this point.
8 But we do know also the Polymyxin B has
9 a neuropathic effect and there is well described for
10 creating in earlier days a neuropathic effect but
11 interoperatively in diaphragmatic paralysis, and there
12 also is the potential of concern for -- especially in
13 advanced pneumonia, that if one is having potentially
14 a neuropathic effect in advanced pneumonia, can that
15 compromise outcome? So, this raises the question of
16 the broader aspect of Polymyxin B and its potential
17 toxicity going beyond that just of nephrotoxicity.
18 So, in summary, we.ve reviewed the
19 developmental challenges, advantages and limitations
20 of the novel gram negative pneumonia. We.ve
21 illustrated these concepts with two studies in
22 experimental NVR pseudomonas and KPC pneumonia. In

1 the spirit of translational research I should also
2 underscore that both of these model systems have laid
3 the foundation for clinical trials. There is one in
4 particular going forward for ceftolozane/tazobactam
5 that we.re pursuing and coupling with rapid molecular
6 detection as frontline therapy for patients with
7 profound persistent -- profound immune impairment
8 related to acute leukemia or to stem cell transplant
9 where we will be bringing ceftolozane/tazo right
10 upfront given that we know we have in this population
11 a relatively high frequency of resistant pathogens.
12 But also potentially being applicable
13 to a wide range of immunocompromised patients that may
14 have other forms of immunosuppression ranging from
15 solid organ transplant to even this broader aspect of
16 immune paralysis that we see in critically ill
17 patients.
18 And, finally, we see the use of rapid
19 models with powerful systems that study new
20 antimicrobial agents for meeting the challenge of
21 multidrug uses in gram negative rods to our patients
22 and to the country.s public health.

1 I want to first of all give tremendous
2 acknowledgement to Dr. Petraitis and Petraitiene that
3 you see at the first top, who has spearheaded these
4 efforts with tremendous expertise and insights. And
5 then the formative group that has been contributing to
6 these laboratory efforts.
7 And then finally to our translational
8 team in Weill Cornell research, our clinical research
9 team that brings these discoveries from bench to
10 bedside, as well as many of our outside collaborators
11 contributing enormous pharmacokinetic and biomarker
12 and molecular expertise.
13 And then certainly with tremendous
14 support, both of our institutions as well as
15 government agencies, our foundations and industrial
16 collaborations. So, once again I want to thank you so
17 much for the opportunity to present this work and to
18 participate in this very important workshop.
19 DR. JOHN FARLEY: Thank you very much,
20 Tom.
21 DR. THOMAS WALSH: Was that coordinated
22 between slides and audio? Did it work out all right?

1 DR. JOHN FARLEY: It did. It did.
2 DR. THOMAS WALSH: All right, thank you
3 so much.
4 DR. JOHN FARLEY: You.re a New Yorker,
5 so you talk fast but we kept up with you.
6 DR. THOMAS WALSH: I wanted to stay
7 within time. I hope it wasn.t too quick.
8 DR. JOHN FARLEY: You did great. And
9 we.ll have more of a discussion. So, the last of our
10 rabbit models to talk about, that discussion will be
11 led by Binh Diep, who is an Associate Professor at
12 University of California, San Francisco. I know
13 personally that Binh works very hard. We did a site
14 visit. It involved getting to his lab at 4:30 in the
15 morning, which is one way to avoid an FDA site visit,
16 but we showed up anyway. And he.ll be joined by Bill
17 Weiss, who.s the Director of Preclinical Services at
18 the University of North Texas, Health Sciences Center.
19 So, look forward to your talk, Binh.
20 DR. BINH DIEP: Thank you, John. These
21 are our disclosures. So, our goals for the
22 development of the acute pneumonia in VABP rabbit

1 models are to use outbred rabbits with normal immune
2 system, not neutropenic animals. We want to conduct
3 acute pneumonia in VABP natural history studies to
4 determine the extent to which the pathophysiology in
5 the rabbit models mimic human non-ventilated HABP and
6 ventilated HABP/VABP.
7 In both models we want to trigger
8 treatment at pneumonia onset, we want to use humanized
9 Meropenem dosing regimen for rabbit model benchmarking
10 for validation. We want to use survival as the
11 primary endpoint, not 2-log CFU reduction in our
12 efficacy studies. And, lastly, we want to determine
13 whether Meropenem treatment with our without ICU
14 supportive care including fluid challenge and
15 norepinephrine could halt VABP disease progression
16 using clinically relevant biomarkers as secondary
17 endpoints.
18 So, these two rabbit models actually
19 have very distinct pathophysiology. In the rabbit
20 acute pneumonia model, we use awake non-ventilated
21 rabbits and this may better mimic non-ventilated HABP.
22 So, in these rabbits we do blind intubation of the

1 rabbits and then we instill bacteria directly into the
2 lungs of the rabbits, and then we withdraw the
3 endotracheal tube, allowing the rabbit to wake up from
4 anesthesia and then the infection to progress.
5 In contrast, the rabbit VABP model uses
6 anesthetized ventilated rabbits and this may better
7 mimic ventilated hospital associated pneumonia and
8 VABP. This model is much more complicated. It
9 requires an ICU setup. So, these rabbits, we can do
10 up to 13 rabbits concurrently in our experimental ICU
11 where they are violated concurrently with a lung-
12 protective low title volume of 6-7 milliliters per
13 kilogram. And these rabbits are instrumented with
14 multiple different catheters for hemodynamic
15 monitoring and also for infusion of fluids and
16 vasopressors.
17 So, this is a video of a patient
18 monitor, one of 13 patient monitors. It looks just
19 like a -- you know, these are actually patient
20 monitors used in ICUs all over the world. And you can
21 see we measure a variety of different parameters. And
22 all of these patient monitors are connected to a

1 central monitoring system where we can actually record
2 data every one minute. And this gives us a very rich
3 history, a natural history of the disease.
4 This is in the acute pneumonia model.
5 Virtually all of the rabbits die of profound
6 respiratory failure. So, this is a lung harvested
7 from a rabbit that.s instilled into the lung with just
8 the vehicle. So, like a lactated ringer solution or
9 UV kill bacteria. And the lung looks pretty normal.
10 The lungs to the right of it were
11 infected with live pseudomonas aeruginosa, Strain
12 6206. And you can see that at 3-hour post infection
13 there.s already massive necrosis, hemorrhage, edema,
14 and this only gets worse over time. So that by ten-
15 hour post infection here, you see the lung has doubled
16 or tripled in weight. And by the time of death, it.s
17 even worse.
18 So, there is an increase in the weight
19 of the lung, or the lung weight to body weight ratio
20 over time, and this is inversely correlated with PO2
21 in arterial blood. So, these rabbits, they look like
22 they die of profound respiratory failure.

1 The VABP model in contrast is very
2 interesting. You also see acute lung injury in these
3 animals. But by the time of death, there.s basically
4 two populations of rabbits: Those with very large
5 lungs, the same as in the acute pneumonia model. But
6 half of the rabbits have small lungs but they still
7 die. And that.s captured here, this population. So,
8 how did these rabbits die? We.re very interested in
9 that natural history.
10 So, to dissect that, what we did was we
11 looked at a variety of different biomarkers in both
12 models. Here are neutrophils. So, neutrophils in
13 both of these models decrease and it bottoms out
14 around 3-4 hours post infection.
15 In the VABP model you see here each of
16 these lines represent one animal. But because rabbits
17 are a large animal, we can sample blood every two
18 hours. And so it gives you a much richer picture of
19 the course of infection.
20 So, neutrophil seems to be gone from
21 peripheral blood. Where do they go? They all get
22 trafficked into the lungs. So, this is at the time of

1 death, and we see massive neutrophil infiltrate into
2 the lung. You cannot recognize the air space anymore
3 in this acute pneumonia model because it.s filled with
4 red blood cells, white blood cells, and with edema.
5 In the VABP model, rabbits with the
6 very large lungs look very similar. But those rabbits
7 with the small lung, you can see the aveolar space
8 still, but there are focal areas of edema but, you
9 know, it.s still massive neutrophilic infiltrate.
10 This is the vehicle control. So, in
11 this model we are very -- because it.s a VABP model,
12 we.re interested in ventilator-induced lung injury and
13 do we see evidence of that? Despite the fact that we
14 use a low tidal volume of 6-7 milliliters per kilogram
15 -- we still see acute lung injury in this model. So,
16 that some of the air space is filled with edema, there
17 is some minimal amount of neutrophils in the airspace,
18 and that.s whether we put in vehicle control or UV
19 kill pseudomonas aeruginosa 6206.
20 So, the VABP model has actually very
21 distinct pathophysiology. The data on the left hand
22 side is from one representative rabbit with a huge

1 lung that died. And the one on the right hand side is
2 from a single representative animal with a small lung.
3 There.s a lot of data here but focus on the orange
4 line.
5 So, the orange line is the mean
6 arterial blood pressure. The baseline, the pre-
7 infection baseline in rabbits is about 50-60
8 millimeters of mercury. And so what we found is that
9 there.s a progressive decrease in blood pressure so
10 that by the time of death in this animal at 15-hour
11 post infection, the blood pressure has dropped by half
12 or more.
13 In this case over here it dropped more
14 than 60 percent. So, it looks like in these -- in the
15 VABP model, you know, they die of -- they could
16 potentially die of severe hypotension.
17 It didn.t look like there.s a problem
18 with gas exchange. PCO2 remains within the normal
19 limits. However, when you look at the PF ratio, PAO2
20 over FIO2 here, there.s a progressive decrease in the
21 PF ratio. And this is the defining feature of human
22 ARDS, and we.re able to recapitulate that here in the

1 rabbit model.

2 Lactate goes up. Okay, lactate goes up

3 for the one with the small lungs as well. Base excess

4 goes down. So, it looks like human ARDS, it looks

5 like septic shock -- are even more evidence of this.

6 So, when you look in the human literature of human

7 ARDS, the majority of these patients also have acute

8 myocardial-depression. And the way that you diagnose

9 that is with echocardiography. And very fortunately

10 for us, the people who work in my lab, three of them

11 are cardiologists and they can do echo on these

12 rabbits.

13 And what we have found is that at pre-

14 infection baseline, the heart is working properly.

15 So, there is a certain amount of blood that.s pumped

16 out of the left ventricle and that.s the left

17 ventricular ejection fraction. It.s between 60 and 75

18 percent at pre-infection baseline in rabbits.

19 Now, in the terminal phase of ARDS or

20 septic shock in the VABP model, all the rabbits have

21 global left ventricular hypokinesia, so that the heart

22 is not pumping as well. And so only about 50 percent

1 of the blood is actually pumped out of the left
2 ventricle. And this is a very, very consistent
3 feature.
4 What else makes this model look like a
5 human infection? We look at platelets over time,
6 except for this one animal in the red. For the other
7 nine animals using the natural history study, you
8 know, by the time that they die, it.s also associated
9 with the bottom of the platelets. So, they clearly
10 have very severe thrombocytopenia in these rabbits.
11 And that is manifest in about 20-30 percent of rabbits
12 as disseminated intervascular coagulation, just like
13 you see in a subset of human patients. So, this is
14 skin petechiae, bleeding in the skin. There is
15 bleeding in the gastrointestinal tract, there.s
16 bleeding into the bladder. This is a very, very
17 severe model.
18 So, what is the trigger to treat in
19 this model? You know, we determined this empirically
20 but we back it up with data. And so what you see here
21 is at five-hour post infection is when we start
22 treatment in the acute pneumonia model. There.s

1 already evidence of pulmonary edema, there.s already
2 evidence of neutrophilic infiltrate, there.s evidence
3 of hemorrhage in the lung. And this, you know, you
4 can see this without radiology. The reason is we can
5 do histology very well here for a much higher
6 resolution picture of the disease.
7 Now, in this model we treat at six
8 hours post-infection. It doesn.t work very well. So,
9 it looks like the golden hour of treatment for these
10 models is five hours or less. If you treat later on
11 at six hours post-infection, it.s too late. And the
12 data that I.ve shown you earlier at five-hour post
13 infection in this model, about two-thirds of the
14 rabbits have hypoxemia. So, this is consistent with
15 the clinical features of human pneumonia.
16 The VABP model, in contrast, can.t
17 treat it at five hours post-infection -- it may be too
18 late because of that hypotension. So, we found that
19 treatment is probably best at three-hour post-
20 infection. We haven.t titrated this out very well.
21 We.ve only done this at three and six-hours post-
22 infection. But three hours definitely works a whole

1 lot better than six hours post-infection for when to
2 initiate treatment.
3 Therapeutic efficacy in the acute
4 pneumonia model is contingent really on the efficacy
5 of the antibiotic. In contrast, in the VABP model
6 because of the ARDS septic shock, treatment requires
7 supportive care, ICU-style supportive care, including
8 fluid challenge and norepinephrine. But it.s not that
9 easy to do this kind of supportive care because half
10 of the rabbits have very big lungs. And the concern
11 there is if we come in with fluid challenge, we could
12 overload the animal with fluid and then they would die
13 from the fluid overload rather than it benefiting
14 them. So, in this model we took a very fluid
15 restrictive approach and we rely earlier on the use of
16 vasopressor rather than fluid challenge to resuscitate
17 these animals.
18 So, efficacy data in the acute
19 pneumonia model we treated the animal with saline and
20 they rapidly die, as expected. However, when we treat
21 with 80 milligrams per kilogram of Meropenem every two
22 hours -- okay, this is every two hours, nasty

1 experiment -- 12 doses total, we have an improved in
2 survival so that 67 percent of these animals survive.
3 And the reason we have to do this nasty
4 Meropenem dosing regimen -- you know, Bill Weiss, our
5 collaborator, will go into it at the end of this talk,
6 how that dose may mimic the human Meropenem PK.
7 The VABP model -- in the VABP model, in
8 contrast, you know, we still get the rabbits that are
9 treated with saline still all die, but those that were
10 treated with Meropenem alone, half of the animals die
11 -- even though treatment in this model was
12 administered earlier at three-hour post-infection.
13 So, it indicates that maybe antibiotic
14 treatment alone is not sufficient. And certainly in
15 human ARDS, especially in the ICU setting, you.re not
16 going to be treating with Meropenem alone, but that
17 supportive care will be given to the patients, so we
18 want to mimic that in the animal model. And here what
19 we founds is that rabbits that were treated with
20 Meropenem plus standard ICU supportive care, including
21 fluid challenge and norepinephrine, they have the best
22 survival.

1 These are preliminary data but some of
2 the P value shown is already statistically different.
3 The difference between the red and the green line is
4 already very near statistical significance, even
5 though we.re only halfway through the study. Oh, I.m
6 sorry. And treatment with fluid challenge and
7 norepinephrine alone doesn.t do very much. How do I
8 go back? Can we go back please, one more? Back,
9 back, back, back, back, back, back. Here we go.
10 Thanks.
11 The blue line, fluid challenge with
12 norepinephrine, it only shifted the survival curve to
13 the right a little bit but they all die. So, we need
14 that antibiotic onboard as well.
15 Now, in the acute pneumonia model,
16 survival is correlated with reduction in lung weight
17 to body weight ratio. No surprises there. In the
18 acute pneumonia model, it.s the same that Meropenem
19 treatment is associated with smaller lungs. But, you
20 know, half of the rabbits have small lungs to being
21 with, so how did we save these rabbits from death? We
22 wanted to know that. So, we look at a variety of

1 different biomarkers.

2 Here are the CFU count in the different

3 organs. And you can see here that survival is

4 associated with -- or the efficacy of Meropenem is

5 associated with its ability to clear bacteria from the

6 organs. In these -- you know, both of these models

7 were established using a pan susceptible strain 6206.

8 Its MIC to Meropenem is 0.25 micrograms per mil. And

9 so, there is, as predicted, there would be bacterial

10 killing that you see here.

11 In this model, other outcomes are

12 possible -- not just CFU count and lung weight. For

13 example, how much fluid did we use? How much

14 norepinephrine did we use? And we actually used

15 amounts that are very similar in patients who are

16 treated for human ARDS.

17 So, we also look at a variety of

18 different biomarkers over time. So, this is the four

19 experimental groups in the VABP model. This is the

20 time post-infection. So, zero-hour post-infection is

21 the baseline. And then 3, 6 -- I.m sorry, 3 and 9

22 hours post-infection at the time before euthanasia.

1 Okay, and what you see here is rabbits
2 that were treated with saline, there is a decrease in
3 the PF ratio. In the rabbits that were treated with
4 fluid challenge and norepi there is also a decrease in
5 the PF ratio. In human ARDS, this kind of PF ratio is
6 considered moderate ARDS.
7 Okay, here are the data for Meropenem.
8 So, Meropenem treatment alone was able to halt the
9 progression of VABB in this model. So you don.t get
10 that PF ratio dropping to a very severe level. With
11 Meropenem and fluid challenge plus norepinephrine you
12 also see that halting of disease progression.
13 We look at other clinically relevant
14 biomarkers like lactate and you see here, lactate
15 increased in the two groups that -- where the animals
16 die. In the Meropenem-only group you see it also
17 increases to eight. Eight in rabbits is not like
18 eight in human. So, in rabbits, the normal range in
19 rabbits is actually anywhere between two and eight.
20 So, in human, you know, lactate of eight is quite
21 severe.
22 But the best outcome, it appears, is

1 with Meropenem plus fluid challenge and norepinephrine
2 where we halt that progression of ARDS. The same goes
3 with base excess here. When we look at white blood
4 cells and neutrophils, just like in human ARDS, one
5 would expect leukopenia and neutropenia, and that.s
6 what we see here. You know, there.s a drop in the
7 number of white blood cells mostly due to neutropenia.
8 And, as I mentioned earlier, these
9 neutrophils get trafficked into the lung in an I08-
10 dependent manner. And you actually see leukocytosis
11 in the groups that were treated with Meropenem. Okay.
12 So, like here. They actually increase in numbers
13 because they survive the infection.
14 Platelets. Platelets drop to a very
15 severe level in the first two groups but that
16 thrombocytopenia is halted with the treatment with
17 Meropenem in the last two groups here.
18 So, in summary, you know, I.ve shown
19 you data from two rabbit models, the acute pneumonia
20 model and the VABP model. You know, our natural
21 history was designed to determine the extent to which
22 the pathophysiology of rabbit -- in the rabbits mimic

1 human non-ventilated hospital-associated pneumonia or
2 the ventilated version of it. And, you know, it would
3 be good to hear from the panel and from the audience
4 whether, you know, the model that I.ve presented here
5 does that. How well it mimics the human disease.
6 The acute pneumonia model uses a wake
7 rabbit; the VAPB model uses anesthetized rabbits
8 that.s ventilated with low tidal volume. The
9 pathophysiology is different. One is of -- where the
10 animal dies of profound respiratory failure; in the
11 other group they die of ARDS septic shock, including
12 myocardial depression.
13 I didn.t have time to show you data but
14 when you look at other biomarkers like cardiac
15 troponin, CKMB, myoglobin, all of those things track
16 with the echocardiography also.
17 So, the primary outcome in both models
18 are survival. The second outcomes include, you know,
19 the usual CFU and lung weight to body weight ratio,
20 but also physiological monitoring and longitudinal
21 biomarker analysis of things like neutrophils and
22 cardiac troponin and whatnot.

1 Antibiotic dosing in the acute
2 pneumonia model can only be done by bolus
3 administration. We have done as much as every two
4 hours, and it.s very feasible to do that in large
5 animals, in rabbits. Antibiotic dosing in the VABP
6 model is by use of a programmable syringe pump that
7 may better allow for mimicking of the human
8 concentration time curve. And Bill will present those
9 data next.
10 Supportive care is not possible in the
11 awake rabbit model. They.re running around. But
12 supportive care is actually an essential feature of
13 the VABP model, where we need to be able to support
14 the blood pressure, support tissue profusion for the
15 animal to not die, allowing time for the antibiotic to
16 work.
17 Now, in terms of feasibility, you know,
18 any labs can do the acute pneumonia model. It.s very
19 simple. It only requires you to be able to intubate
20 the rabbit. Put bacteria in the lung. It.s just like
21 a mouse. The only problem is, as Dr. Walsh was
22 mentioning, you know, it.s a higher standard of care.

1 Maybe at Cornell they are required to check on the
2 rabbits every -- twice a day. At UCFF we are required
3 to check on the rabbits every two hours.
4 So, for us, you know, dosing every two
5 hours is no big deal because we.re there anyway. And
6 this is because there.s a lot of regulation associated
7 with the use of USDA species, especially Type E, that
8 these animals go under where we don.t treat whatever
9 pain and suffering that we cause to the animal.
10 And the only way to alleviate pain and
11 suffering in these animals is by humane euthanasia.
12 And the way that we achieve that is by carrying around
13 a lactate meter. So, these animals -- it.s time for
14 them to go, to be euthanized when their lactate is
15 above 10 millimo per liter. It.s an objective way to
16 identify animals that are in respiratory distress, so
17 you can euthanize them. So, these animals -- these
18 models can be done humanely, it.s just that it
19 requires a higher standard of care to be able to catch
20 them.
21 The VABP model is very complicated. It
22 requires an experimental ICU setting and it requires a

1 team of four physicians with 12 years -- combined
2 years of ICU experience to be able to do this. And so
3 these are the people who work on the rabbit VABP model
4 and these are the people in my lab who work on the
5 acute pneumonia model.
6 BILL WEISS: So, in the interest of
7 time, we decided to put the summary of the PK all on
8 one slide to make it a little bit easier to discuss.
9 In doing the rabbit model that.s been described, the
10 efficacy, it lends itself to possibly getting better
11 humanized dosing because it is a larger species and
12 you can do a lot more with that rabbit.
13 And we also heard this morning that
14 there were two ways to maybe go about this.
15 Intermittent dosing, which several examples were given
16 for MIRING models, or continuous infusion. So, the
17 data that.s presented here on the left hand side is
18 the acute model. And as has been described, these are
19 conscious rabbits, you can.t do an infusion. Rabbits
20 are very nervous creatures and you have to be very
21 careful with them. So, this is -- the acute model was
22 done at 80 migs per kig, as he said, Q2-hour. And the

1 idea there was to try to simulate lower dose
2 Meropenem, the 1 gram Q8-hours with a very short
3 infusion.
4 When you look at the literature, that
5 particular dose, the measure of AUC varies a little
6 bit, but we found one paper -- Binh found one paper
7 that looked at both the 1 gram and the 2 gram, so
8 we.re going with that data. So, it.s an AUC of 124
9 microgram hours per mil. The time of MIC listed here
10 is based off the strain that Binh used in his rabbit
11 model, which is the 6206, which has a low MIC of .25.
12 Clinically, that one gram Q8-hour dose
13 should reach the target for Meropenem, which is at
14 least 40 percent of the dosing interval for MICs up to
15 two. So, that dose should cover a wide range. So, it
16 should cover other MICs other than the one Binh used.
17 You can see in the graph the solid red
18 line is the PK after a single 80 mig per kig dose.
19 And that if we extrapolate that out every two hours,
20 it gives, you know, trough and C-max values. The
21 green line is the PK taken from the one paper after
22 the one gram Q8-hour or the 10 infusion. So, again,

1 as we.ve seen this morning, it.s not perfect but you
2 get an approximation of the PK you see in human dosing
3 for VABP patients with one gram dose.
4 The AUC and up case, looking at that
5 was higher than the human dose at the same, but then
6 if you look at some of the data for Meropenem with
7 Monte Carlo simulations, that AUC can vary either side
8 of that. So, it is in the same ballpark as was seen.
9 And in the model that Binh just described, I saw about
10 67 percent survival with this dosing regimen
11 simulating the one-gram dose.
12 Now, the graph on the right was done
13 doing the staggered continuous infusion. So, how did
14 that work? The infusion was done over eight hours at
15 different intervals. So, it was like 1 to 2, 2 to 3,
16 3 to 4, changing the dose each time to simulate PK
17 that was equivalent to, I think it was, 20, 28, 35,
18 10, 5 and 1 milligram per kilogram. So, there.s a lot
19 that went into just getting that regimen in terms of
20 preliminary dosing in all those doses and then
21 modeling it and simulating it to try to simulate what
22 we wanted -- what Binh wanted to achieve.

1 So, with that regimen simulating now
2 for VABP patients the higher dose Meropenem, which is
3 the 2-gram Q8-hour over a 3-hour infusion, that AUC
4 was 232. With the dosing that Binh gave that I just
5 described, the AUC was 273. You can see the two lines
6 overlap very nicely in terms of the plasma exposures
7 observed. And with the supportive therapy with this
8 type of dosing, the efficacy in terms of survival did
9 increase significantly up into the high 80s at that
10 point. So, the rabbit will allow this type of
11 modeling and this type of dosing to better simulate
12 the human exposures.
13 Now, we will say that in the acute
14 model, that PK data was in infected animals. The PK
15 data for the staggered infusion is in uninfected
16 animals. It has been done and actually I think the
17 samples are in my lab waiting to be analyzed now to
18 see whether or not the exposure was similar in
19 infected versus uninfected for the staggered infusion.
20 The other things we haven.t taken into
21 account here is protein binding. Human plasma,
22 Meropenem is low, it.s about 6 percent. And based on

1 literature and what we.ve tried to measure, it can
2 vary anywhere from maybe 10 to 20 percent in rabbit
3 plasma, which is not significantly higher than human
4 and probably will have minimal impact on the numbers
5 we see here. And that was it in a nutshell.
6 DR. MARINA KOZAK: Thank you so much.
7 So, our last large animal model, extra-large animal
8 model talk will be by Dr. Andrew Phipps. Dr. Phipps
9 is a subject matter expert supporting BARDA.s
10 antibacterial program with over 20 years of experience
11 in drug development, comparative medicine,
12 microbiology and animal models.
13 DR. ANDREW PHIPPS: So, thank you,
14 Marina, for that introduction. And I.d like to thank
15 you all for listening to me talk about our work on the
16 porcine model of ventilator-associated bacterial
17 pneumonia caused by pseudomonas and Acinetobacter. I
18 have no disclosures. And I.d like to start with my
19 acknowledgements up front. A lot of work has gone on
20 by colleagues at BARDA, colleagues at FDA and also the
21 NIAID BARDA FDA working group.
22 So, we started the morning talking

1 about mice, and then we moved on to rabbits, and now,
2 as Marina said, we.re going to talk about an extra-
3 large animal model of the large animal models. But
4 before we do that -- maybe...
5 DR. MARINA KOZAK: Maybe turn the
6 mouse?
7 DR. ANDREW PHIPPS: Let me do the
8 mouse. Woops. There we go. So, I.d like to talk a
9 little bit about BARDA.s nonclinical division. So,
10 BARDA has a nonclinical division. We have an IDIQ
11 contract with several research organizations that
12 actually do our animal model development work. We
13 have a biological network, we have a RAD NUC network.
14 We.re also developing capability in BSL-4, ABSL-4
15 network, and then we have COM network. The goal here
16 is to do animal model development and also evaluation
17 of medical countermeasures that covers the CV4 mission
18 of BARDA, and this work is occurring under our
19 biological network.
20 So, the work I.m going to talk about
21 today has been carried out at two organizations under
22 our network. And I wanted to talk a little bit about

1 borrowing some of the concepts from the animal rule.
2 So, how can we apply animal models in late stage drug
3 development? We can do that when human efficacy
4 studies are not ethical and field trials are not
5 feasible. We would like to have a well-understood
6 disease mechanism and prevention or reduction by the
7 product in the animal model that we.re working with.
8 We.d like to understand the action
9 within the animal model or the animal models, and that
10 they should be predictive of the human response.
11 We.ve talked a little bit today about endpoints, and
12 so we.re looking at endpoints that are related to the
13 desire benefiting humans. So, we.d like to be able to
14 translate how the human would feel, function or
15 survive. We also would use pharmacodynamics or
16 pharmacokinetic data for translation of an effective
17 dose to humans.
18 So, if we can obtain efficacy data from
19 an adequately well-characterized animal model, it
20 could be used and supplement the clinical data from
21 patients with a variety of infections caused by
22 pseudomonas in one or more descriptive studies. There

1 are currently no adequately characterized animal
2 models for the indications being considered and unlike
3 trials for biothreat agents, it.s ethical to conduct
4 human efficacy trials. However, feasibility of
5 conducting those trials is an issue.
6 So, what are some advantages of the
7 porcine model? Similar to the rabbit, the anatomical,
8 physiological and biochemical similarities to humans,
9 the gross and microscopic anatomy of the porcine lung
10 is similar to human lungs. Pigs have a similar array
11 of innate immune function in the lungs, and so we.re
12 talking about an immunocompetent model here. We.re
13 not using immunocompromised or neutropenic animals.
14 These pigs are 12 to maybe 15-weeks of
15 age and weigh anywhere between 20 and 30 kilograms, so
16 their large size is amenable to the use of equipment
17 that.s typically used for humans in critical care
18 scenarios. And we know, going back at least 20 years,
19 that their previous studies using swine, that they.ve
20 demonstrated that these animals can be mechanically
21 ventilated for up to 3-4 days after bacterial
22 inoculation, which would allow for sufficient time for

1 the development of disease, initiation of therapy and
2 monitoring of a response to therapy. So, there are
3 several publications looking at this model.
4 So, what have we done so far? So, we
5 actually -- and I.ll talk a little bit about why we
6 necessarily had to do this, but we have created and
7 characterized strains of ceftriaxone-resistant
8 pseudomonas. So, our pseudomonas strain is ATTC27853
9 and we used a serial process to actually increase the
10 ceftriaxone MIC to greater than 256 micrograms per
11 mil. The Acinetobacter strain is already resistant to
12 ceftriaxone, and I.ll talk a little bit about that
13 with the challenges and why we need a ceftriaxone-
14 resistant strain for this model.
15 We also have worked to establish a
16 model for prolonged ventilation in the porcine model.
17 So we use all female Yorkshire land-raised cross-bred
18 juvenile pigs. These pigs are anesthetized and
19 mechanically ventilated for 96 hours. And, as I
20 pointed out, mechanically ventilated pigs, a majority
21 of them will go on to develop a spontaneous pneumonia.
22 Typically, organisms that we would see would be

1 Pasteurella multocida, introvactor species,
2 staphylococcus species, streptococcus -- so, similar
3 but not exactly the kinds of organisms that are
4 associated with HABP/VABP in humans. But in order to
5 prevent them developing spontaneous pneumonia, we need
6 to treat them with ceftriaxone from the beginning of
7 the experiment.
8 So, we found out very early on in the
9 pilot that we needed the ceftriaxone treatment and,
10 therefore, the challenge strains have to be
11 ceftriaxone-resistant, otherwise the animals will
12 develop pneumonia within a period of time -- you know,
13 48 hours, which compromises our ability to use them in
14 the study.
15 After we.ve established the pilot, we
16 will establish the bronchoscopic challenge and dose
17 range finding for each strain, and then we.d want to
18 move on to characterize the natural history of the
19 disease in the porcine model. We.ll talk a little bit
20 about what we.re monitoring but we.re looking for
21 disease development and progression, and also the
22 establishment of euthanasia criteria.

1 So, I.m very happy that Binh Diep set
2 me up for all of this and talked a little bit about
3 the complexities in using anesthetized mechanically
4 ventilated models, but the establishment of euthanasia
5 criteria and endpoint survival is not trivial because
6 these animals are basically maintained on supportive
7 care. So, we have to have criteria to use to say that
8 they have met certain objective criteria ideally to
9 say that, you know, they no longer are able to
10 survive.
11 And then eventually we would like to
12 use the developed model to evaluate the efficacy of
13 antibacterial drugs to which the strains are
14 susceptible and resistant. So, we would move on to a
15 proof of concept study using an antimicrobial with
16 known activity against our strain of pseudomonas to
17 demonstrate, as has been done in the rabbit model,
18 that there would be a difference in either endpoints,
19 which could be survival or a combination of
20 biochemical and other parameters that we would
21 measure.
22 So, what are some of the challenges and

1 considerations in using pigs? Well, so unlike rabbits
2 and other laboratory animal species, pigs present
3 somewhat of a challenge in actually establishing
4 venous and arterial catheterization. It.s a little
5 more complicated to do based on their anatomy.
6 There.s not as many visual cues to use, and it.s not a
7 trivial item.
8 The other thing is that placing a
9 urinary catheter in a male pig is practically
10 impossible, and so in order to put a urinary catheter
11 in, we.ve decided to use all female pigs, for which
12 this is much straightforward.
13 Intubation is also not trivial. So,
14 these animals are maintained for 96 hours and one of
15 the things that we have to do is to use a high volume,
16 low pressure endotracheal tube to prevent trauma. And
17 then also the parameters for mechanical ventilation.
18 As Binh Diep pointed out, we use sparing parameters,
19 lower title volumes, positive and expiratory pressure.
20 Basically, what we.re trying to do is to set the
21 animal up for the development of pneumonia but, yet,
22 we don.t really want to induce acute lung injury very

1 quickly.

2 We also have to consider the

3 maintenance and support. So, unlike the rabbit model,

4 we use a continuous rate infusion for anesthesia, so

5 we use a mixture of drugs in combination to maintain

6 anesthesia. We need to provide IV fluids and

7 dextrose, we have vital sign monitoring, we can

8 perform hematology and clinical chemistry. And then

9 when we reach the endpoint of the study, we have to

10 consider necropsy and bacteriology.

11 So -- and I apologize for not having

12 nice pictures but I think that you can sort of

13 imagine, based on the prior presentation, about having

14 an animal that.s being mechanically ventilated. So,

15 unlike the rabbit, and I.m assuming from your cartoon

16 that the rabbits are actually on their back -- they.re

17 face down, yes. So, you cannot maintain a pig in a

18 position on their back for long periods of time. So,

19 these animals are actually in, what we call, ventral

20 recumbency. So, they.re face down.

21 We have to figure out ways of

22 restraining them in this position. We also have to

1 deal with pressure sores and so we have foam padding.
2 And then we also have positioning -- we keep them with
3 their head at a negative 15 degrees relative to the
4 horizontal plane, which allows for drainage of fluids
5 away from the lung. And previous models have actually
6 used the opposite -- they use the Anti-Trendelenburg
7 position where they actually elevate the head, which
8 we found to complicate this model.
9 We do have some issues, like I said,
10 with pressure sores on the sternum, the hind limbs and
11 the forelimbs, so we.re using padding and somewhat
12 changing the position of the pigs over the 96-hour
13 period to prevent this.
14 So, monitoring -- and I appreciate the
15 video -- basically, we use the same types of monitors
16 in a clinical ICU setting. We.re able to monitor
17 heart rate, mean arterial pressure, core body
18 temperature. We use a pulse oximeter, ECG, we monitor
19 urine output, arterial blood gas, respiratory rate.
20 We look for any spontaneous respiration. We can
21 measure total minute volume, entitled co2, FiO2. We
22 have our mechanical parameters like plateau pressure,

1 peak -- excuse me -- inspiratory pressure of
2 compliance, resistance. We can calculate arterial O2
3 divided by FiO2, which is the fraction of inspired
4 oxygen. We do maintain a constant cuff pressure on
5 the endotracheal tube. We do some quantitative and
6 qualitative estimates of tracheal secretion. We can
7 perform hematology assessments, clinical chemistry.
8 We.re looking at C-reactive protein and procalcitonin.
9 So, we.re monitoring a large number of
10 parameters continuously so these animals are monitored
11 continuously by staff. There.s veterinarians on staff
12 24/7 for the entire period in a critical care setting.
13 We.ve talked a little bit about this.
14 So, for ceftriaxone, plasma protein binding is not
15 well-characterized in pigs, and so we wanted to look
16 at -- in the literature, a dose of 50 milligrams per
17 kilogram given every 12 hours by a 30-minute infusion
18 has been used in these animals. So, we went ahead and
19 started to look in the PK of ceftriaxone in these
20 animals over a 12-hour period. So, what I.m showing
21 here is plasma concentrations. This is total drug,
22 Dose 1 and Dose 5. And using this, we actually did

1 some modeling based on plasma protein binding and
2 looking at various, either 30 percent unbound, 50
3 percent unbound, 70 percent unbound, or 100 percent
4 unbound. In humans, plasma protein binding of
5 ceftriaxone is very high. In large animal species it
6 tends to be lower.
7 Using a target of 70 percent free time
8 above MIC, if we actually look across and assume that
9 there.s either around 30 percent binding or 50 percent
10 binding, and we extrapolate that to 70 percent free
11 time above MIC, we should have coverage up to around a
12 ceftriaxone MIC of 2 micrograms per mil.
13 So, since our challenge strain has an
14 MIC of 256, we don.t anticipate there would be any
15 activity of the ceftriaxone. However, we know from
16 our pilot studies that this dose and regimen is
17 sufficient to prevent the development of spontaneous
18 pneumonia.
19 So, for bacteriology we.re very
20 interested in looking at blood culture at the time of
21 euthanasia. So, since this is a large animal model,
22 we have the ability to collect 100 milliliters of

1 blood for the purposes of doing blood culture so we
2 can run 10 adult-size BACTEC blood culture bottles.
3 Now, in differences between the mouse
4 model and the rabbit model, when you actually look at
5 the size of the porcine lung, it.s not possible to
6 actually homogenize and plate the entire lung. And so
7 this is one of the issues about doing quantitative
8 bacterial assessment, is that we need to have a
9 reproducible sampling plan.
10 So, we.ve developed a pre-specified
11 tissue sampling plan where 8-10 samples of the lung is
12 actually sampled, weighed, homogenized, and then
13 plated for quantitative bacteriology. In addition,
14 any colonies that we isolate go on to have
15 identification by MALDI-TOF, and we do antibiotics
16 susceptibility testing. And that.s because in these
17 animals we want to know is there still background
18 organism that.s not pseudomonas or Acinetobacter
19 present? And, if so, what is that organism and what
20 is the MIC against especially ceftriaxone?
21 So, when we were doing this without
22 antibiotics, this became an exercise in clinical

1 microbiology because you would get all sorts of
2 organisms coming out in polymicrobial infections.
3 We.d have to go through and identify those and look at
4 the antimicrobial susceptibility. That.s much reduced
5 with ceftriaxone, although it.s still possible that
6 you will get other organisms when we do the
7 bacteriology.
8 And I want to spend a little bit of
9 time talking about the proposed euthanasia criteria.
10 So, very similar to the rabbit model, we do provide
11 supportive care. We do not use norepinephrine, so
12 we.re not using any vasopressors in this model. We do
13 provide fluid support. And so basically you have to
14 have some objective criteria to determine when this
15 animal has actually reached its endpoint.
16 So, remember, they.re anesthetized,
17 they.re fully sedated, they feel no pain, there.s no
18 nociceptions. So, basically, we have to come up with
19 some parameters. And the first parameter is actually
20 technical. So, any adverse mechanical event that
21 cannot be remedied. So, in other words, if we have to
22 stop ventilating the animal for any reason, we.re not

1 going to wake this animal up. It.s met its endpoint.
2 So, we.d like to minimize the number of technical
3 endpoints that we would reach.
4 So, an example -- let.s just say that
5 the endotracheal tube becomes displaced. It.s not
6 possible to replace the endotracheal tube so,
7 therefore, the animal can.t continue. So, severe
8 hypoxia -- we.re defining that as PAO2 less than 40
9 millimeters with two measurements five minutes apart
10 with the FiO2 at 100 percent. So, basically severe
11 hypoxia.
12 Again, since we.re measuring mean
13 arterial blood pressure, persistent hypotension -- so,
14 less than 30 millimeters of mercury for more than 30
15 minutes. Basically, this animal will not survive in
16 this situation, and so its reached what we would call
17 an endpoint. And then for electrocardiography,
18 asystole or no heartbeat for more than three minutes.
19 So, otherwise, you know, you can continue to
20 mechanically ventilate the animal but you have to have
21 endpoints that we can use to say that we.ve reached
22 non-survival.

1 So, necropsy, we.re looking at gross
2 necropsy findings. I talked about sterile collection
3 of tissues for bacteriology. We also collect lung
4 samples for histopathology so we have a histopathology
5 grading score. We.re grading those lesions. And if
6 this were to move forward and part of the natural
7 history study, we would basically be blinding the
8 histopathologist as to which animal they were looking
9 at, so as not to introduce any bias. And then we also
10 have a collection of a limited set of tissues for
11 histopathology.
12 So, conclusions -- we.ve been able to
13 successfully ventilate more than five animals for 96
14 hours. Again, these are Yorkshire land-raised pigs,
15 all female pigs, 20-30 kilograms. This large animal
16 model is amenable to physiologic and microbiologic
17 characterization of the natural history of the
18 disease, which I think is very important to
19 characterize.
20 The large animal studies, as we.ve
21 talked about, are challenging to establish and
22 conduct. And so this is one of the limitations of the

1 model, is that the complexity and the requirement for
2 a critical care setting limits the number of animals
3 that we can actually do. So, at most, it.s probably
4 possible to mechanically ventilate two animals
5 simultaneously. We certainly can.t do 12. 13. But I
6 think that we have to balance this with the advantages
7 of using the model over a small animal model.
8 The other thing is I think that
9 hopefully we can keep these animals alive a lot
10 longer, which allows us to have a more -- I don.t want
11 to say relevant but representative disease progression
12 as you would see in human beings. Allow time for the
13 intervention. And as we go through the natural
14 history study and establish a baseline of the disease
15 progression, we.ll be able to look at these parameters
16 and understand how these parameters change just in the
17 mechanically ventilated pig, and then follow that up
18 with the natural history once the animals have been
19 infected with pseudomonas or Acinetobacter.
20 So, given the complexity, I think that
21 we.re a little bit behind the work in the rabbit model
22 but our hope is that we can actually progress this

1 relatively quickly into the inoculation phase
2 following the characterization of the inoculation
3 dose, then we will bring that fully all the way
4 through a natural history study, and then be able to
5 do a proof of concept study.
6 So, I put this up here, and this is the
7 same as Tina Guina.s slide earlier today on how to
8 contact BARDA, and I think you for your time.
9 DR. JOHN FARLEY: Thanks, Andrew, and
10 thanks to all the presenters this afternoon. Some
11 really interesting stuff to talk about. We.re going
12 to take a 15-minute break and come back at about five
13 minutes before three, and then finish up with a panel
14 discussion. Thanks.
15 (Break)
16 DR. JOHN FARLEY: ...and take their
17 seats. I want to check that we have Bill -- William
18 and Tom available on audio. How are we doing with
19 opening up audio? Do we have William and Tom on
20 audio? (Off-mic comment) Oh, good, thanks.
21 So, as we get things together, we have
22 a microphone in the audience. I don.t want the

1 audience to feel like they.re not welcome to
2 participate in the discussion. So, if you head up to
3 the mic, we.ll see you and we.ll invite you in to join
4 in the conversation.
5 Okay, good. So, why don.t we flash up
6 the questions. Can we do that? Or do we not have a
7 question slide? Marina and I were talking and we
8 actually had sort of some more specific issues than
9 the questions that we thought we might start with.
10 So, since it.s always awkward for the first few
11 minutes, I.ll go ahead and ask the first question and
12 sort of introduce one topic.
13 So, I think one of the things I.ve been
14 very impressed with with really all the rabbit models
15 is the natural history studies and the justification
16 of a trigger to treat. But what I.m interested in is
17 in the acute pneumonia models, we sort of ended up
18 with very different trigger to treats times if you
19 compare Binh and Tom, right? I believe that Tom.s
20 trigger to treat was 12 hours, if I.m not mistaken,
21 and Binh.s is earlier.
22 DR. BINH DIEP: Was it six hours in

1 Tom.s model?
2 DR. JOHN FARLEY: Yeah, I think 12.
3 DR. BINH DIEP: 12?
4 DR. JOHN FARLEY: Yeah. So, maybe you
5 could talk through sort of your thoughts, and then
6 maybe once Tom joins us we can hear what his thoughts
7 are. That sounds like it might be him. So...
8 BINH DIEP: So, as I understand it in
9 the two models, the two acute pneumonia models using
10 awake rabbits are quite different. We use the rabbits
11 that have normal immune systems, the other one is a
12 neutropenic rabbit model. The inoculum that we use is
13 -- the inoculum size for both models, I believe, are
14 rather similar. It.s about 1 x 10 to the 8th.
15 The strains are different. From our
16 experience, one parameter matters a lot, and it is
17 this: The inoculum, even though it.s 1 x 10 to the
18 8th, that is in a volume for us of 2.2 milliliter for
19 the VABP model and 1.8 milliliter for the acute
20 pneumonia model. There was a --
21 DR. THOMAS WALSH: I can hear them but
22 nobody can hear me.

1 DR. JOHN FARLEY: We can hear you now,
2 Tom. Binh is just... Tom? Tom, we can hear you.
3 DR. THOMAS WALSH: Can you hear us?
4 Because we.re really concerned you can.t hear us.
5 DR. JOHN FARLEY: We can hear you. Can
6 you hear me?
7 DR. THOMAS WALSH: Yes, yes. Because
8 William and I were trying to access earlier and we
9 weren.t -- we could hear you but it did not appear as
10 though you could hear us. But you can hear us now, is
11 that correct?
12 JOHN FARLEY: That.s correct.
13 DR. THOMAS WALSH: And can people hear
14 William?
15 WILLIAM HOPE: Can you hear me?
16 JOHN FARLEY: Can you hear me? And,
17 William, we can hear you too. All right.
18 WILLIAM HOPE: Okay, we.re all good,
19 we.re all good.
20 DR. THOMAS WALSH: Excellent. Very
21 good.
22 DR. JOHN FARLEY: Excellent. We.re all

1 on. So, what I had started the discussion with was
2 the sort of differences in trigger to treat in the
3 rabbit models. Because there.s been a lot of very
4 nice elegant natural history studies done by you, but
5 you end up in very different places.
6 So, Binh was just talking through his
7 trigger to treat justification. So, maybe you can
8 summarize real quick.
9 DR. BINH DIEP: So, you know, the
10 inoculum matters a lot. And the way that we inoculate
11 our rabbits is with a large volume. We ensure that
12 all six lobes of the rabbit lungs get bacteria. And
13 the way that we prove that is, just like in one of the
14 earlier presentations with the mouse, we use a blue
15 dye or India ink, and we found that they.re everywhere
16 in all six lobes of the lung.
17 And this actually matters a lot because
18 even with a higher dose of bacteria, if all the
19 inoculum gets into the right lung, for example, the
20 animal will never die. They will never show any signs
21 of hypoxemia. They will live until whenever -- until
22 they clear the infection.

1 I understand it in the Walsh model, the
2 rabbit model with neutropenia, a smaller inoculum is
3 used perhaps --
4 DR. JOHN FARLEY: Well, we have Tom on
5 the phone so we.ll maybe --
6 DR. BINH DIEP: Right. 300 microliters
7 or something.
8 DR. JOHN FARLEY: Yeah. We.ll let Tom
9 go next.
10 DR. BINH DIEP: Right.
11 DR. JOHN FARLEY: So, maybe, Tom, you
12 could talk through a little bit your method of
13 inoculation, your inoculum size and strain?
14 DR. THOMAS WALSH: Precisely. So, if
15 we focus on the Pseudomonas aeruginosa, we.ve studied
16 a number of genetically defined bacteria initially
17 screened in mouse models -- then moved up until the
18 rabbit model system. And they have relatively similar
19 variance properties.
20 The next step then is to ascertain
21 inoculum. There.s a general standard that we.ve used
22 and that is we communize the tracheal bronchial tree

1 insofar as ascertaining that the tracheal bronchial
2 tree is colonized. And then true to form of our
3 patients as they go into immunosuppression, the
4 colonization transforms into infection. That
5 infection can be achieved with a relatively small
6 inoculum, meaning, approximately, 300 microliters. It
7 may differ depending on the organism or the intended
8 inoculum. But generally, 300 microliters is
9 administered in just a very fine aerosol with direct
10 endotracheal direct exam intubation. And with that
11 then you can see the emergence of the infection in the
12 next 24 hours.
13 Now, at the earliest onset, we can
14 initiate therapy within 6-8 hours and that.s at the
15 earliest onset that one would see infiltrates. We can
16 extend that out farther but then you.ll have a little
17 bit more in the way of infiltrates. We.re trying to
18 ascertain the earliest timing possible. There is a
19 bracket there, and I think the difference is in --
20 compared to the UCSF study, maybe surely -- well, one,
21 the volume, and two, the immune suppression.
22 I think the volume plays a key role.

1 Our intent is not to oversaturate the lung. When we
2 see the emergence of Pseudomonas pneumonia, if we were
3 to look at multiple ventilated associated pneumonia
4 patients and we look at Pseudomonas, typically, it
5 does start as a segmental or pulmonary infiltrate. It
6 may then go on to other segments of the lung. But it
7 doesn.t start as a diffuse alveolar interstitial
8 process.
9 And so with that we.re trying to
10 emulate that which we see in this rather slower
11 emergence of infection. Ultimately, all lobes are
12 infected but the colonization to infection is one that
13 we believe is quite realistic and moving toward our
14 patients. And I think the volume is a critical factor
15 insofar as achieving that difference. So, I think
16 therein lies the difference probably in just the
17 volume, given that the inoculant is quite similar.
18 JOHN FARLEY: Other questions or
19 thoughts from the panel on kind of the mechanics of
20 the rabbit models themselves?
21 MAN 1: I have a comment about
22 (inaudible) arise from and my work with phylogenetic

1 FDA Division on inhaled drugs. So, have you measured
2 the particle -- the droplet size distribution of the
3 aerosolized droplets which eventually get infected for
4 the rabbits? Because that will determine where it
5 goes.
6 DR. THOMAS WALSH: Sure. So, our
7 objective is not to create an LD or aerosol. We know
8 that we can colonize the tracheobronchial tree similar
9 to that which our patients have. So, it basically is
10 at the end of a small 16 gauge catheter with very,
11 very gentle administration that will seed the larger
12 tracheobronchial tree. Unlike, say, an aerosolized
13 tobra and aerosolized amikacin where you.re delivering
14 fine particles of 3-5 micron diameter all the way into
15 the alveolus. That generally is not what we see in
16 our compromised patients. It.s usually a
17 tracheobronchial communization and then starts
18 extending further in.
19 So, that initial tracheobronchial that
20 is in the large main stem bronchi in segmental bronchi
21 is much more of what we are trying to achieve in
22 comparison to, say, the very finely defined particles

1 that we would achieve, say, with aerosolized amikacin,
2 tobramycin or other agents.
3 BINH DIEP: For our rabbit model, we do
4 nebulize drugs like tobramycin and monoclonal
5 antibodies. But in terms of setting up the infection,
6 it.s not by nebulization of Pseudomonas aeruginosa.
7 What we found is that it.s necessary in order to
8 create this fulminant pneumonia that we need to infect
9 all lobes of the -- all six rabbit lung lobes.
10 And the way that we accomplish that is
11 putting big volume. That big volume alone doesn.t
12 kill the rabbit. The rabbit -- let.s say the volume
13 is about 10 milliliter of lung volume, and here we put
14 in to the lung of the rabbits 2.2 milliliter for a
15 VABP model.
16 JENNIFER HOOVER: Can I ask a general
17 question about the use of rabbits?
18 JOHN FARLEY: Sure. Absolutely.
19 JENNIFER HOOVER: So, rabbits, I think,
20 can be sort of prone to becoming ill by use of
21 antibiotics because it disrupts their microbiome.
22 Have you guys had any -- seen any experiences with

1 that and have any suggestions or thoughts on that
2 point?
3 DR. THOMAS WALSH: I could address that.
4 We have literally three decades of experience in
5 working with that with model systems. And as I
6 alluded previously, in addition to maintaining the
7 high standards of care through IACUC, USDA, AAALAC,
8 we.ve also worked hard to establish standards and
9 modulations for animal husbandry. And one of the real
10 challenges in managing rapids is exactly as you
11 indicated, in ascertaining the management of gas
12 intestinal microbiome.
13 Depending upon the antimicrobial agent
14 or even stress, one can start to see the emergence of
15 two forms of diarrhea. And the literature sometimes
16 is confusing on this, but we.ve characterized it very
17 well microbiologically and identified two clear
18 microbiological patterns. The most common that we
19 encountered is diarrhea caused by clostridium
20 spiroforme, which is the equivalent of clostridium
21 difficle.
22 The organisms are relatively closely

1 related. They both elaborate toxins. And in rabbits,
2 the costridium spiroforme produces a classic -- we map
3 rabbit pellets meticulously and we can way in advance
4 when there is this alteration that may be leading to
5 the development of costridium spiroforme diarrhea.
6 In order to prevent that, we have
7 rabbits on 50 milligram per liter of oral -- in the
8 drinking water of vancomycin. As you know, vancomycin
9 is not gastrointestinally absorbed but what that does
10 is suppress the costridium spiroforme. That.s not
11 unlike what we see in our patients. At the earliest
12 onset, those patients, immunocompromised patients may
13 very well go on oral vancomycin.
14 In this regard we.re preemptively
15 managing, and that has had a major effect in reducing
16 the morbidity and mortality of gastrointestinal
17 infection. Now, sometimes it breaks through, and what
18 we then see is -- as soon as we start to see the
19 alteration in stool, which in earlier times, in the
20 different models we were able to identify, yes, this
21 is c-spiroforme. Then we start a 50 milligram oral
22 dose Q-12 that in the vast majority of situations

1 shuts down.

2 There have been other situations, for

3 example, where we have come in and where rabbits.

4 facilities have been awash in costridium spiroforme

5 and have come in with our protocols, and save those,

6 literally, a whole rabbit colony.

7 The other form that you see is what.s

8 classically known in veterinary medicine as Tyzzer.s

9 Disease or typhlitis. Sometimes the two can overlap.

10 The c-spiroforme and Tyzzer, but Tyzzer is a very

11 distinctive one in which you see much more of a watery

12 diarrhea. And that.s one that is probably more of a

13 microbiomic disruption. It may have several different

14 causes, but we found in our hands that -- while it can

15 be disruptive and can lead to consider weight loss,

16 it... (Sound drops out)

17 JOHN FARLEY: We appear to have lost

18 Tom. Tom, can you hear us? If you.re still talking,

19 we actually can.t hear you. William, are you there?

20 WILLIAM HOPE: I am, John.

21 JOHN FARLEY: Great. Why don.t we wait

22 to get Tom back, and I think, Judy, I wondered, you

1 look like you wanted to say something and I bet it has
2 something to do with your Cipro experience back in
3 anthrax days.
4 JUDITH HEWITT: Well, not exactly. But
5 my question for people with rabbit models is what --
6 how much mouse data and what quality of mouse data
7 would you like to see before you start a rabbit study?
8 BINH DIEP: You know, I think rabbit
9 models are prohibitively expensive to be used as a
10 screen. And this is, you know, much better suited to
11 be done in mouse where you find, PKPD drivers of
12 efficacy, where you look at the concentration in the
13 epithelial lining fluid with destructive method of BAL
14 collection. All of this is really better done in the
15 mouse.
16 When it comes to rabbit models, it
17 becomes very expensive. And so usually when we
18 collaborate with industry, things have already been
19 very well characterized in mouse models. And, you
20 know, when we do collaborate, this is another species.
21 And if a drug that works in more than one animal
22 species will have probably a greater likelihood of

1 working in humans.

2 Maybe it will give you pause if

3 something works, you know, amazingly in mice and

4 doesn.t work in the rabbit, maybe it should give you

5 some pause and think about your developmental program.

6 But to use rabbits as a screening tool

7 is probably not feasible. You know, we.re talking

8 about -- when direct cost is included. For example,

9 like the VABP model, it.s $12-15,000 a rabbit. And

10 so, even when you can do a lot of rabbits at the same

11 time, 13 rabbits, it.s really not suitable to be used

12 as a screening tool. Not because of -- we.re not

13 limited by how many rabbits we can do, but it.s really

14 because of the cost.

15 TINA GUINA: I have a question to sort

16 of follow up on this. So, we.ve seen a great

17 presentation both from you, Binh, and Dr. Walsh, and

18 you have described a number of parameters and

19 biomarkers that you traced, including his pathology

20 and various physiologic science.

21 And in terms of model development and

22 model development for product developers, it.s really

1 important to -- there are two big questions in mind.
2 One is how important it is that these models really
3 reflect pathophysiology of human disease? And then
4 the second one, what really are the important models?
5 Sorry, endpoints for a drug developer. Right?
6 Because there are so many parameters, in the end, I
7 assume there.ll be a number of natural history
8 studies, and then even to look across the studies and
9 sort of identify the most critical parameters.
10 So, maybe we can discuss altogether
11 first what is -- how important it is that animal model
12 really reflects human pathophysiology, because a model
13 is just a model and it.s never going to be perfect and
14 what is good enough, right?
15 And then maybe the second question we
16 can discuss is what really are the critical endpoints?
17 And if you don.t them yet, how are we going to get
18 there?
19 BINH DIEP: Maybe I can start. For us,
20 the endpoint in our rabbit model is survival. And if
21 we don.t have survival, we don.t have anything. But
22 if we do have a difference in survival, all the

1 biomarkers that you can look at will follow because
2 they track with animal survival. And so if you.re
3 looking at multiple organ dysfunction, you are looking
4 at acute liver injury, you.re looking at total
5 bilirubin, ASDALT, you.re looking at creatinine and
6 BUN for kidney injury.
7 Or in the case I.ve shown you with the
8 cardiac -- myocardial dysfunction that we see with
9 cardiac troponin, CKMB myoglobin. All of those, they
10 tend to track with survival. So, if there is a
11 difference in survival outcome, everything else
12 follows, whether you measure it or not.
13 So, that.s why I think for a natural
14 history study it.s rather important to characterize
15 these biomarkers because if the biomarkers mimic human
16 infection, then the model may better translate to the
17 efficacy of any drugs that you test in that model.
18 But in the end it.s really about survival.
19 DR. THOMAS WALSH: Hi, this is Dr.
20 Walsh. I was cut off. I am so very sorry. Did you
21 hear -- I know a little bit of time has transpired --
22 did you hear my comments concerning the alteration of

1 the microbiota of the rabbit?
2 JOHN FARLEY: We did.
3 DR. THOMAS WALSH: Oh, okay, fine.
4 JOHN FARLEY: Now, we.re kind of onto a
5 different thread. And maybe I can ask Tina to sort of
6 restate that thread and you can jump in.
7 DR. THOMAS WALSH: Thank you, thank
8 you. And sorry for the miscommunication on that.
9 TINA GUINA: Sure, happy to. Tom,
10 thank you for joining back here. So, there are a
11 couple of questions that are important for product
12 developers, right? Models are just models and how
13 important it is that the animal model really reflects
14 the pathophysiology of human disease. I mean, many of
15 us here have worked on animal models for biodefense.
16 And you can try your best, you can work with nonhuman
17 primates but it.s never a perfect model. So, that.s
18 the first question -- how important that is to a
19 product developer or for regulatory acceptance.
20 And the second one is what are really
21 the critical endpoints in these models? We.ve seen
22 from many presenters here excellent work, looking at

1 PK, PKPD, organ burden, survival, number of
2 biomarkers, number of the important physiologic
3 parameters. And obviously these important endpoints
4 are going to be important for -- different endpoints
5 are going to be important for different models.
6 But in your mind, looking at a product
7 developer who has a small budget and trying to do
8 their best, and knows the regulatory agency are
9 supporting their product development -- what are
10 really important endpoints that we think are critical
11 to demonstrate the efficacy so that we have the
12 confidence in drugs that are going into clinical
13 development?
14 DR. THOMAS WALSH: Of course. And,
15 ultimately, I think in working with, let us say, the
16 model of a small biotech company, Tina, to which you
17 alluded. I think, first of all, one has to have a
18 goal, a strategy, looking way ahead. Where exactly do
19 you envision the compound to be used?
20 Having that sense of where a compound
21 is going helps to define organism and helps to define
22 host and, thereby, helps to define specifically which

1 animal model systems will be most useful.
2 Coming back to that then, one starts to
3 work forward. Obviously, survival is paramount. But
4 in addition to survival, one would like, much like we
5 do clinical trials, one would also like to have a
6 series of robust -- other robust endpoints that can
7 further help to define this. Now, they may not be
8 rigorously attached to a PKPD model because of the
9 potential for variability. But for the sense of
10 clinical impact, as we discussed this morning, that
11 still is really paramount.
12 So, you.d like to be able to see,
13 depending on the model system, a reduction in CFU.
14 But as we learned and we understand this morning for
15 Acinetobacter, for example, that may not necessarily
16 pertain from what we.ve seen with pseudomonas and for
17 other bacterial pathogens that is applicable, that is
18 important. So, again, identifying specifically the
19 pathogen and the proper host.
20 But you.d like to have survival --
21 certainly everyone would agree is paramount, and there
22 should be some degree of parallel consistency with the

1 other markers. For example, we.ve discussed a
2 residual bacterial burden, the lung weight pulmonary
3 injury, physiological parameters, whether it.s
4 oxygenation C-reactive protein, IO1 data, IL6. Any
5 one of these markers hopefully will correlate, and
6 increasingly we know these are also used as prognostic
7 parameters in patients.
8 So, I think survival is paramount but
9 you also want robust systems. And I think the large
10 animal model systems can complement the murine systems
11 because of their ability to serially track these
12 trends. But you also want them to parallel what we
13 also know happens in our patients.
14 JOHN FARLEY: Okay, so we.re going to
15 take Jason at the microphone and then we.ll see if
16 William has any comments in response to the questions
17 and then we.ll pick up with the panel.
18 JASON MOORE: Thank you, John. My name
19 is Jason Moore. I.m from the FDA as a clinical
20 pharmacology reviewer. Within the theme of general
21 translations, I had a specific question for Dr. Hope
22 regarding the rabbit meningoencephalitis model.

1 So, can you potentially comment on
2 differences in penetration perhaps between rabbits and
3 humans and how we may accommodate for that as we seek
4 to translate the results of the rabbit
5 meningoencephalitis model to the clinical setting?
6 Thank you.
7 WILLIAM HOPE: Can you hear me?
8 JOHN FARLEY: We can.
9 WILLIAM HOPE: The ability to directly
10 bridge through CFF is a legitimate one, just as you
11 would accept bridging through epithelial lining fluid
12 in terms of penetration into that space. And so I
13 think that the dynamic relationships are secure and
14 can be adjusted through that space. And it.s
15 obviously clinically relevant. And I guess we
16 explored that idea with cryptococcal meningitis, which
17 is an exemplar in many respects.
18 I guess the difficulty though, and to
19 your question, is what to do about the cerebrum
20 because the penetration into the cerebrum in neonates
21 is obviously much more difficult to define and be
22 confident about. Now, obviously, they.re completely

1 different compartments biologically and
2 pharmacologically and maybe prognostically. So, guess
3 that.s where there.s a limitation potentially of all
4 experimental models, but especially the rabbit.
5 DR. THOMAS WALSH: This is Tom. May I
6 comment as well on that question? What we have
7 learned as well in CNS models, particular in the model
8 for Candida meningoencephalitis and several other of
9 the fungal encephalitis, and I think it.s certainly
10 applicable from the work that.s been done in several
11 animal model systems for CNS is that while we can look
12 at the penetration across blood-brain barrier, intact
13 blood-brain barrier, and attempt to compare one,
14 across species and, two, to compare to humans, the
15 critical nature is that once has an infection, there
16 is marked disruption of the blood-brain barrier.
17 And understanding then that many of the
18 subtleties that main pertain to neonatal versus adult
19 and neonatal versus even older children may really not
20 pertain, once you have a very active infection where
21 we.ve seen particularly in the cerebrum that with the
22 disruption of blood-brain barrier, not only is it a

1 subtle impact -- potentially subtle impact on CSF but
2 it.s a striking impact in delivery of drug into CNS
3 tissue.
4 And so in that regard there may be a
5 benefit in terms of the infection itself lending
6 itself to a greater degree of tissue-drug delivery.
7 WILLIAM HOPE: And then can I also add,
8 John, that -- I mean, I think -- maybe I just didn.t
9 make it clear enough in my talk, but I think that just
10 the dangers of trying to bridge on PK alone. So, you
11 see Tobramycin getting into the central nervous system
12 but I don.t think that no three or four decades have
13 given anybody any confidence that aminoglycosides as
14 monotherapy should be used as CNS drugs.
15 So, there are some dangers about using
16 and relying on PK in general, even over and above what
17 Tom has just said.
18 JOHN FARLEY: Sure. And just to sort
19 of round up that thread from the FDA.s perspective --
20 so, Sumathi and I remain very excited about your work
21 as pediatricians. Because a key question is CNS
22 penetration particularly in the neonatal space and

1 developing drugs for that population. And I think we
2 should press on with combining your data with sparse
3 neonatal CSF samples that are difficult to obtain, but
4 sparse ones can be obtained. And I think that the
5 work you.re doing with Dr. Greenberg at Duke to do
6 that remains very important as an approach. So, we.ll
7 sort of press on there.
8 So, I think the work you.ve done is
9 important and don.t get discouraged by the Candida
10 meningoencephalitis recent action. Because I think
11 they.re very different.
12 WILLIAM HOPE: Well, I think we all
13 knew, John, that that was a difficult decision for
14 you. So I don.t think -- well, I.m not being critical
15 but it was interesting, wasn.t it, the interplay with
16 that information and how to weight it. It was an
17 interesting debate. Anyway, I.ll stop there.
18 JOHN FARLEY: Any other comments on
19 this thread? I want to take us in a slightly
20 different direction of regulatory impact.
21 WILLIAM HOPE: Can I ask a question
22 about pneumonia, John?

1 JOHN FARLEY: Sure, why don.t you go
2 ahead?
3 WILLIAM HOPE: I might have missed it
4 but has anybody, in terms of the larger animal models
5 with pneumonia looked at E. coli? Because that is the
6 problem in mice, is establishing an E. coli model
7 where it.s a leading human pathogen for HABP/VABP.
8 And you.re often required to -- well, most of those
9 programs will run through Klebsiella which is much
10 easier to establish. But I.m just sort of interested
11 whether E. coli can be established in the rabbit or
12 the pig.
13 JOHN FARLEY: Yeah, so maybe we can
14 broaden that question to experience in other bacteria
15 ACA in the rabbit setting.
16 DR. THOMAS WALSH: We have worked with
17 KPC, Klebsiella -- KPCN and DM1 -- but we have not
18 worked with E. coli. We.ve targeted on what would our
19 most critical epidemiologic challenges have been, but
20 have not worked with E. coli.
21 BINH DIEP: We, in the rabbit VABP
22 model, we have tested a whole bunch of different

1 Klebsiella of different serotypes -- Serotype 01, 02,
2 04. And it.s rather easy to infect and kill rabbits
3 in the VABP model with Klebsiella pneumonia of
4 different serotypes.
5 JOHN FARLEY: So, that actually kicks
6 us off in a direction that I thought would be good to
7 pursue, and it kind of has to do with tech transfer
8 issues and ultimately regulatory impact. Because the
9 idea would be to present a model that could be run in
10 a variety of labs that would be accessible to
11 industry. I mean, that.s sort of our raison d.þtre.
12 So, I guess, Binh, you.re running --
13 just in terms of efficiency, I think you.re running 13
14 rabbits at once and it.s a limitation of your
15 equipment. Is that right?
16 BINH DIEP: Yes. And probably not any
17 more than that can be done, even if we.re not limited
18 by the physical size of our ICU. This is about
19 manpower. Usually in the ICU setting there.s an ICU
20 nurse, a team of physicians. And here we have at any
21 one point time in our rabbit ICU, two physicians and
22 two to three technicians helping them. So, it.s a

1 team of five around the clock for the duration of the
2 study, which is usually around 60 hours. So, we
3 cannot do more than that.
4 But then we also cannot do typically
5 less than 13 because then it will be cost prohibitive
6 to break up the studies into two different times.
7 JOHN FARLEY: Right. And, Tom, how
8 many rabbits are you running at a time?
9 DR. THOMAS WALSH: We can run anywhere
10 from 12-16 at any one time. If necessary, if pressed
11 harder, we could do more. We have done somewhat more,
12 up to 18. But, typically, our size is 12-16.
13 JOHN FARLEY: Right. And, William?
14 WILLIAM HOPE: We can run six. And so
15 we have to do cohorts of six, and that is a bit of an
16 issue for us. There.s a housing problem, a husbandry
17 problem, but also just a resource in terms of people.
18 JOHN FARLEY: Right, okay. And the
19 second line of questions are harder and they sort of
20 follow up on partly where Tina was going, which is --
21 you know, the issue of translatability of acute
22 pneumonia models versus VABP models. And, you know,

1 what we thought originally was maybe we should do a
2 model where the rabbit looks just like the patient in
3 the ICU and they.re on the ventilator, etc. But maybe
4 that.s not a direction one should go in because the
5 acute pneumonia models seem simpler to me and more
6 transferrable. So, I.ll just open the door there and
7 see what folks are thinking.
8 TINA GUINA: And thank you for that,
9 John. I just want to make a comment also based on
10 experience that I have, and worked many years also
11 with Judith Hewitt and a number of people in
12 developing biodefense models. And I hope she.ll have
13 something to say too.
14 I really commend everyone who has done
15 very detailed studies of natural history, looking at
16 all possible biomarkers. Because excellent, possibly
17 detailed natural history studies are the foundation of
18 understanding the model. So, while we may end up
19 using simpler models, and that was the reason for my
20 questions -- what are really the critical endpoints?
21 -- I really think that, if possible, if we can fund
22 this and if we can really dedicate ourselves for a

1 little bit longer period of time to really
2 understanding these models, VABP and acute pneumonia
3 and collecting as much data as possible, then
4 performing analysis on what may be critical parameters
5 that are important in human disease across the
6 studies, as we have done for some of our biodefense
7 models and published recently on that -- then that can
8 inform what the critical parameters are. And then
9 maybe it will be simpler to run these studies because
10 we.ll identify trigger to treat that.s critical
11 inocula -- what works for different strains? What are
12 the most important biomarkers? What do we have to
13 track, and what really is the -- what kind of
14 resources we need to put around that.
15 And I.ll leave it at that. And I would
16 like to hear what others have to say. Judy, do you
17 want to add? I would love to hear from you.
18 JUDITH HEWETT: I.m going to throw
19 something else into the basket. PK of drugs is not
20 under our control. It.s driven by the animal that
21 we.re putting these drugs into. And so really this is
22 just sort of a comment that I think we need as many

1 different animal models as we can get for the occasion
2 when we put a drug into a rabbit, for example, and it
3 just won.t tolerate that drug, you know, where does
4 that leave us? It.d be really nice to have a pig or
5 something else. Because it may not have happened yet
6 but it will happen.
7 And I agree with your comments, Tina,
8 about natural history studies being very well
9 characterized. I think it.s really nice to see even
10 all of the effort that.s going into the mouse studies.
11 I mean, granted, when you have a larger animal on a
12 respirator you have an opportunity -- especially with
13 the larger animals, you have a greater opportunity to
14 sample them and really look carefully at natural
15 history.
16 But I do think it.s important also,
17 even for the mice, especially if we.re going to sort
18 of exhaust everything we can get out of many mouse
19 studies before we go into these larger species. So,
20 I.m very appreciative of all the work that.s gone into
21 all the mouse studies that were presented here today,
22 talking about numbers of animals and variety of

1 different strains that were tested in mice, and males
2 and females, and just a lot of parameters that really
3 are important when you get into the clinical space.
4 And we really just cannot ignore them in the
5 preclinical space.
6 ACHIM WACH: Maybe to the point of PK I
7 can make a comment from the small company. So, here
8 we have tested or generally test in at least four to
9 five species before we go into humans, of course. But
10 this is maybe special because our molecules are
11 peptides which are treated or metabolized differently
12 in the different species. So, this is one thing.
13 The other thing is coming also back to
14 Tina.s comment and taking it from the other side. The
15 problem we have is that we are quite afraid about
16 taking the wrong timing for the treatment. When I
17 hear Binh talking about that one, our difference might
18 make the world turn around completely, that is our
19 biggest problem. We know very well what we are
20 looking for, what kind of conditions we would like to
21 carry, ventilation, sedation, whatever, co-medication,
22 whatever you have. But if we missed the right point

1 of starting the treatment, everything will be void for
2 us.
3 CARA CASSINO: Yeah, if I can build on
4 Achim.s comments as another small drug developer
5 company. The situation that we face is kind of
6 similar in that we.ve observed variability in the
7 different animal species with the compounds, the
8 license that we.re working on.
9 Say, for example -- so, I think which
10 model do you want may depend on the purpose that
11 you.re going to use it for. And I can think of two.
12 So, one is a comment and one will be a question. If
13 you imagine a scenario where you may have a very
14 interesting biologic compound that.s highly active
15 against resistant pseudomonas but you can.t really get
16 reliable measurement in rodents, then you have no
17 choice basically to either give up or think about how
18 to work with folks who.ve refined the larger animal
19 model. And the go-to place that we would go, and
20 we.ve already done some work, is in the rabbit.
21 And for that scenario we would be
22 thinking well, maybe we would want to develop this

1 antipseudomonal compound for HABP, hospital-acquired
2 pneumonia. That would be an obvious go-to place. So,
3 what we would be looking for is a reliable model that
4 could help us both with defining efficacy with a
5 definitive endpoint such as survival and additional
6 softer endpoints that might be supportive. And I do
7 completely agree that they will follow survival, if
8 you.re -- you know, the way you.ve laid it out.
9 We also would like to be able to use
10 that then to help us understand dosing so that we
11 could come to a rational way to propose dosing in our
12 ventilator or just hospital-acquired or both. It
13 probably would be a HABP/VABP trial. So that we could
14 support dosing and have an intelligent dialogue with
15 the agency around what that would be when we go into
16 our large scale, expensive, big project as a small
17 company. That might be a HABP/VABP, which as
18 everybody knows, is no small feat to do.
19 So, those are the kind of components,
20 and to the greater extent that this is studied and
21 different folks are working on it and we come to some
22 common understanding, that would be very helpful

1 because the mouse pathway in all of this and the
2 rodent pathways are much more well-hewn and described
3 in the small molecule arena. So, it.s a little bit
4 easier to follow that. And once you get into another
5 specie, we really want to partner with people who are
6 interested in expanding the knowledge. So, that.s one
7 example.
8 And then there.s another whole thing
9 that.s a little bit different, which is if one, for
10 example, had a broad spectrum compound that was highly
11 active against CRE, against CRA, against Colistin-
12 resistant CRE and CRA, that you can.t even figure out
13 how you might even get enough patients to do a study.
14 Then I would say we would be very interested in
15 talking about is there a prospect of an animal model
16 that together with a small amount of clinical data
17 might help us understand whether this can actually
18 work.
19 Because those really bad, scary bugs
20 will be very hard to study, as you all know, in clinic
21 and I wondered what the agency.s perspective on that
22 scenario is and whether that.s somewhere that you

1 might consider in a future state once some of these
2 earlier stage compounds, if they come to fruition, do.
3 JOHN FARLEY: Yeah, I can totally
4 respond to that first and then invite others. So, I
5 think you.re right on in terms of what we.re thinking
6 about in a future state. And it actually goes along
7 with the recent workshop we had on antibacterial drug
8 development and those challenges.
9 So, we absolutely -- that is the niche,
10 one of the niches that we see for further developed
11 animal models. We think there will be a clinical
12 trial and we will get to a trial that will at least
13 produce some data in those patients with better -- you
14 know, very rare and have organisms but those organisms
15 are very high priority.
16 I mean, the easiest is a change of
17 comparator in these trials so that you actually can
18 enrich an all-comers trial for patients with some
19 resistant pathogens. But there are other options that
20 we.re talking through but that.s actually the easy one
21 that Sumathi.s been advocating for for several years.
22 CARA CASSINO: Right. So, in that

1 scenario then, it would seem to me that having an
2 animal model that was closer to the human experience
3 would be incredibly valuable.
4 JOHN FARLEY: Huge. Because then the
5 scenario is you.re going to win in the ITT, which is
6 kind of going be all-comers and everybody, but that
7 subgroup of resistant pathogen patients becomes very
8 important. And this provides some other data to
9 support observations about that subgroup, if that
10 helps.
11 CARA CASSINO: Support for that, yeah.
12 Thank you, that.s helpful. Thank you.
13 JENNIFER HOOVER: Can I give a third
14 industry view, Anne, before we let you speak? So,
15 building on what they.ve said, which I agree with
16 completely, I think -- to Tina.s first question, how
17 important is it that the model truly models the
18 pathophysiology to me depends a little on the MOA of
19 the asset. So, of course, the ideal situation is it
20 models it as closely as we think we can get, and then
21 you can use that model for everything. Air quotes.
22 So, that would kind of be my short answer to that.

1 The second one around the endpoints, I
2 think this is really, really important for us because
3 -- so, first of all, just to compliment the folks on
4 the work they.ve done so far, I think it.s incredible.
5 But from an industry perspective, what will be
6 challenging for us is if there are multiple iterations
7 of a rabbit model, let.s say, and we have to then
8 choose which one to use, how do we do that?
9 So, is there a way to kind of decide,
10 maybe based on the natural history that.s been shown
11 or, you know, various other parameters what.s kind of
12 going to be a standard? And, again, I.m using my air
13 quotes -- standard protocol that we could use going
14 forward?
15 And then, from my perspective, I.m a
16 huge believer in benchmarking. So, ideally, what I
17 would like to see is whatever model is chosen that
18 it.s benchmarked really well with multiple different
19 classes in antibiotics, ideally from my perspective,
20 using PKPD target-based dosing, not just modeling the
21 clinical human dose. So, we really understand how an
22 asset should be have -- if it.s good, if it.s bad, or

1 if it.s somewhere in the middle. And we really need
2 to have that ahead of time before we go into these
3 long, expensive, complicated studies as a sponsor, we
4 actually know what go looks like before we actually
5 fund the study.
6 JOHN FARLEY: Anne?
7 ANNE EAKIN: Thanks. Great. So, I
8 just had a couple of points or questions I wanted to
9 throw out to the panel to get your thoughts on. So,
10 one is, you know, reflecting on the biodefense
11 pathogens and the animal rule models that have been in
12 place, one big component of that was a very thorough
13 understanding of the clinical manifestations of the
14 disease. And I.m just wondering do we feel like we
15 have enough information about what the clinical
16 parameters are that are important, that we are then
17 trying to model with our animal models? So, that.s
18 just one question.
19 And then the other is around species
20 and multiple species. Two very common groups of
21 animals that are used by product developers are rats
22 and nonhuman primates for tox studies. And we haven.t

1 really talked much about infection models in those
2 species, and I.m just wondering what people.s thoughts
3 are on those as potentially being an easier transition
4 than rabbits or certainly pigs. Thanks.
5 DR. THOMAS WALSH: This is Tom. Are
6 you able to hear me?
7 JOHN FARLEY: Yeah, Tom, go right
8 ahead.
9 DR. THOMAS WALSH: Fine. So, we.ve
10 contemplated rats. We.ve looked at them and
11 conferring in an earlier time -- I worked with rats as
12 well -- one of the concerns is in the system, first of
13 all, in a large animal, trying to catheterize, trying
14 to have limited blood supply when you.re trying to
15 simulate a model system. But also a tremendous amount
16 of variability within the rat.s system.
17 What we found in New Zealand Whites,
18 even though it.s an outbred strain, is their
19 physiological consistency, really right down to,
20 literally, tenths of a milligram of anesthesia from
21 year to year, to year -- the high reproducibility of
22 the untreated controls, the predictability that we

1 see. We.ve not been able to -- I.ve not seen that as
2 well in the rat model system. So, while one could try
3 to argue for potentially a one-size-fits-all going in
4 terms of tox, where rats are obviously widely used, I
5 think that the robustness of the large animal systems,
6 if we.re going to look at an animal system, the mouse-
7 rabbit system is a very powerful one.
8 And I would hasten to add as well that
9 our rabbits -- clearly through nephrotoxicity have
10 been exquisitely predictive. They respond to saline
11 loading. They correlate very nicely with peak plasma
12 concentrations and trough concentrations with
13 aminoglycosides.
14 So, certainly if one is looking
15 broadly, the rabbit system has been very helpful in
16 terms of its toxicity. They.ve also predicted a
17 number of allergic reactions that we.ve seen that have
18 correlated clinically. So, I think one can even turn
19 the question back and say, okay, yes, rats are widely
20 reproduced but do we really -- is that the sine qua
21 non? Should we also be looking to try to potentially
22 tie together efficacy and toxicity more so in the

1 rabbit model?
2 JOHN FARLEY: Other thoughts from the
3 panel?
4 JURGEN BULITTA: It.s relatively
5 obvious but I don.t think it has been explicitly
6 stated. So, the larger animal models offer one
7 advantage for the mathematical modeling folks, and
8 that is you can take zero sampling. And when you have
9 the ability to make inferences about the PK bacterial
10 load in whichever biomarker or safety measure you wish
11 to do increases dramatically because you get intra-
12 individual information. That is a wonderful thing.
13 Tina, for -- I believe early on it may
14 be difficult to get to like a real hard endpoint for
15 FDA purposes. But what I would do if I was a small
16 drug development company is just go to the clinicians
17 and ask them what type of biomarker do you wish to see
18 in this type of infection which I.m targeting, and
19 then get a consensus opinion from the clinicians what
20 do we like to see in the rabbit or pig model to be
21 represented in the animal system for making inference
22 for patients? But that is an MD question, not

1 (inaudible).
2 DR. THOMAS WALSH: Again, understanding
3 where ultimately the target is, what is the patient
4 population, who is the host population, what is the
5 organism, what are the disease that are being
6 targeted, and then working back. And with a very
7 well-defined preclinical series of models, it can help
8 immensely in targeting.
9 BINH DIEP: Anne also mentioned about
10 the nonhuman primates and sometimes rabbits are better
11 than nonhuman primates in modeling a human infection.
12 I come from the world of staphylococcal pathogenesis,
13 and there there are toxins that are produced by staph
14 aureus that targets human cells as well as rabbit
15 cells but not monkeys.
16 An example of this would be the Panton-
17 Valentine leukocidin, Leukocidin E and D. There.s a
18 whole group by component leukocidins that target only
19 human and rabbits but not monkeys. So, really the
20 choice of the animal model to use depends on what it
21 is that your product targets. If your product targets
22 specific toxins, then you need to test it in the

1 appropriate animal model, and that appropriate animal
2 may not necessarily be nonhuman primates.
3 DR. THOMAS WALSH: I would echo that as
4 well. Thank you so much for bringing up that point.
5 Because if you go back to the genetics, for example,
6 of MRSA in variance properties, there was raging
7 controversy in the Journal of Science and JID and
8 others of the debate on PVL. Yes, it is a variance
9 factor, no, it isn.t. And yet you had parallel
10 clinical data saying from in children and pediatrics
11 and adults saying, yes, this clearly correlates with
12 the impact.
13 And we.ve learned very nicely from
14 genomic data that the rabbit and humans have found a
15 PVL receptor. And when you start looking at the
16 genetic knockouts -- the knockouts and the wild type,
17 the correlation is very striking.
18 So, in MSSAMRSA models, one clearly
19 wants the animal model system, preferably the rabbit,
20 to be able to be reflecting that. And so I think it,
21 once again, underscores the complementarity of model
22 systems in knowing that these larger animals may be

1 very helpful in defining the new development for
2 antimicrobials.
3 JENNIFER HOOVER: Maybe I.ll just
4 comment a little bit more on rats because we use rats
5 a lot in our lab. I would say that rats are probably
6 not going to mimic human physiology much better than
7 mice do, but I think rats do offer some distinct
8 advantages.
9 We do a lot of humanized dosing in
10 rats. We do it by continuous infusion. We purchase
11 the rats cannulated from the vendor, and when they
12 arrive, we just plug them into a little infusion line.
13 It.s very simple, it.s very easy. We can take 9-10
14 serial samples from the rats, so we have that
15 advantage as well.
16 And we have a pneumonia model we
17 haven.t talked about today. It.s actually an auger
18 based pneumonia model. And I know there.s caveats to
19 that, however, we.ve had a lot of success developing
20 pneumonia with a lot of different strains of all the
21 pathogens we.ve talked about today, plus Haemophilus
22 influenza, which is difficult to study, as most of you

1 probably know.

2 So, there are definitely advantages I

3 think to rats, so maybe we shouldn.t brush them under

4 the table quite so easily. But I don.t think they.re

5 going to get us to the same place that rabbits and

6 pigs potentially would.

7 JOHN FARLEY: And, Anne, I just wanted

8 to follow up on your endpoint comment. So, I think my

9 colleague from ContraFect and I tend to think a little

10 bit differently than you guys who are really in the

11 details on animal model development. Because we.re

12 thinking ahead to the new drug application, and

13 ultimately to the advisory committee meeting.

14 So, what would be sort of the product,

15 you know, in terms of a model that we would like to

16 present? And I think it would be one with a trigger

17 to treat that everybody could agree is meaningful, and

18 then one with an endpoint that one would agree is

19 meaningful.

20 CARA CASSINO: It would be clearly

21 meaningful. And we.re looking at our agents as an

22 opportunity to improve clinical outcome. So, I would

1 throw on that one where we might be able to test in a
2 superiority design in addition to standard of care for
3 diseases that are not well served by current
4 antibiotics.
5 So that makes -- I didn.t want to go
6 there but that makes the whole animal model thing --
7 it throws another thing in the mix, of course, which
8 is first establishing the efficacy and then thinking
9 about what I just said with an additional agent.
10 So, we have a little experience with
11 that in the endocarditis arena, which helped us a lot
12 actually get our lead compound into Phase II and now
13 Phase III staph aureus endocarditis with our Exebacase
14 lysin in addition to standard of care. And the rabbit
15 model helped us immensely in terms of understanding
16 that.
17 So, for pneumonia it.s even more
18 complicated, although it.s not like staph aureus
19 bacteremia carditis is not complicated -- but that
20 would be a direction that we would go, thinking of the
21 endgame. What.s the product and what.s the need?
22 JOHN FARLEY: And, of course, the

1 endpoint in the animal model, you also need to sort of
2 have a plausible mechanism of action with data within
3 the model. So, bacterial reduction leading to
4 improved survival is certainly persuasive.
5 JENNIFER HOOVER: Actually, can I probe
6 a little bit the idea around survival? So, we.ve
7 seen, I think, in some of the presentations that we
8 didn.t get 100 percent survival even with an
9 antibiotic that should be effective. So, when we talk
10 about endpoints and survival now being something we.re
11 clearly interested in, do our novel compounds have to
12 achieve 100 percent survival?
13 DR. THOMAS WALSH: Is that a scientific
14 or regulatory question?
15 TINA GUINA: Yeah, exactly.
16 JOHN FARLEY: What kind of question was
17 that?
18 TINA GUINA: I was going to ask how
19 much survival is enough? Is that a question? Yeah, I
20 would like to hear from people who are developing
21 models what are their thoughts on that?
22 DR. THOMAS WALSH: There are many

1 variables that may contribute to survival. Certainly
2 you can have subtleties, certainly in the more
3 rigorously immunocompromised models and the more
4 aggressive models, that there are other subtle factors
5 including inflammatory response which may not be
6 ameliorated by the antimicrobial.
7 That.s why it.s so important to have
8 the other biomarkers. So, if you do end up, say, with
9 90 percent survival, you look at the other biomarkers
10 and you see resolution of mediators of organism
11 mediated pulmonary injury, you see resolution --
12 dramatic resolution down to the lower limited
13 quantitation of residual bacterial burden, resolution
14 of inflammatory biomarkers. It tells you, yes, this
15 drug is working.
16 So, the idea of letting perfection be
17 the enemy of success is one that we have to be -- of
18 which we.d have to be careful. There may be other
19 factors you may want to explore. But moving forward,
20 you can say, yes, I can eradicate this infection, and
21 ultimately that.s going to be a critical factor.
22 BINH DIEP: I would also like to make a

1 comment on this. In the rabbit VABP model, you know,
2 despite the use of fluid challenge and vasopressor and
3 a humanized dosing regimen of Meropenem, we don.t
4 achieve 100 percent survival. And in mind it.s
5 actually a good thing. Because in human patients who
6 are enrolled in trials of HABP/VABP, the mortality
7 rate is 20-30 percent.
8 And so, you know, 100 percent survival
9 is probably not realistic. If it.s 100 percent
10 survival, your model is probably too easy to treat.
11 Too easy to treat.
12 JOHN FARLEY: Yeah. And from sort of
13 the regulatory perspective, I.ve had sort of regular
14 arguments with agency statisticians over this point.
15 But we.re in Fisher.s Exact Test Land, right? And so
16 moving one or two animals from one cell to the other
17 makes a difference statistically, but really when you
18 look at the totality of the data for that model it
19 looks pretty persuasive, so...
20 I.m going to open to any additional
21 comments because, although it.s posted for 4:30, the
22 agenda says 4 o.clock and some of you have to get to

1 the airport, I.m sure. And we do have a final
2 presentation but I.d invite any other comments -- kind
3 of a final summary presentation. But, please, go
4 ahead with other comments.
5 LYNN MISEL: So, I have one idea to
6 recommend and that is as we.re trying to develop
7 models with clinically relevant organisms that reflect
8 the human clinical condition, it would be fantastic --
9 and we want to share resources amongst the scientific
10 community -- it.d be fantastic if we could have access
11 to a panel of organisms from human clinical isolates
12 that are defined if they.re a HABP, a VABP, a UTI, a
13 bloodstream infection source.
14 And I think that the AR bank is a
15 phenomenal resource but it doesn.t offer that type of
16 data on organisms. It.d be keen to know if that would
17 be helpful to other groups.
18 MATTHEW LAWRENZ: I agree with that 100
19 percent. We.ve tried to get clinical data on those
20 banks and it.s just no available to that. And so
21 that.s why we pick strains at random and hope that we
22 pick some that are real and some that aren.t. But I

1 don.t know if they came from a cystic fibrosis
2 patient, I don.t even know if they.re a clinical
3 isolate actually, so...
4 JOHN FARLEY: That.s good. And we will
5 take that back. We have an internal USG group that
6 meets on animal models. Everyone in the room is much
7 smarter than me. But we.ll take that back as an ask.
8 Any other comments? I.ve asked Ed
9 Weinstein to play what I call the historic John Rex
10 role, which in workshops is one of the hardest jobs,
11 which is to kind of put together a summary of what he
12 heard today and where he thinks we might, in terms of
13 ways to go forward. So, thanks.
14 EDWARD WEINSTEIN: Well, thank you,
15 John. So, as you can see from the title of the slide,
16 this is the end of the workshop and you made it
17 through a tough day in the middle of a health crisis
18 so thank you.
19 So, one of the ways to think about this
20 is actually to look backwards before looking forward.
21 So, the last workshop we had was about three years ago
22 and I.d like to discuss some of the advances that we

1 made in terms of clinical relevance, the
2 interpretability and reliability of studies before
3 touching upon the points from discussion today.
4 So, in terms of the animal model
5 advances to clinical relevance, we realize that the
6 natural history of disease in animals informs the
7 study design and the natural history data provides a
8 rationale for the trigger to treat. And this can be
9 important because we discussed today, there.s a
10 spectrum of disease starting from prophylaxis moving
11 onto an acute model, and finally a sepsis or a late
12 model of disease. And the trigger differentiates the
13 difference between these different disease states in
14 terms of your output from the model.
15 Some models no longer require
16 immunosuppression to establish bacterial infection.
17 That.s important because certain kinds of
18 antibacterial drugs are bacteriostatic in their
19 action. They require help from the immune system to
20 clear infection.
21 There.s also been a generalized
22 recognition of the importance of the use of humanized

1 dosing. And as we just heard, the animal model
2 endpoints such as mortality are more closely aligned
3 with the endpoints in clinical trials.
4 In terms of reliability and
5 interpretability, the data can still be noisy and
6 reproducibility remains a challenge. Some of the
7 variables are known and they can be harmonized,
8 spectral strain, inoculum, inoculum size, root
9 infection, the choice of animal species, genetic
10 background and conditioning of the animals, the
11 trigger to treat controls study endpoints.
12 And some tough lessons have been
13 learned along the way. So, for example, we learned
14 that endogenous flora can cause coinfection in the pig
15 models, that idiopathic rapid drug elimination rates
16 such as Ciprofloxacin in rabbits, and Meropenem in
17 mice, and even toxicities such as doxycycline in
18 African Green Monkeys can be a problem. And some
19 important questions still remain. So, work is needed
20 to achieve models that can credibly forecast the
21 results of clinical trials. And changes in CFU are a
22 reasonable endpoint but the clinical significance

1 still remains unknown. Lastly, the ability to
2 reproduce animal models in different laboratories is
3 still untested.
4 So, looking at some of the discussion
5 points from today, it looks like there.s some
6 excellent opportunities for improvement There.s more
7 than just CFUs as an endpoint. Different models can
8 capture multiple aspects of the clinical disease to
9 become more relevant.
10 It was noted that radiology has been
11 underutilized. Other variables such as blood gas,
12 chemistry, cytokine responses can be useful to help
13 improve the outcome of the data that we get from the
14 animal models. And there.s no one size that seems to
15 fit all. There are different animal models required
16 during different points of development and it depends
17 upon the scientific question that.s being asked versus
18 a question such as -- first doses just to prove
19 efficacy, proof of principle versus early dose
20 determination; drug activity versus specific strains
21 later in development. And challenges remain in the
22 close PK modeling of some antibacterial drugs. And

1 some new strategies were discussed and maybe needed
2 such as the use of Cilastatin with Meropenem.
3 This last point says from discussion
4 but this might be more of a point for discussion. And
5 the question is how can we use and rely on animal data
6 to support an NDA? And when these animal experiments
7 are performed in tandem with adequate and well-
8 controlled clinical trials they can give supporting
9 information on certain aspects such as activity
10 against rare pathogens or certain resistance
11 phenotypes. And as Dr. Farley pointed out, you can
12 also give evidence to the activity of individual
13 components of a drug regimen.
14 Use of PKPD analysis for humanized
15 equivalent exposure is important to strengthen these
16 data -- the activity demonstrated in multiple animal
17 models with multiple parameters. Because it seems
18 from our discussion today that there.s still a lot of
19 uncertainty about the best route forward.
20 It sounds like appropriate experimental
21 controls would be required but the exact stable of
22 comparator still remains to be decided. And, lastly,

1 the potential description of the animal studies is
2 possible in product labeling. And it wouldn.t be
3 under clinical studies, of course, not in Section 14,
4 but perhaps under 12.4. So that the results of these
5 studies wouldn.t be in vain, they would see the light
6 of day in product labeling.
7 And so, again, I just want to thank
8 everybody, especially the panelist of presenters, the
9 people in the audience and folks online for spending
10 the entire day with us and for such an extensive and
11 helpful discussion. I want to thank the FDA Animal
12 Model Review Team, Touche Ameni, and Sunita and James
13 Burn, as well as Dr. Farley and Dr. Sumathi Nambiar
14 for setting up this workshop.
15 There are a few workshops that are
16 coming up and they just flashed up the slide in case
17 you may be interested in spending another day with us.
18 JOHN FARLEY: Thanks, Ed. And I want
19 to add my thanks to the panel and wish you safe
20 travels. WE are going to attempt to publish this
21 workshop summary, so we may be reaching out to some of
22 you in the near future about that. So, thanks very

1 much. Really appreciate it.

2 DR. THOMAS WALSH: Thank you very much.

3

4

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