Understanding the Development Challenges Associated with Emerging Non-Traditional Antibiotics

Duke-Margolis Center for Health Policy

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Understanding the Development Challenges Associated with Emerging Non-Traditional Antibiotics

E-Mail Questions to
Duke.Abx@Duke.edu

@DukeMargolis

Clinical trial designs for non-traditional antibiotics

John H. Rex, MD
Chief Medical Officer, F2G Ltd;
Expert-in-Residence, Wellcome Trust
Operating Partner, Advent Life Sciences
Email: john.h.rex@gmail.com
Newsletter: http://amr.solutions

Kevin Outterson, JD
Executive Director, CARB-X
Professor of Law, Boston University
Email: mko@bu.edu

Note: We are going to cover a LOT of material fairly quickly and taking notes will be hard. These slides will be available shortly via a newsletter and blog post on John's website (see above).

Perspective

- Today's conversation is going to be challenging!
- Please know that both us are VERY interested in finding a way forward for compounds of this type
- But, the core problem is a deep science question that can't be wished away
  - How do you show the value contributed by these tools?
- We think the best way forward is one of pragmatic optimism in search of realistic scientific solutions
  - So, we are very glad to be having this conversation!

Agenda

- Defining scope:
  - The core problem
  - Language to guide conversation
- Discussion of non-traditional products that…
  - Seek to treat infections
  - Seek to prevent infections
- Why this matters to CARB-X: Summary & next steps
- Supplemental slides
  - Useful literature, both general and from Animal Health

The core problem

- All products must showcase their distinctive value
- This is not a regulatory issue per se. Rather, this is what we naturally ask of anything
  - Prove to me that it works!
  - How is it better / useful?
  - In what settings can that advantage be seen?
- For antibiotics, limits on the routinely possible studies (next slides) create a substantial hurdle
  - Superiority is (usually) out of reach
  - Non-inferiority studies are relatively unsatisfying
- **Beg for the bad news***: If you're not clear on this, you are heading into a world of hurt

*Swanson's Rule #27 from Swanson's *Unwritten Rules of Management*. William Swanson was CEO of Raytheon for many years and his set of 33 rules is legendary.

Trial Design 101: Two study designs – *everything* reduces to one of these

- Superiority studies
  - X vs. Y, with an aim to show X beats Y
  - TEST vs. placebo or TEST vs. Standard of Care
  - Preferred design – result is unambiguous
  - Everybody likes the idea of Better
- Non-inferiority (NI) studies
  - X vs. Y, with an aim to show X ≈ Y
  - Messy, harder to do accurately, confusing
- But, we (almost) always use NI for new antibiotics
  - **Why?**

The paradox of antibiotics

- We want new drugs for bad bugs
  - The advantage of NEW is easily shown in the lab on the basis of MIC testing or in animal models of infection
- But, asking for clinical data leads to a problem
- Example: Limb-threatening infection due to MRSA*
  - It is not ethical to randomize to methicillin vs. NEW
  - Must instead do something like vancomycin vs. NEW
  - In that population, vancomycin is highly effective
  - Must NOT enroll if resistant to NewDrug or comparator
- Hence, antibiotic trials are (usually) designed to avoid superiority

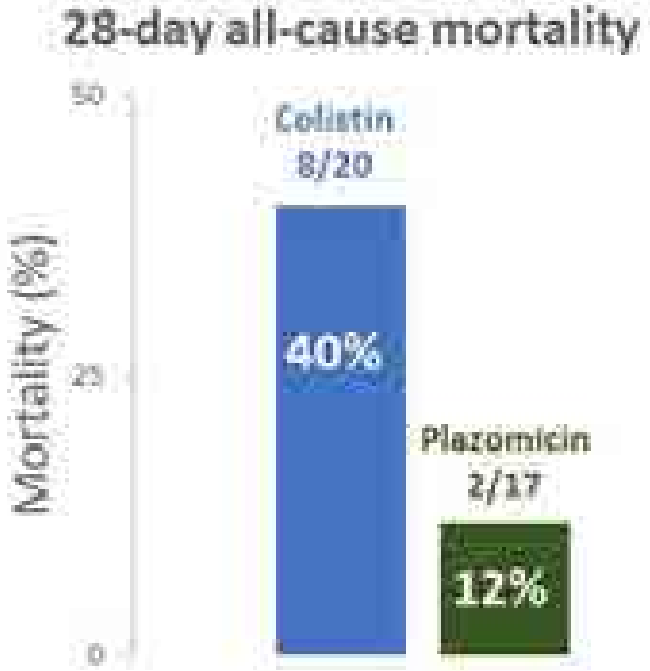
*MRSA = Methicillin-resistant *Staphylococcus aureus*

This idea is very, very hard

- Non-life-threatening illness (e.g., migraine)
  - Delayed effective therapy is not dangerous
- Cancer: Placebo is (usually) not possible, but there is always room to improve on 5- or 10-year survival
- **Infections: We routinely Cure potentially fatal illness**
  - And, it's hard to improve on Cured
- But, the idea of non-inferiority is confusing
  - "We want a *better* drug."
  - Understood, but insisting on clinical superiority before approving new agents means progress only when/if the pipeline (again) is inadequate for the studied population
- Next 2 slides: Let's discuss in two other ways

In Infection, superiority means something bad has happened: Plazomicin and CRE[1]

- In 2012-13, colistin was the only alternative for CRE. A study of plazomicin vs. colistin-based SOC[2] for CRE was plausible
- Plazomicin wins, but efforts to control CRE made it very hard to find cases & enroll (note small N). Cost was $1m/case!
- And, 40% mortality is not good!
- Future studies will need to use plazomicin (or one of the other new agents with comparable data) as the comparator



1. CRE = Carbapenem-resistant Enterobacteriaceae
2. SOC = Standard of Care

But, superiority trials are used in other areas! Tell me again: *Why not in Infection?*

	Migraine	Cancer	Infection
1. Durable cure is routine	No	No	*Yes*
2. Placebo is routinely acceptable	Yes	*No*	*No*
3. Transmissible resistance arises → new agents always needed	No	No	*Yes*
4. New agents are really for use…	Today	Today	*Tomorrow*[1]

Points 1 & 2: Superiority is routinely used in some areas not but others

- *Migraine (non-life-threatening example):* Placebo with rescue is possible
- *Cancer:* Durable cure is not routine and continual improvement (e.g., improve 5- or 10-year survival) is hence possible. Also, resistance is not transmissible.
- *Human Infection:* Placebo not usually acceptable & it's hard to improve on Cured!

Points 3 & 4: We need to develop new anti-infectives despite this limitation

- There are negative Public Health issues if superiority is (or becomes) possible!

1. This points to part of the reason why new antibiotics suffer from several forms of market failure. For more on this, see the DRIVE-AB report, various blogs on John's website, and any of Kevin's various publication (the 11 Apr 2018 op-ed in STAT News is a very good place to start: https://www.statnews.com/2018/04/11/innovation-new-antibiotics-left-sweet-spot/).
2. For reference, the corresponding answers in Animal Health are Yes, Yes, Maybe & Today. See this cite for more on Animal Health issues: Page SW, Gautier P. Use of antimicrobial agents in livestock. Rev Sci Tech 31:145-88, 2012.

Solution: The (emerging) 2-study path for new traditional antibiotics

- 1x NI RCT* vs. a good comparator
  - UDR (Usual Drug Resistance) setting: **both agents are predicted to be active**
  - Done in one of the major indications (cUTI, cIAI, etc.)
- 1x salvage study for highly Resistant pathogens
  - Randomized vs. Best-Alternative Therapy (BAT) if possible, Open-label if N too small for this
- Example: Plazomicin initial registration program
  - NI RCT: 1x cUTI NI RCT vs. meropenem
  - Salvage: 1x study in CRE vs. colistin (prior slide)

*NI RCT: Non-Inferiority design Randomized Controlled Trial. See extended discussion of these trials in Rex JH et al.: Progress in the fight against multidrug-resistant bacteria 2005-2016: Modern non-inferiority trial designs enable antibiotic development in advance of epidemic bacterial resistance. Clinical Infectious Diseases 65: 141-146, 2017.

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What is a non-traditional?

- We are going to differ from prior papers
  - ***Mechanism or chemical structure is not helpful***
  - ***What matters is what it does or does not do***
- Fleming* antibiotic:
  - Qualitatively, is like penicillin
  - SSSS: Has the **spectrum** for a defined **syndrome** and the **speed** required to be suitable as the **sole therapy**
- Non-Fleming = non-traditional = everything else
  - Phage, antibodies, small molecules, large molecules, microbiome … it doesn't matter

*Sir Alexander Fleming (6 Aug 1881 – 11 Mar 1955) was a Scottish physician, microbiologist, & pharmacologist. His best-known discoveries are the enzyme lysozyme (1923) and benzylpenicillin (Penicillin G, 1928).

Other language to note and then (mostly) bypass in this talk

- Alternatives to antibiotics
  - A very broadly used term, sometimes taken to be the same as non-traditional and sometimes taken as a superset that includes non-medicinal tools (e.g., a super smooth catheter to which nothing sticks)
  - We mostly just treat as equivalent to non-traditional
- Potentiator or Enhancer
  - These terms are applied to many types of combinations. We find them too ambiguous to be helpful.
  - Because of that, we tend to avoid this language. We'll below try some alternative language

Back to the mainstream…

- For a therapeutic, SSSS opens doors
  - **Spectrum** for a **syndrome, speed** of a **sole therapy**
  - If SSSS, there is at least one setting where you can enroll empirically into a standard NI RCT of NEW vs. a standard comparator
  - This is a predictable path to registration
  - There is some flex on spectrum (see later)
- For prevention, SxxS is the minimum bar
  - Spectrum must cover target pathogen(s)
  - Sole agent seems required on a practical basis
  - But, and as discussed below, prevention has other issues

The (lesser) problem of the MIC*

- We are very used to doing an MIC to predict utility of a given agent for a given bug
- But, some categories of products (e.g., true virulence inhibitors) lack an easy path to a test that resembles an MIC
- We think this is a problem we can manage
  - We don't require it for other drug classes
- But, it may mean loss of PK-PD as a strong support for the data used to achieve registration
  - Unless we can find a way to replace the support provided by PK-PD for predicting efficacy of the dose/exposure, we may need to prove utility by doing at least two RCTs rather than one (yuck!)

*MIC = Minimum Inhibitory Concentration, a laboratory test used to measure the activity a given drug vs. the patient's infecting organisms. The MIC is the source of the traditional S & R (Susceptible & Resistant) metrics.

What about other potential benefits of non-traditional products?

- Some features of non-traditional products have a very attractive intuitive feel
  - "It's narrow → less pressure on other bacteria."
  - "It works via the host and hence resistance can't arise."
  - "It will have fewer side-effects."
- Perhaps true but very hard to prove in a clinical trial
  - **Less development of R:** Carriage of resistant bacteria is imperceptible, but trial endpoints must be grounded in clinical reality
  - **Safer:** AE rates are pretty low with most modern agents – it's hard to show convincing superiority on safety

Will diagnostics fix any of this?

- Unfortunately, diagnostics do not (yet) have the speed & efficacy of a Star Trek tricorder
- Issue #1: Diagnostics do not create cases
  - If rare bacterium X is present in 1% of cases…
  - … you still have to screen 100 to find that one
- Issue #2: Time is ticking, referral is not a path
  - In cancer and rare diseases, we don't dawdle but there is time to both make a diagnosis and refer as needed
  - With Infection, minutes count. The patient must present at site that is already running the study
  - This magnifies the problem of finding those rare cases
- These limits noted, we'll look for possible uses

Finally, know also that we're skipping product-specific issues

- Examples
  - Immune response to product: Lysins (and anything else that is effectively a large protein) might face this
  - Delivery of product: Antisense products may require special delivery tools
  - Need for product customized to an individual patient: Phage cocktails might need to be customized
- We view all of these as secondary – if a product were compelling, we'd solve these sorts of issues

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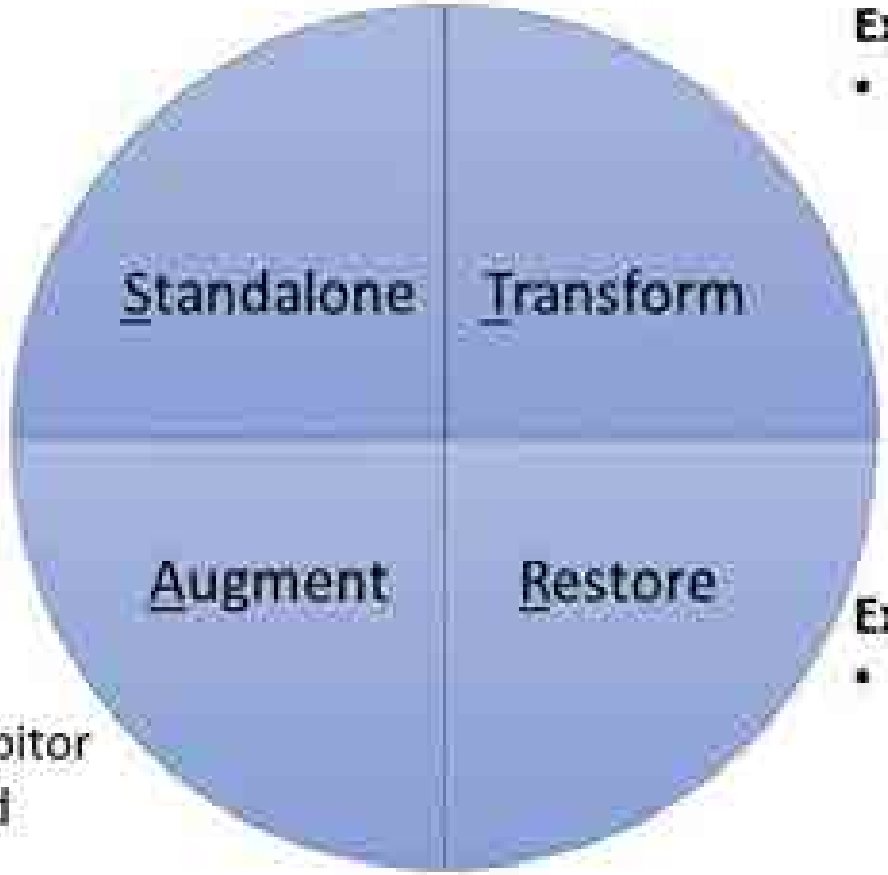
STAR: Four treatment archetypes[1]

Examples
- Phage
- Lysins
- Antisense



Example[2]
- Gram-negative activity from colistin + approved Gram-positive antibiotic

Example[2]
- Virulence factor inhibitor + approved antibiotic

Example[2]
- BL-BLI (Beta-lactam beta-lactamase inhibitor) combinations

1. Note that these archetypes could also be used for traditional (Fleming) antibiotics. Examples of Standalone and Restore are pretty common. Transform and Augment are possible in theory but are rare in practice.
2. The terms "Potentiator" or "Enhancer" have been used for products in all 3 of these categories

STAR: Four treatment archetypes

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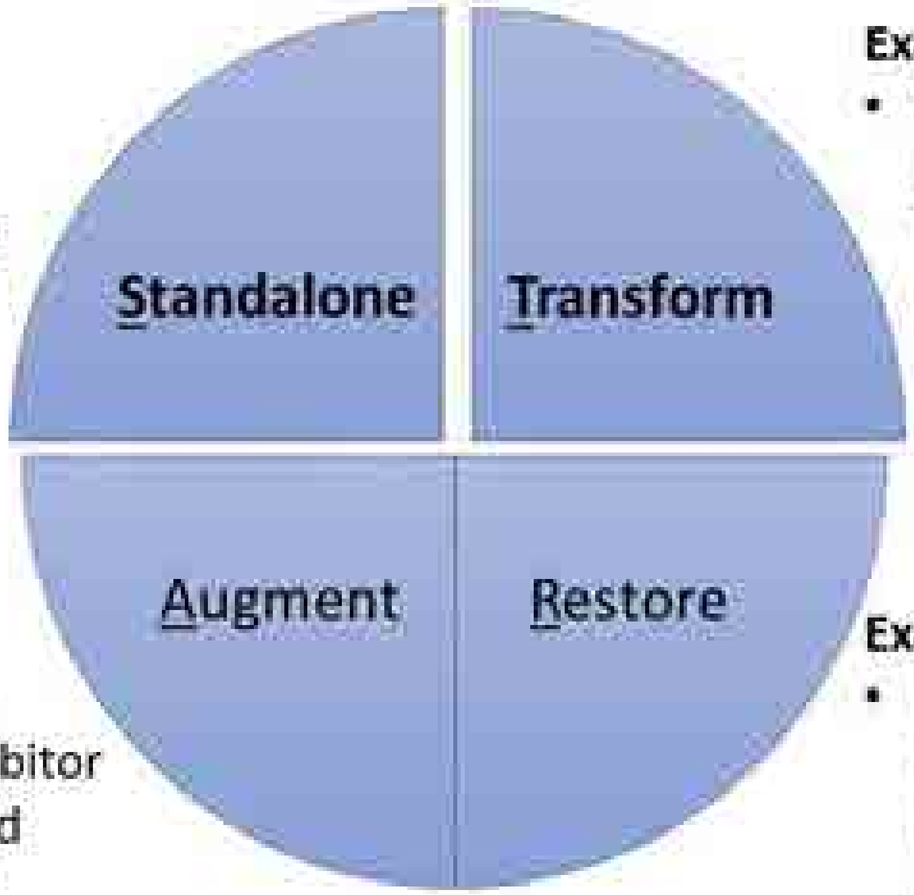
Example*
- Gram-negative activity from colistin + approved Gram-positive antibiotic



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Standalone, Transform: Direct activity

- xxSx: Spectrum, syndrome, **speed**, sole therapy
- Examples:
  - **Standalone (NEW on its own):*** Phage, lysins, antisense
  - **Transform:** NEW added to 2nd agent not otherwise active on the target (e.g., polymyxin + known Gram-positive agent where combo has Gram-negative activity)
- In either case, an entity complete in itself
  - Even if it has more than one component
  - Usually has an MIC
- Advantages: Standard NI designs may be suitable
- But, if narrow-spectrum or not (fully) standalone…

*This would also describe ANY new mechanism standalone molecule, small or large, that is SSSS.

Narrow-spectrum problem (1 of 2)

- Narrow-spectrum antibiotics require a setting where activity for a specific pathogen can be seen in isolation. There are 4 possible patterns:
- Pattern A: Organism = Syndrome (*N. gonorrhoeae*)
  - Straightforward study design
- Pattern B: Organism appears within a syndrome **and** symmetrical gaps in the spectrum of existing agents make it possible to show activity of NEW:
  - Example: ertapenem[1] does not cover *P. aeruginosa*. So, NEW + ertapenem vs. imipenem shows activity of NEW.
  - Low rate of *P. aeruginosa* is the remaining problem
  - A diagnostic could support selective enrollment

Ertapenem is a carbapenem that lacks activity against Pseudomonas aeruginosa. Imipenem is a carbapenem that DOES cover P. aeruginosa. So, you could say that ertapenem has a Pseudomonas-sized hole in its spectrum relative to imipenem.

Narrow-spectrum problem (2 of 2)

- Pattern C: Organism is one of several causes of a syndrome and existing agents often cover organism
  - Ex: *Klebsiella* as a component of cIAI & pneumonia
- This pattern further subdivides into…
  - Normal commensal vs. Always a pathogen
- C1: Commensal pathogen, e.g. *E. coli*
  - The signature of the bug is present in everybody
  - Must find a setting that favors actual infection
  - Possible example: *E. coli* in uUTI might be possible to diagnose with a non-Star Trek diagnostic
- C2: Always a pathogen, e.g., *Salmonella*
  - This might be a sweet spot for a rapid diagnostic

(Not Fully) Standalone problem

- For one of several possible reasons (e.g., lack of speed or limited potency), NEW alone is not deemed sufficiently active to be monotherapy
  - Equipoise cannot be achieved for NEW vs. OLD design
- Instead, NEW + OLD must be compared with OLD
- In this case, NEW + OLD must show superiority to OLD based on a clinical endpoint grounded in how a patient feels, functions, or survives
- This problem also seen with the Augment category and will be discussed further when we get to that

STAR: Four treatment archetypes

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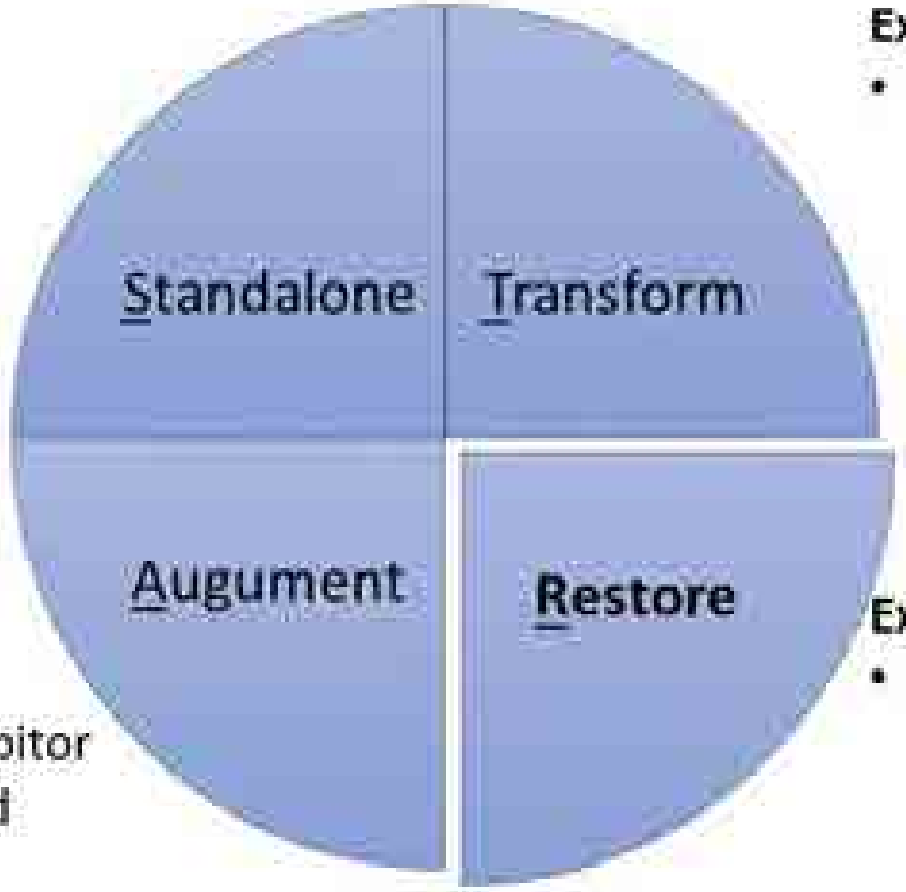

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Restore an existing agent

- Example: Beta-lactamase inhibitor (BLI) that restores activity of a beta-lactam (BL)
  - BL has worked in past, but R mechanisms now block it
  - With BLI, MIC of BL moves from >128 back to 0.5 mg/L
- Advantages: There is a clear path to development
  - The prior history of the base product gives great comfort
  - PK-PD-based support for dosing should be possible
  - In short, is often very close to SSSS
- Distinctive hurdles
  - Partners must have matching PK (needed by all combos)
  - Narrow-spectrum problem may occur if bacteria in which activity change can be shown are rare

STAR: Four treatment archetypes

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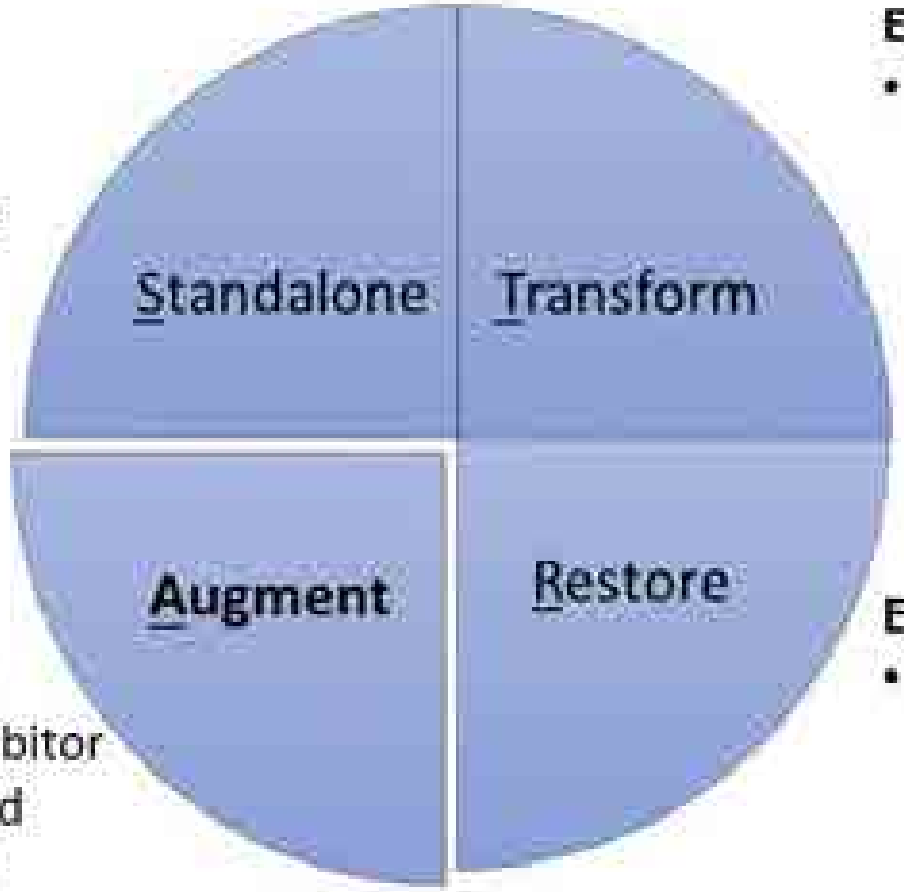

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Augment an existing therapy

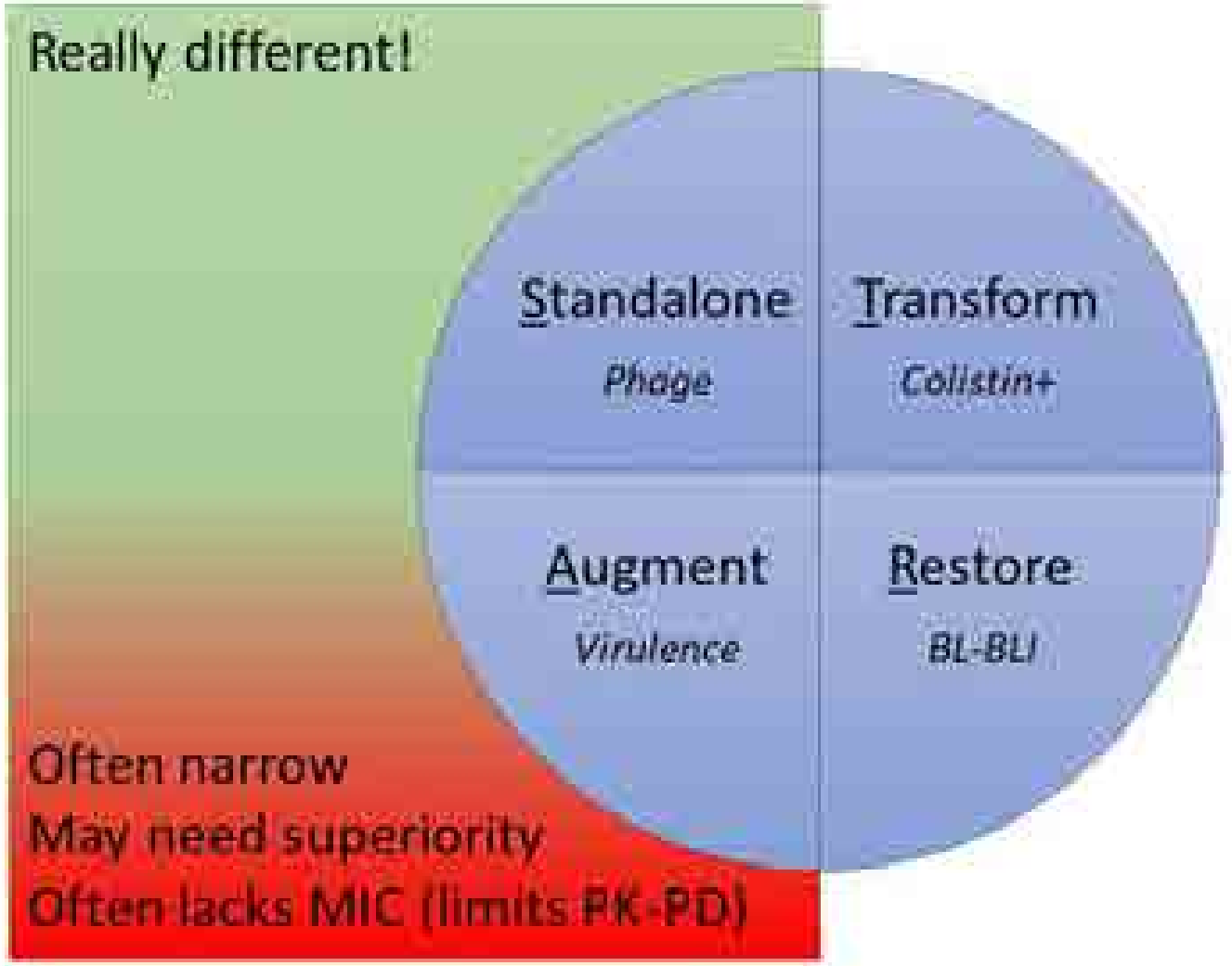
- Example: Virulence inhibitor or such
  - Usually lacks an MIC equivalent and has no discernible in vitro effect on the base therapy in the laboratory
  - Not sufficient alone: Must also give an active antibacterial (e.g., toxin inhibitor + a Fleming antibiotic)
- Distinctive hurdles
  - **Base therapy needs to work**
    - Might protect a base therapy from emergence of resistance but doesn't solve existing resistance problems
  - Dose: Lack of an MIC → harder to apply PK-PD
    - If the PK-PD rationale has gaps, it becomes harder to validate dose/exposure logic. You may need two studies
  - Superiority problem: Must show NEW + OLD > OLD
  - May need a novel endpoint to show value (next slide)

Superiority & Endpoints

- Ultimately, these agents force a study of this form
  - NEW + SOC vs. SOC
  - And, we will want to see that NEW + SOC **is superior to** SOC
- Are there settings where this might be possible?
  - Endocarditis is a good candidate: more rapid bloodstream clearance might have a measurable clinical effect
  - But, this is a hard study to enroll and there is so much noise in the data – clinical improvement may be tough
- **Endpoints:** Would different endpoints help?
  - A challenging question! Whatever is proposed must be compelling.
  - Are there population-level variations on "feels, functions, survives" that we should begin to recognize?
- Finally, know that this is not a regulatory problem per se
  - The agencies are simply the first to point out the issue
  - Why should I use this? Why should I pay for this?

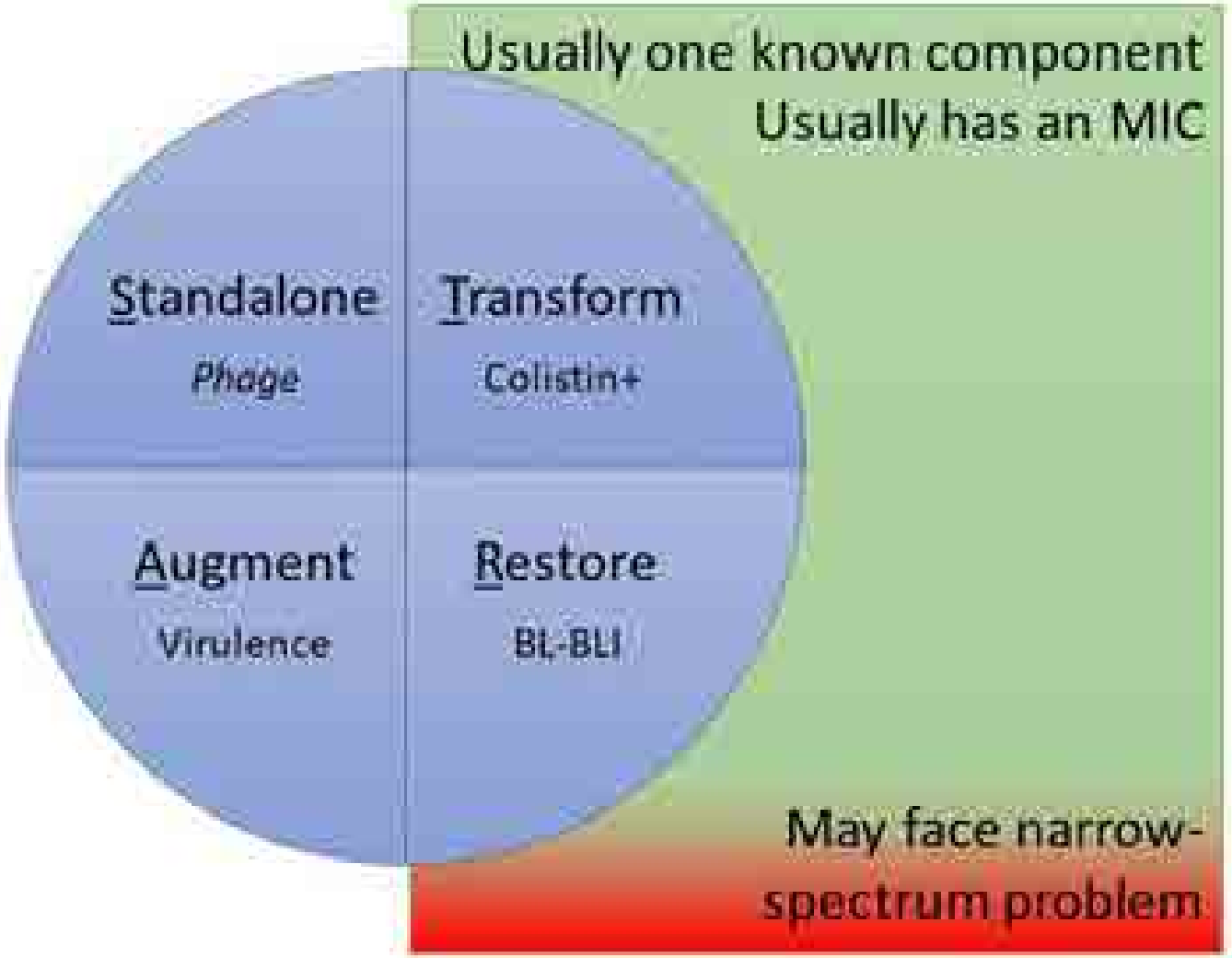
Comparing the four archetypes

Standalone & Augment: Novel & difficult



Comparing the four archetypes

Transform & Restore: Fewer development issues



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*The discussion that follows really applies to any preventative product.

Prevention: Surprisingly hard!

- Ex: Antibodies or microbiome products seeking to reduce carriage of specific bacteria
- Key hurdle: Reducing carriage is not enough
  - Must show an effect on a subsequent infection or other clinical benefit
  - Must show this *on top of* best available prevention
  - Frustratingly hard & may require very large studies
- And…
  - Effect & effect size must be interesting
  - NNT (number needed to treat) must be reasonable
  - What replaces the displaced bacteria? Shifting from carriage of VRE* to *Candida* may not be a good thing!

*Vancomycin-resistant Enterococcus

Case study: Pfizer's *S. aureus* vaccine (1 of 3)

- 7 Nov 2017: Vaccines and Related Biological Products Committee (VRBPAC) discussed Pfizer's investigational *Staphylococcus aureus* vaccine for pre-surgical prophylaxis in elective orthopedics
- Two core questions:
  - How big does the study have to be if you must show reduction in a serious (non-trivial) clinical infection?
  - In what population can you do this?

Pfizer's *S. aureus* vaccine (2 of 3)

- P3 trial in population with highest rate of surgical infection (despite good care) they could find:
  - Open, posterior approach, multi-level, instrumented, spinal fusion orthopedic surgery.
  - Read that carefully!!
- Post-op infection rate predicted to be 1.4%
  - Pfizer is running a trial that (clinicaltrials.gov) will enroll over 3 years about 2,600 subjects at 1:1 vaccine:placebo*
  - Has 88% power to detect ≥70% infection rate reduction
  - This would be a fall from 1.4% to 0.42%
- Question to the Advisory Committee
  - If no safety issues, would data showing efficacy generalize to other orthopedic procedures?

*Placebo was really best standard of care + placebo

Pfizer's *S. aureus* vaccine (3 of 3)

- So … can we generalize to hips, knees, and so forth?
- FDA briefing book comment
  - As "… rates of invasive *S. aureus* disease across other elective orthopedic surgical populations are … ~0.25% to ~0.5% within 90 days of surgery …"
  - "… conducting a randomized, placebo-controlled clinical endpoint efficacy trial that includes other elective orthopedic surgical populations would … (be) … operationally impractical."
- The math: required sizes are 10-20,000 **per arm**
- If 0.25% → 0.125%, NNT* = 800. What's that worth?
  - NNT for influenza vaccine: 10-40 (Kolber MR et al. CanFamPhys 60:50, 2014)
  - NNT for HPV vx & cervical cancer? ~300-350 (Brisson M et al. CMAJ 177:464-8, 2007)
- All together, no simple answer given efficacy of other tools

*NNT = Number Needed to Treat for 1 person to benefit

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Perspective summary

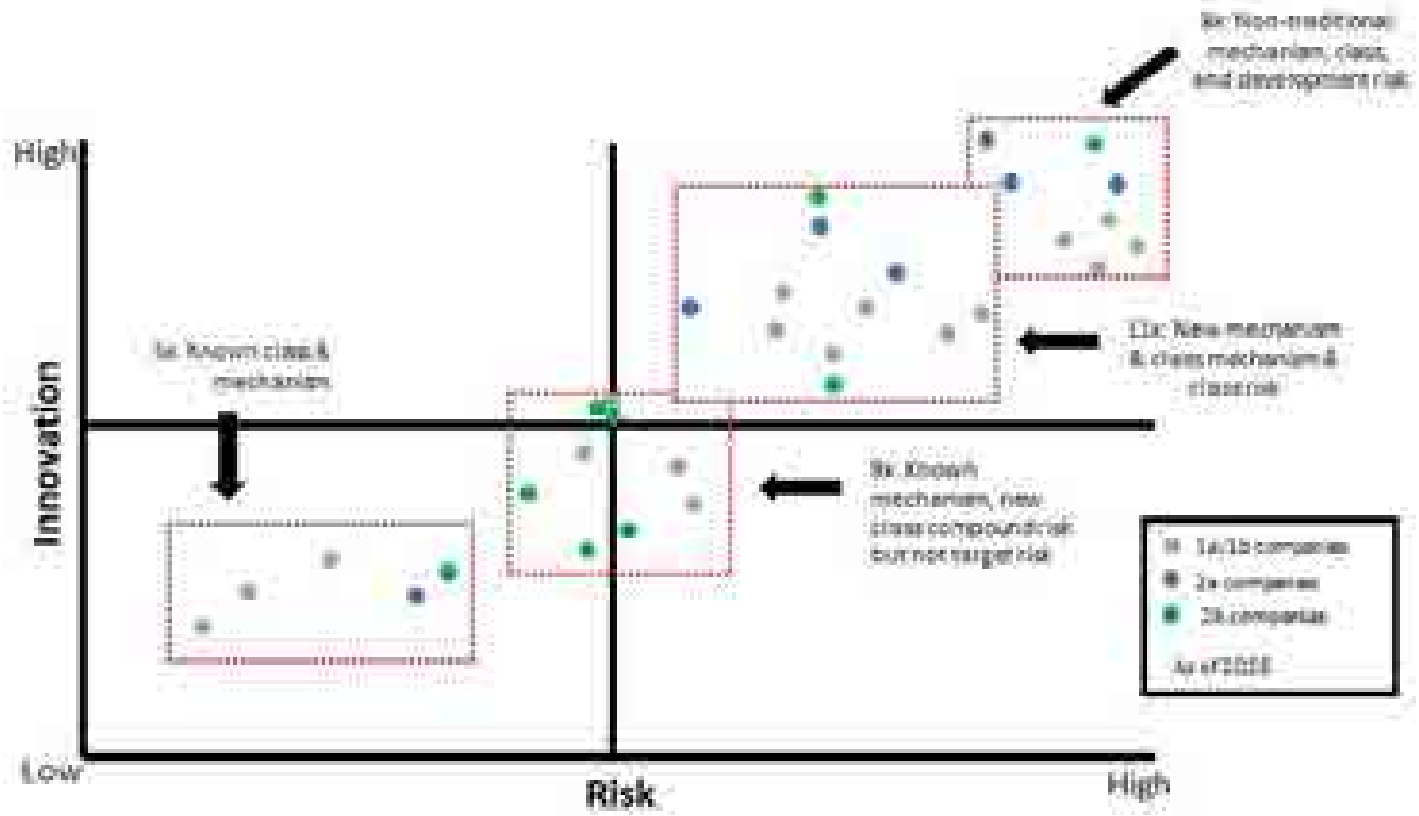
- Fleming: We generally know how to develop these
  - SSSS: **Spectrum** for a **syndrome, speed of sole therapy**
- Outside this zone: Non-Fleming
  - Standalone & Augment: Often VERY hard (superiority often needed)
  - Restore & Transform: Easier but not easy. Narrow-spectrum issue can be a challenge
  - Prevent: Surprisingly hard (big N needed)

- At heart, the problems are not regulatory … agencies are simply the first of those who ask hard questions
- *Beg for the bad news:*
  - Wishing won't fix this!
  - And, CARB-X is now investing heavily in this area…

CARB-X mission & scope

- Invest >$500M over 5 years
  - Focused on priority drug-resistant bacteria
  - Agnostic on modality: therapeutics, diagnostics, prevention, devices
- Goal is to reduce the human health impact from drug-resistant bacteria
- Both traditional and non-traditional products (next slide)

CARB-X Therapeutics Portfolio: Innovation and Risk Analysis



CARB-X role in today's workshop

- Support the ecosystem, well in advance
- Facilitate discussion of actual products
  - Difficult for FDA to evaluate hypotheticals
  - Give companies accurate picture of clinical trial design hurdles to elicit creative work now
- Examples of thinking to explore:
  - Endpoints:
    - Population-level clinical benefits (clinically relevant reductions in resistance or carriage)
    - Cf. HPV (reduction in carriage, plus reduction in clinically relevant intermediate stages)
  - Human challenge models,* as a bridge from animal models to salvage studies

*Roestenberg M et al. Lancet ID June 2018 (in press)

Additional (bad) news…

- FDA approval ≠ sales
  - Recent antibiotic adoption curves have been challenging for developers
  - Approval as NI to well-understood generic (cheap) SOC is certainly part of this
- **Trials must also create data that both payers and clinicians find compelling**
  - And, we must be good stewards of new agents
- Pull incentives (like market entry rewards) may solve some of these problems, depending on design (next slide)

Pull incentives for non-traditionals

- Core problem: designing trials today mainly for *tomorrow's* patients
  - Direction of travel is clear, but not rate, inflection point, or availability of generic competition (due to resistance)
  - Cf. oncology, CV, behavioral: market sizes are relatively clear
- Pull incentives can solve the payer/sales problem, but not the regulatory approval issues described above
- But: governments could buy out and park products just short of full approval (preparedness model), moving them forward to confirmatory P3 trials once the epidemiology (unfortunately) advances

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General literature

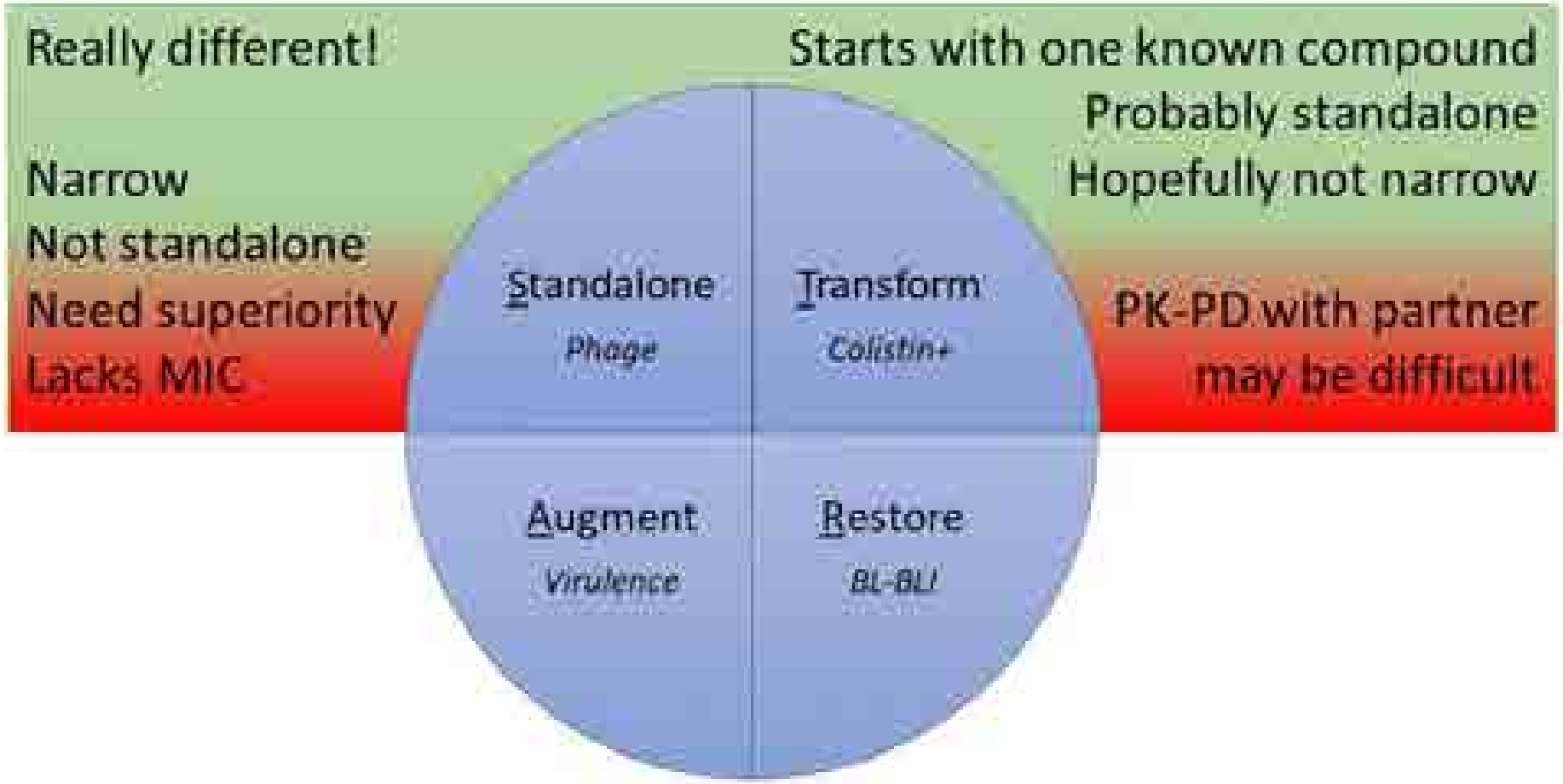
- Czaplewski et al.: Alternatives to antibiotics – a pipeline portfolio review. Lancet Infect Dis. 16(2):239-51, 2016.
- Tse et al.: Challenges and Opportunities of Nontraditional Approaches to Treating Bacterial Infections. Clinical Infectious Diseases. 65(3):495-500, 2017.
- http://www.pewtrusts.org/en/multimedia/data-visualizations/2017/nontraditional-products-for-bacterial-infections-in-clinical-development
- Rex et al.: Progress in the fight against multidrug-resistant bacteria 2005-2016: Modern non-inferiority trial designs enable antibiotic development in advance of epidemic bacterial resistance. Clinical Infectious Diseases 65: 141-146, 2017.

Animal Health Literature

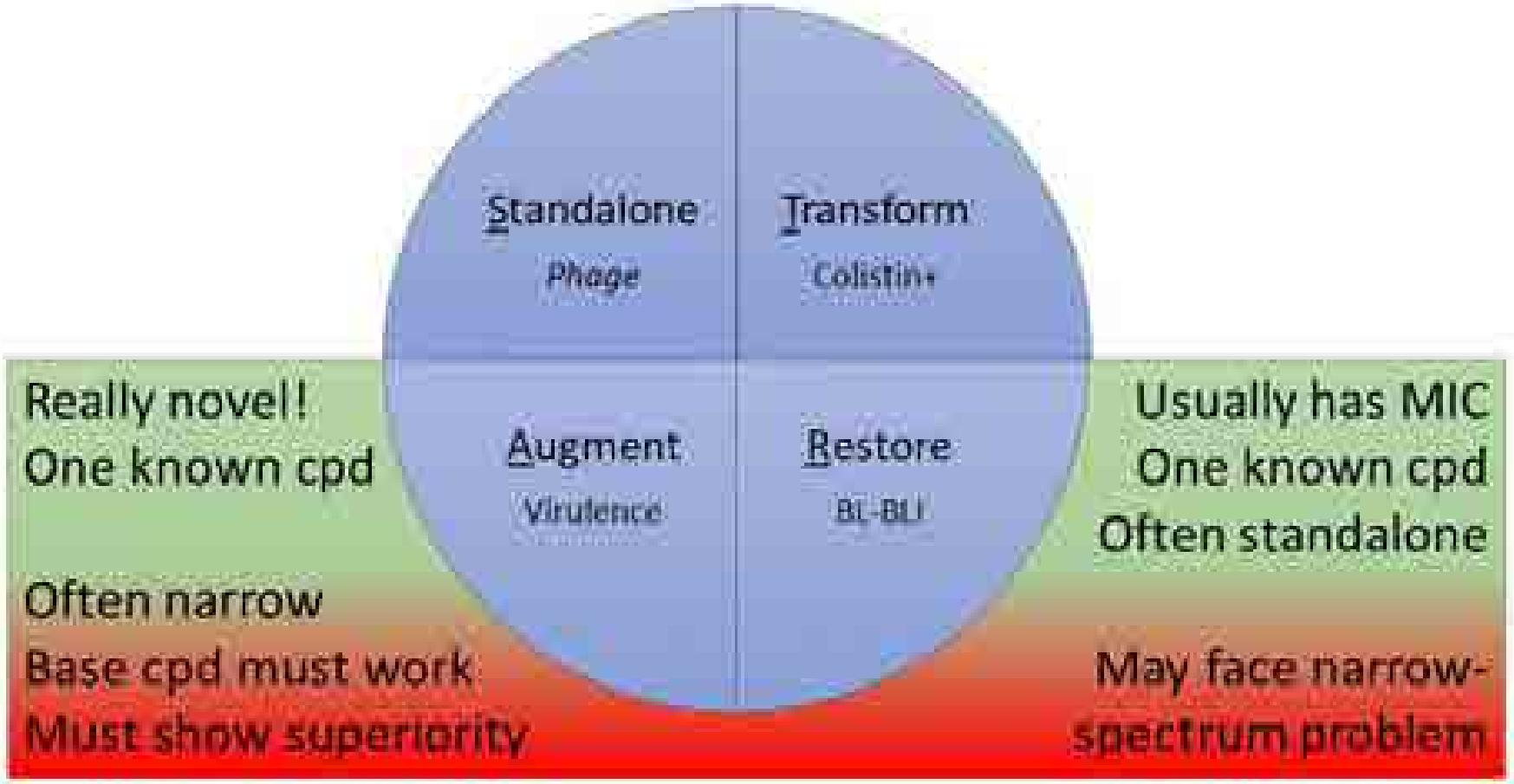
AH spends a lot of time thinking about these types of tools

- USDA Alternatives to Antibiotics 2nd meeting held at OIE in Paris 12-15 Dec 2016:
  - https://www.ars.usda.gov/alternativestoantibiotics/Symposium2016/index.html
  - See Session 6 where there are 5 excellent talks: EMA, FDA, China Institute for Veterinary Drug Control, and two Industry perspectives
- A 2013 summary (slide deck) by Cyril Gay (USDA)
  - http://www.oie.int/eng/A_AMR2013/Presentations/S8_1_CyrilGay.pdf
- A 2013 review (manuscript) by Seal BS et al. (USDA)
  - https://www.ars.usda.gov/alternativestoantibiotics/PDF/reports/ATA%20challenges%20and%20solutions%202013.pdf

Treatment: Four archetypes



Treatment: Four archetypes



Thank you!

John H. Rex, MD
Chief Medical Officer, F2G Ltd;
Expert-in-Residence, Wellcome Trust
Operating Partner, Advent Life Sciences
Email: john.h.rex@gmail.com
Newsletter: http://amr.solutions

Kevin Outterson, JD
Executive Director, CARB-X
Professor of Law, Boston University
Email: mko@bu.edu

Understanding the Development Challenges Associated with Emerging Non-Traditional Antibiotics

E-Mail Questions to
Duke.Abx@Duke.edu

@DukeMargolis

Session 1: Developing non-traditional antibiotics with the potential to be studied in clinical trials as monotherapies

E-Mail Questions to

Duke.Abx@Duke.edu

@DukeMargolis

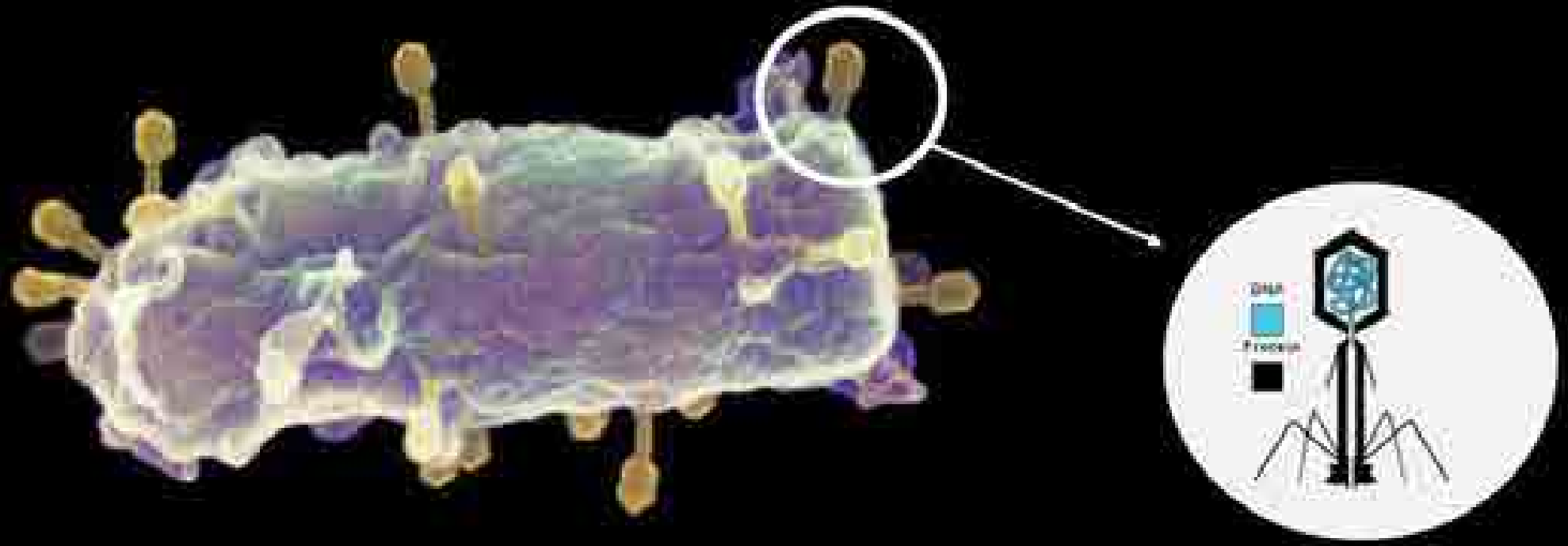
Adaptive Phage THERAPEUTICS

Greg Merril, CEO

gmerril@aphage.com

Adaptive Phage THERAPEUTICS

Phage vs. Bacteria



- 4B years co-evolution = huge diverse population of powerful bacteria killers
  (Phage kill 40% of bacteria in oceans every day)
- Phage safe to humans & even for non-targeted bacteria

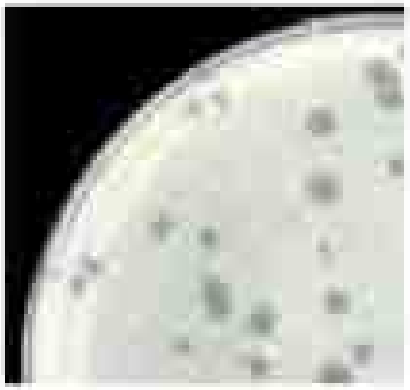
- Envisioned by NIH researcher Carl Merril, MD in 2003
- Navy initiated phage hunt in 2010

PhageBank™

1

Collected
Environmental samples and clinical isolates

2



Isolated
Phage that target ESKAPE are isolated

3

Safety Screen
Screened for deleterious genes

4

Banked
Cleared phage added **PhageBank™**

Adaptive Phage THERAPEUTICS

- 2012: Navy developed assay

HRQT™

The Host Range Quick Test

1

Pathogen Loading

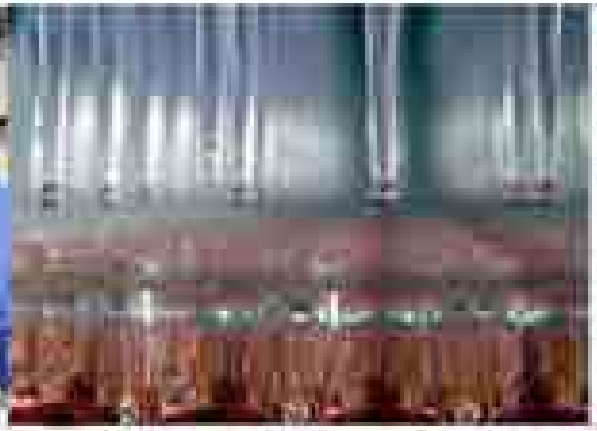
Cultured bacteria from patient is grown and robotically distributed into multiwell plates

2

PhageBank™

Hundreds of potential matching phage strains are pulled from PhageBank

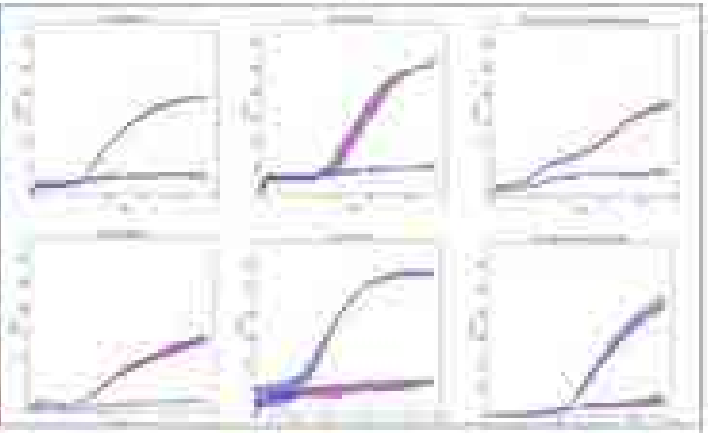
3



Assay

Robots load hundreds of strains of phage into individual wells containing the patient's bacterial culture

4



Kill Curves

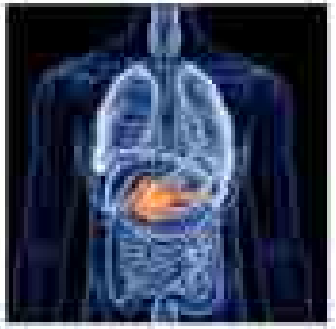
Machine vision system plots bacteria death and optimizes selection of phage and phage combinations

Adaptive Phage THERAPEUTICS

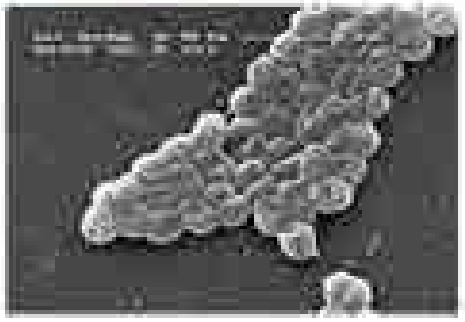
Case Study

Tom Patterson

November 2015: Egypt vacation



- Acute abdominal pain
- Nausea

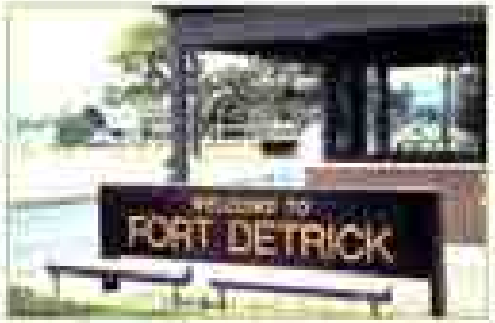


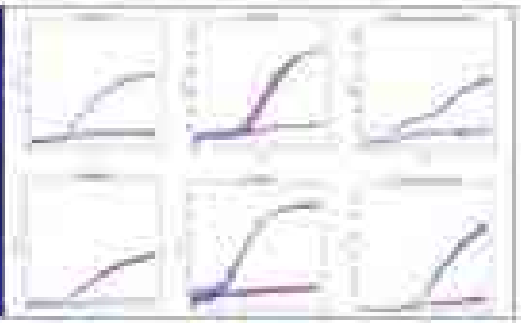
- At hospital acquired *A. baumannii* infection
- Evacuated back to USA

Adaptive Phage Therapeutics

Case Study Tom Patterson

- **March 11, 2016:** UCSD sent a culture to Dr. Biswas at NMRC
- **March 17, 2016:** iv infusion of 5 precision-matched and purified phage





Dr. Biswas, utilized innovative rapid phage/pathogen matching system (HRQT™) – testing 100 phage (PhageBank™) vs isolate

Adaptive Phage THERAPEUTICS


Case Study April 2016: Tom is ready to go home
STOP

Here's where APT comes in…

2016:
World-wide exclusive license to **PhageBank™** and **HRQT™**

CRADA:
- NMRC expanding **PhageBank®**,
- NMRC sequencing and screening phage
- APT to commercialize
- APT to lead treatment efforts for eIND patients

Other active collaborations:

- Children's National Medical Center
- Emory University
- Howard Hughes Medical Institute
- Princeton University
- Stanford University
- UC San Diego School of Medicine
- Yale University

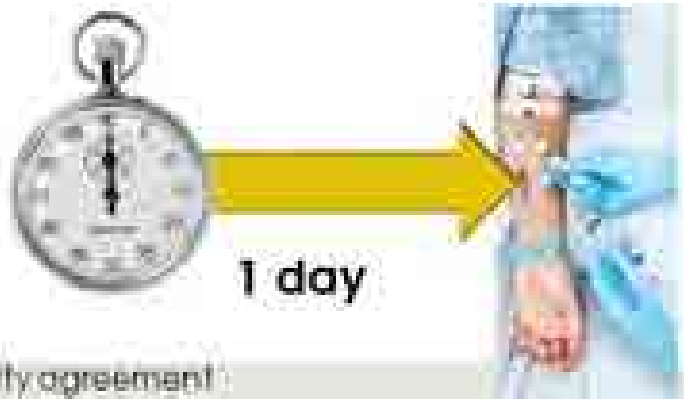
Challenge: Scalability – slow and expensive

Approach	Time	Step 1	Step 2	Step 3	Step 4	Step 5
eIND	7 Days	Acquire Isolate	HRQT	Grow phage	Purify phage	Deliver phage

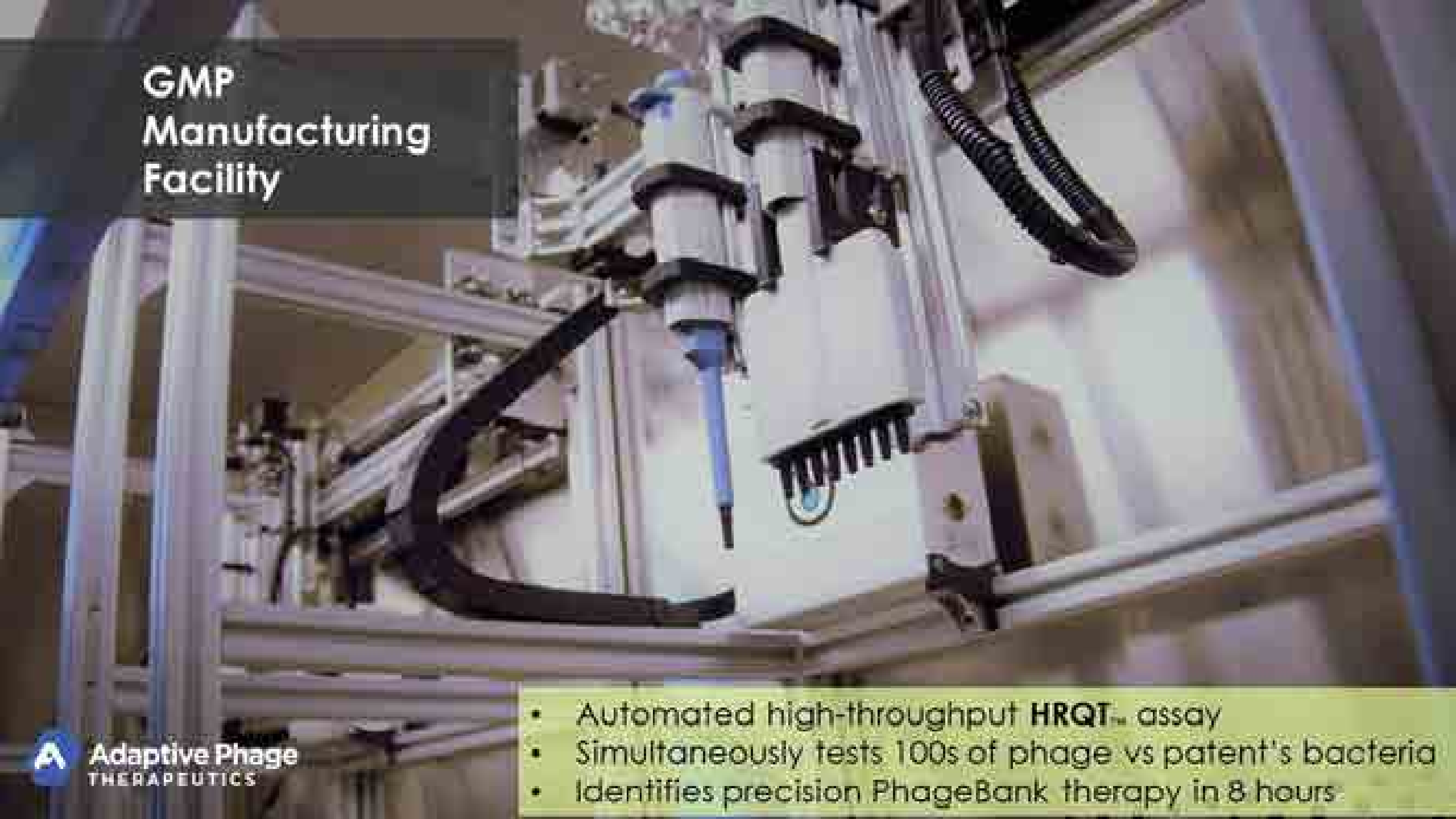
7-10 days

Translate eIND process to commercial viability

Approach	Time	Step 1	Step 2	Step 3	Step 4	Step 5
eIND	7 Days	Acquire isolate	HRQT	Grow phage	Purify phage	Deliver phage
IND/Commercial	1 Day	Acquire isolate	HRQT	Deliver phage		



Subject to confidentiality agreement



GMP Manufacturing Facility

- Automated high-throughput **HRQT**™ assay
- Simultaneously tests 100s of phage vs patent's bacteria
- Identifies precision PhageBank therapy in 8 hours

Adaptive Phage THERAPEUTICS

GMP Manufacturing Facility

Robotic Aseptic Filling

- Rapid changeover
- 1,000s of vials per batch
- 3 phage batches per day

Phase I/II Trial inventory (100 strains) within 45 days

Adaptive Phage THERAPEUTICS

APT addressing challenges of precision approach

Challenge	Resolution
Speed to match phage to patient	• HRQT assay – optimized with robotics • Working on machine learning/AI
Time to screen, grow, & purify	• Pre-screen to eliminate lysogenic and undesirable phage • pre-manufacture single dose vials of all phage in PhageBank
Cost	• Bulk PhageBank manufacturing NOT Just-in-time
Logistics time	• Step 1: centralized HRQT and PhageBank distribution **(2-3 days)** • Step 2a: HRQT in distributed CLIA labs **(1-2 days)** • Step 2b: AI + PhageBank localized "ATMs" **(under 1 day)**
Regulatory path	• Work with FDA to regulate expanding PhageBank
Showing efficacy as mono therapy	• Carefully designed clinical studies • Iterative approach (limited patient cohorts, limited indications limited pathogens… then iterate)


Adaptive Phage
THERAPEUTICS
TEDCO
PORTFOLIO COMPANY

ADVANCING TOWARDS THE CLINIC

NOVEL MODALITIES

June 2018

LOCUS BIOSCIENCES

ENGINEERING PRECISION MEDICINES

Our experience working with the FDA on engineered phage therapy indicates a rapid preclinical development for CRISPR-Cas3 platform assets with clear path to the clinic

DRUG DEVELOPMENT
Novel Platform Technology

Weaponized CRISPR-Cas3 phage cocktails selectively eliminate target bacterial species while leaving all others unaffected

CRISPR-Cas3

Bacterial immune system repurposed to kill pathogens

Cas3 shreds DNA causing rapid death in target cells

Bacteriophage

Viral delivery specific to target bacterial species

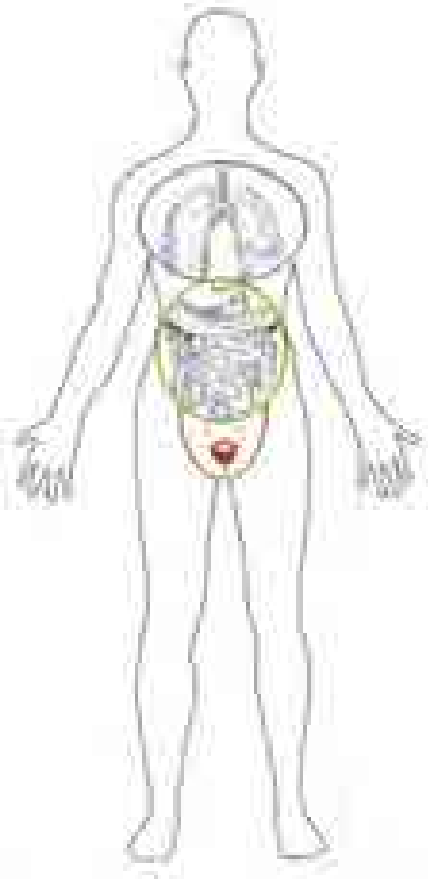
Ubiquitous in the environment, Generally Regarded as Safe (GRAS) by FDA

FDA
Center for Biologics Evaluation and Research

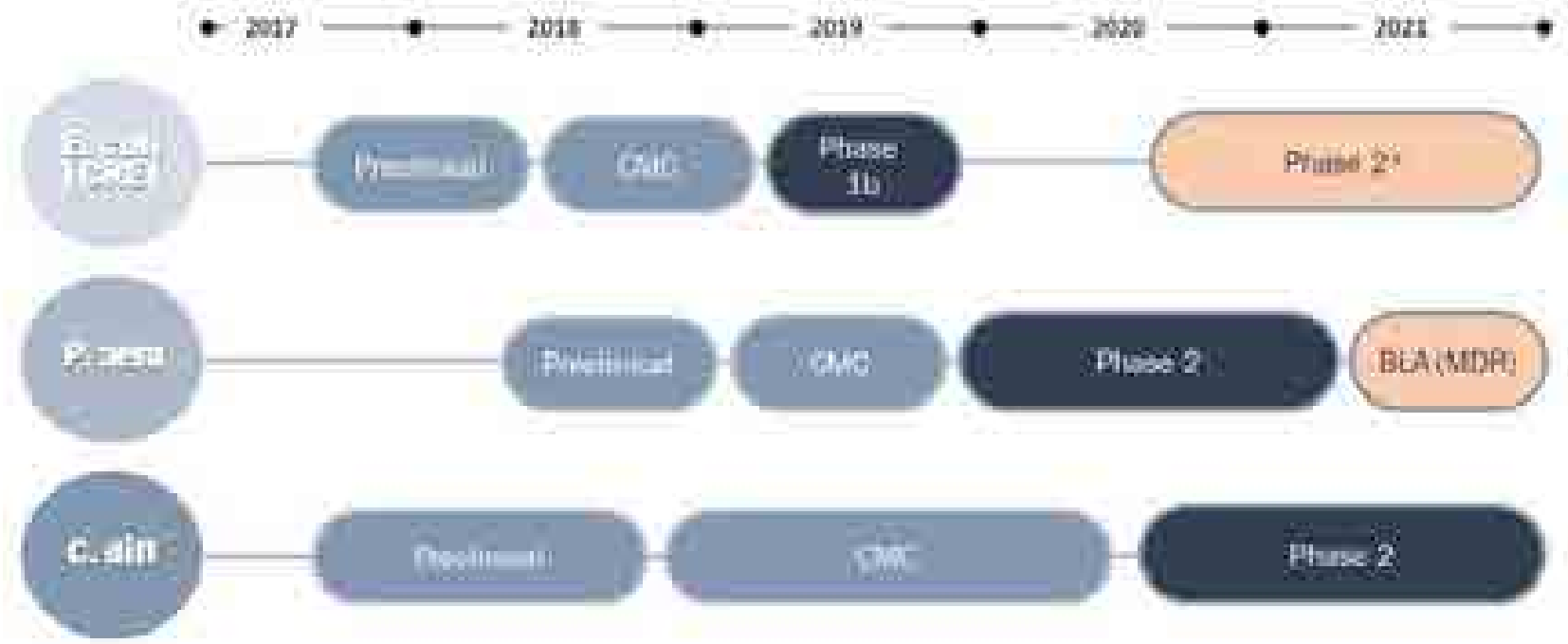
- FDA's current perspective on phage safety supports rapid and highly-predictable discovery & early development based on limited toxicology and dose range finding requirements
- Informative safety protocols potentially accelerate assets into abbreviated (MDR only) Tier-3 regulatory frameworks established to address the unmet need for new antibacterial treatments

Locus' first three development programs were carefully selected to prove CRISPR-Cas3 efficacy across three routes of administration

Indications	Strategic Context	Administration
Urinary Tract Complicated urinary tract infections (cUTI) from *E. coli*, then CRE	**First-in-Human (POC)** Initial safety, PK, and exploratory efficacy proving MOA for first-in-class CRISPR drug product	**Instillation** Intra-bladder instillation
HABP/VABP Hospital-Acquired & Ventilator-associated Bacterial Pneumonia	**Multi-Drug Resistance (MDR)** Caused by *P. aeruginosa* including MDR, carbapenem and colistin resistant bacteria	**Inhalation** Nebulized solution
Recurrent CDI Secondary & tertiary infections from *Clostridium difficile*	**Microbiome Imbalance** Elimination of *C. difficile* from the gut without removing good bacteria	**Oral** Capsule or oral liquid



Series-A funding and Type-B FDA meeting feedback support first-in-human trials by 2019 for first asset and advancement of second asset to IND



- Solving phage efficacy concerns by harnessing CRISPR-Cas3 while leveraging known phage safety
- Targeting pathogen-specific drug approvals (e.g. MDR Pseudomonas) instead of conventional indication-based approvals (e.g. pneumonia)
- Unique opportunity to execute a systematic set of clinical studies across pathogens and zones of infection (UTI, Lung, etc.)
- Leveraging regulatory & CMC solutions across all platform assets accelerating pathways to the clinic

Raised $21m in 24 months led by ARTIS Ventures and Tencent Holdings

ARTIS VENTURES

Tencent 腾讯

ABSTRACT VENTURES

North Carolina Biotechnology Center

CRISPR-Cas3 engineered phages are effective across organisms and sites of infection, demonstrating superior outcomes in animal models of disease

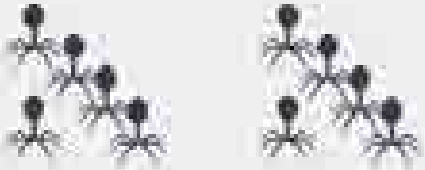
DISCOVERY & BIOINFORMATICS

Genomic Targeting

Repositories

- Collections of clinically relevant isolates blocked into panel sets
- Genomics used to develop crRNA guides targeting conserved genes
- Arrays of 4 RNA guides used to prevent target site escape

Host Range Selection



Phage Banks

- Species-specific collections of overlapping host ranges
- Cocktails created for greater than 85% coverage of isolate panels
- Activity against targeted strains independent of MDR status

+ Precision Engineered Phage Cocktails

CONSTRUCTION & IN VIVO

Synthetic Biology

Endogenous & Exogenous

- crRNA guides alone activate Cas3 already present in 50% bacteria
- Guides+Cas3 are synthetically engineered into phage genomes
- 10-12 weaponized phage moved into *in vivo* optimization

Bacterial Burden Reduction

Persistence & Distribution

- High concentration of drug persist for 6-8 hours (and clear as fast as 72 hours) in target organs
- No significant toxicology signals across 7-days of max dose

+ Increased efficacy with CRISPR-Cas3

First-in-human study will assess the safety, pharmacokinetics and potential efficacy of LBx-UT01 in *E. coli* colonized adults with top-line data expected in 2019

First-in-Human

Phase 1b

- Safety, tolerability and PK study in patients with urinary tract colonization dosed at maximum feasible dose BID via catheter instillation
- Confirm pharmacokinetics related to phage persistence time in the bladder, distribution and elimination
- Expect high therapeutic index as bacteriophages are non-toxic and unable to infect human cells
- Feasibility study completed with 9 interested sites across the US

+ 30 UT colonization

Proof-of-Concept (MDR)

Phase 2

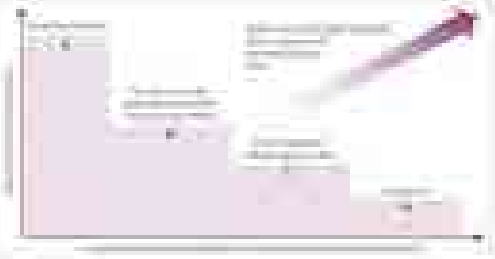
- Randomized, controlled, double-blind clinical trial in adult patients with complicated urinary tract infections (cUTI) that are suspected to be caused by MDR strains including 30% with pyelonephritis
- Patients randomized 1:1 to receive either (a) LBx-UT01 BID for 60 minutes by catheter installation plus placebo IV infusion or (b) SOC IV infusion plus placebo bladder installation
- Resolution of cUTI symptoms at end of therapy and test of cure (TOC – 7 days after end of therapy) with demonstration of bacterial pathogen reduction below 10^4 CFU/mL on urine culture (Microbiological Success) reassessed at TOC

+ 128 cUTI Patients

Pivotal

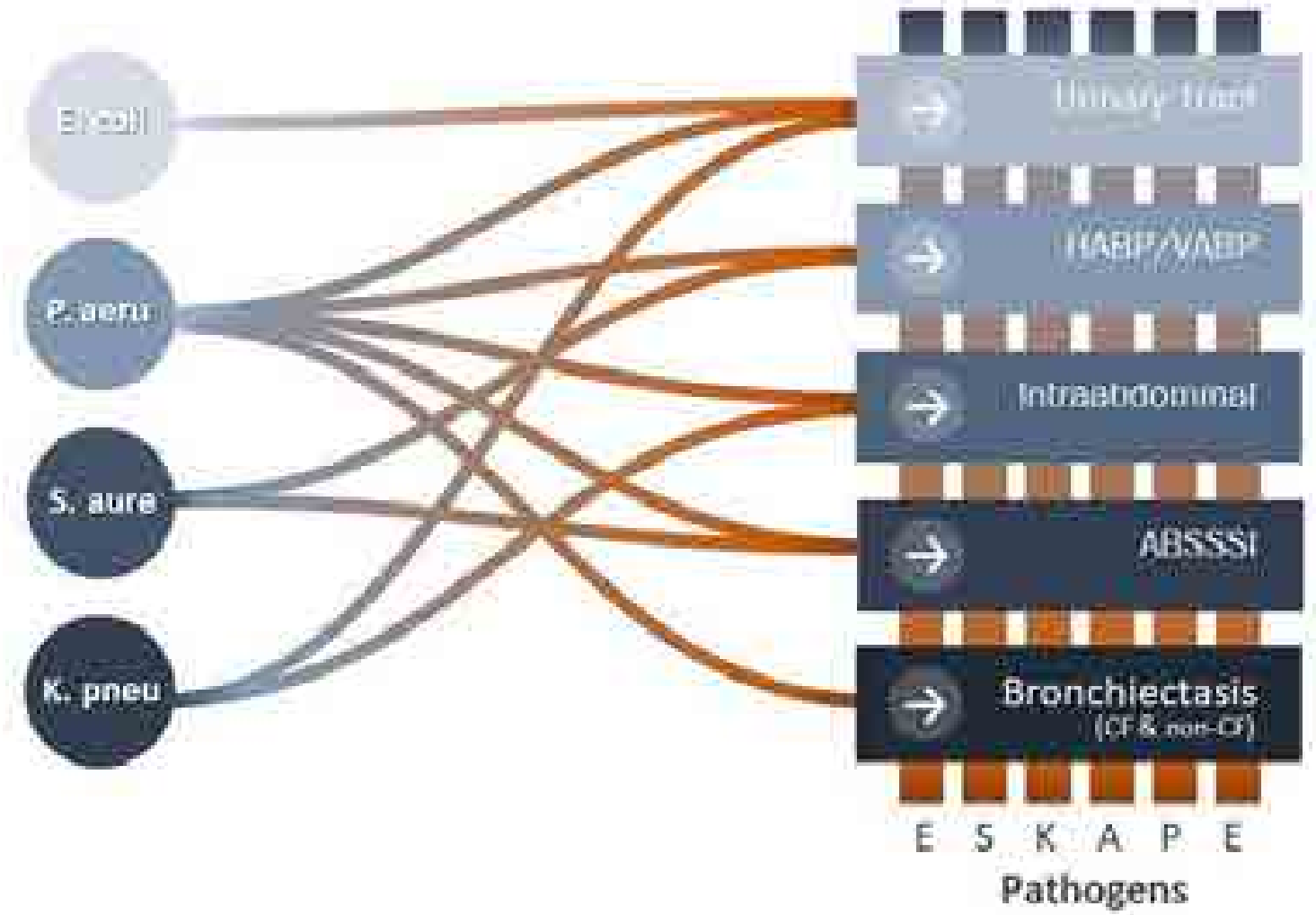
Phase 3

- Initial FDA interactions will determine what expanded data sets are necessary
- If Phase 1b/2 data provides sufficient evidence of efficacy and safety, smaller data sets may be sufficient for pivotal MDR



+ TBD

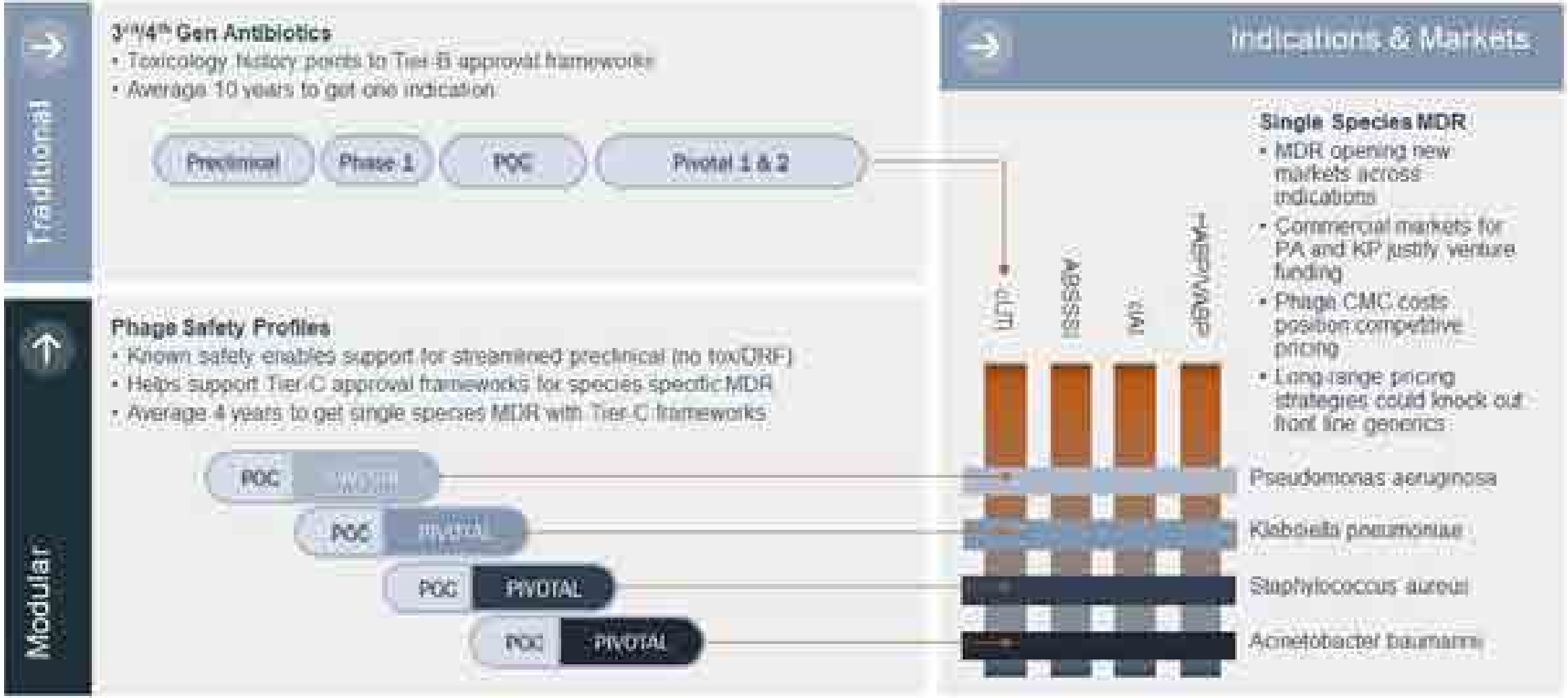
Leveraging a single species MDR using "multiple study site approach" leveraging multiple indications creates a modular drug development approach



Multiple Study Sites

- **Phase 1b monotherapy to establish safety and PK for each route of admin**
- Single-species PoC/pivotal trials across multiple study sites (multiple indications)
- Creates modular species vs. zones of infection matrix for product approvals
- Inverse of (and complementary to) traditional broad-spectrum approach

If we can use a modular development framework against MDR, we can cover the same ground in less time, for less cost and with reduced risk



The challenges associated with developing phage therapies could potentially become their greatest opportunities

- Use phage safety to pursue cost & time efficient trials in single species MDR
- Establish regulatory/ clinical frameworks that move away from broad spectrum

- Biology will always favor resistance
- ciPhages can be used in a "Vaccine-like" adaptive approach

- Chance to set pace of US-led field & work with FDA
- Drive down cost for biologic alternatives to small molecule antibiotics

- Renewed interest in Phage Therapy has driven >$ 100M in private investment
- Public sector seemingly still on sidelines for funding Phage Therapy
- Align interests to bring Big Pharma back into antibacterials - 3rd & 4th gen solutions are not viable!

Our leadership team brings proven drug development and executive experience together with industry-leading scientists

Paul Garofolo
Chief Executive Officer & Co-founder

Paul Kim, PhD
Locus Advisor; SVP of Program Management for Puma Bio

Dave Ousterout, PhD
Co-Founder & Chief Technology Officer

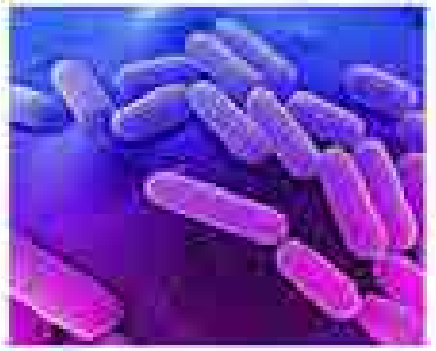
Peter Pequeler, MD
VP of Medical Affairs & Clinical Development

Joseph Nixon
VP of Business Development

Louise Hall
VP of CMC & Program Management

Locus Biosciences

3
Indications



Research Triangle Park
Innovation Center

CRISPR-Cas3
Pioneers

16
Employees
9 PhDs

$21+m
Funds Raised

120+
Preclinical
Studies

5
Global
Patents

ORAGENICS

Alan F. Joslyn, PhD
President & CEO
813 286 7900 ext 232
ajoslyn@oragenics.com

Oragenics, Inc.
4902 Eisenhower Blvd, Suite 125
Tampa, FL 33634
www.oragenics.com

DEVELOPING NOVEL ANTIBIOTICS AND BIOTHERAPEUTICS THROUGH SYNTHETIC BIOLOGY

Duke-Margolis Health Care Conference Presentation

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Development Program Overview

ORAGENICS

Novel Lantibiotic Platform for Multidrug Resistant Bacterial Infections

CDC Antibiotic-Resistant Threats, 2017 (cases/yr, US)

Drug-resistant pathogen (blue = gram (+) grey= gram (-))	Infections/year
Clostridium difficile	**500,000**
Carbapenem-Resistant Enterobacteriaceae (CRE)	9,000
Neisseria gonorrhoeae	246,000
MDR *Acinetobacter*	7,300
Drug-Resistant *Campylobacter*	310,000
Extended Spectrum β-lactamase Enterobacteriaceae	26,000
Vancomycin-Resistant *Enterococcus* (VRE)	**20,000**
MDR *Pseudomonas aeruginosa*	6,700
Drug-Resistant Non-Typhoid *Salmonella*	100,000
Drug-Resistant Typhoid *Salmonella*	3,800
Drug-Resistant *Shigella*	27,000
Methicillin-Resistant *Staphylococcus aureus* (MRSA)	**80,000**
Drug-Resistant *Streptococcus pneumoniae*	**1,200,000**

Center Disease Control U.S. MDR pathogen update 2017

C. difficile and *C. difficile* Infection (CDI): Epidemiology

- *C. difficile* is an infection of the colon causing colitis by producing toxins that damage lining of the colon
- 500,000 infections annually resulting in 29,000 deaths
- 83,000 will experience at least one recurrence
- Deaths have increased 400% since 2000
- Healthcare-associated infections occur: 37% hospital onset, 36% nursing home onset, 27% community onset
- *C. difficile* associated diarrhea is associated with a 1-2 week hospital stay
- Emerging problem: 8% of CDI associated with onset of concomitant Vancomycin Resistant Enterococci (VRE) infection

Competitive Overview

Currently Approved Therapies:

- Metronidazole
- Vancomycin
- Fidaxomicin
- Rifaximin
- Zinplava (monoclonal antibody)

Projected 2019 U.S. sales for *C. difficile* therapies: **$426M***

Therapies under development:

Follow-on generations of existing antibiotics, enzymes and enzyme/protein synthesis inhibitors, vaccines, microbiome/fecal transplant therapies, and toxin binding polyclonal antibodies.

* Source: EvaluatePharma

Lantibiotics: Novel Platform of Antibiotics to Treat Serious Life-Threatening Infections

- Lantibiotics are novel class of peptide antibacterial compounds naturally produced by variety of Gram-positive bacterial strains to attack competing bacterial strains
- Platform: > 700 lantibiotic structures created through saturation mutagenesis, potentially generating a pipeline of new compounds
- Prior development limited by manufacturing technical hurdles
- Platform provides potential for development in multidrug resistant infections:
  - Methicillin Resistant *Staphlococcus aureus* (MRSA)
  - Vancomycin Resistant Enterococci (VRE)
  - Virulent *Clostridium difficile*
  - Gram(-) infections

Mutacin 1140: a lantibiotic produced by *Streptococcus mutans*

Lantibiotic Profile

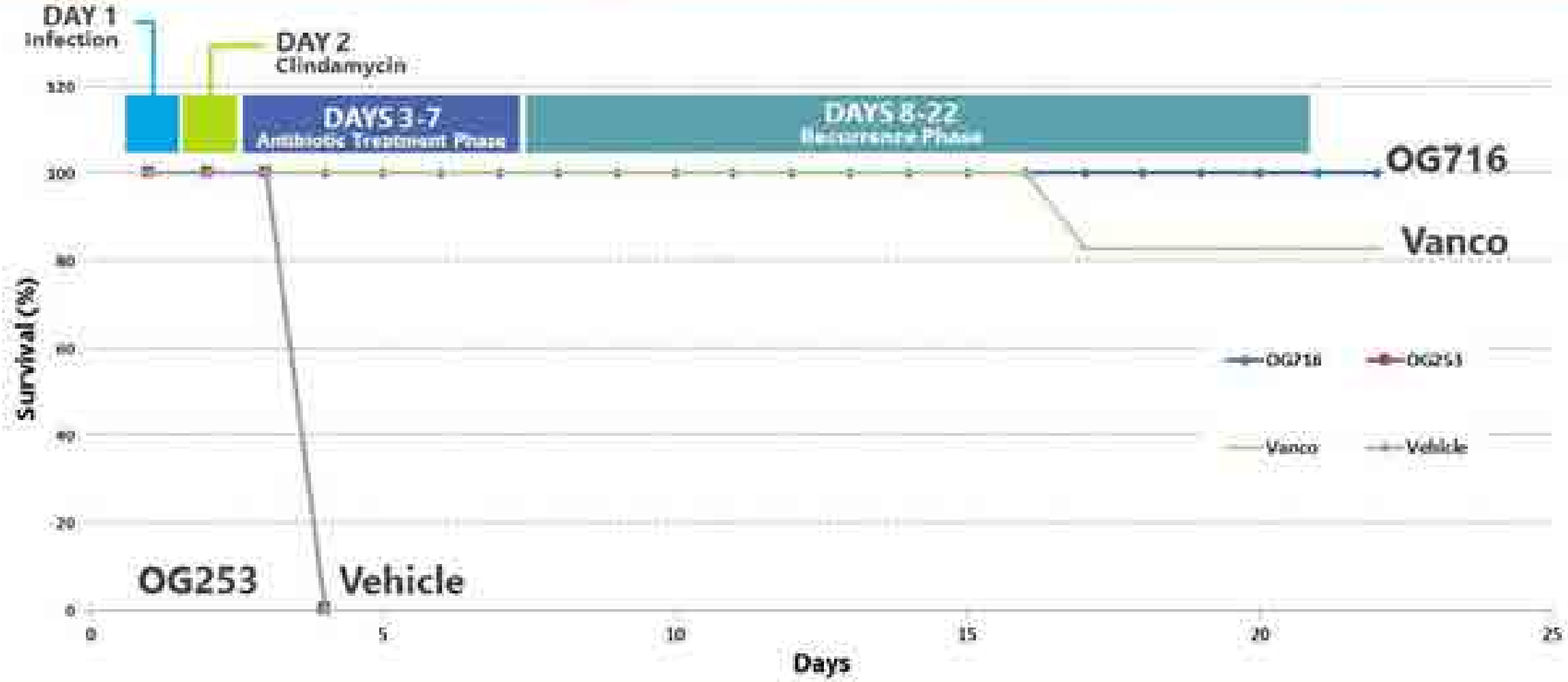
Preliminary MU1140 (parent compound) preclinical data:

- Novel mechanism of action (unique binding to Lipid II)
- No cross-reactivity with existing classes of antibiotics
- Minimal in vitro cytotoxicity in mouse and human cell lines; minimal immunogenicity

OG716 selected as lead compound for treatment of *C. difficile* infections

- Orally active
- Microbiology profile favorably compares to previous compounds
- Potent against *Clostridium difficile* in standard animal infection model
- Intellectual property extends into late 2030s for second-generation compounds

Oral OG716 Superior at Preventing *C. difficile* Deaths in Hamster Model



Lantibiotic Development Challenges

- Technical/Manufacturing:
  - BSL2 production microbe (*Strepococcus mutans*)
  - 1400L fermentation scale yields ~150 grams
  - Expensive purification process
- Commercial:
  - Limited "Big Pharma" Partnering Activity
  - Antibiotic stewardship: "Save the Best for Last" to prevent resistance development
  - (-) Net Present Value
- Corporate Financing/Program Development Costs:
  - Post IND Costs >$100MM
  - Manufacturing Runs (>1 kg): ~$1.5MM
  - Phase 2/3: >1000 patients and at least 3 years to NDA

Lantibiotics: OG716 *C. difficile* Program Milestones

4Q16

Tech Transfer of Manufacturing Process

Fermentation complete; purification underway

1Q17

Manufacture of API

Ongoing at 1400L scale transitioning to GMP manufacture

4Q18

Toxicology and Microbiology Underway

Single dose-escalating rat study complete and results discussed with FDA; rat and monkey 14-day tox studies under development

2Q19 (estimate)

File IND

Timing of filing of the IND is subject to having sufficient available capital to complete requisite studies

ORAGENICS

Q: Is there a pathway to early introduction of new antibiotics in limited patient populations to treat MDR infections and improve economics for small companies?

Thank you

Session 1

Panel Discussion &
Audience Q&A

E-Mail Questions to
Duke.Abx@Duke.edu

@DukeMargolis

Session 2: Generating agents that restore activity to—and are used in combination with—existing antimicrobials

E-Mail Questions to

Duke.Abx@Duke.edu

@DukeMargolis

SPERO THERAPEUTICS

Potentiation Strategies and Challenges for Development

Troy Lister, VP Research, Spero Therapeutics

Forward-looking Statements

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Potentiation Approach Seeks to Normalize the Battle for Gram-Negative Intracellular Residency

- Outer membrane architecture – LPS
  - Multiple porins for chemotype specific (or non-specific) uptake,
  - Passive (up to) dual membrane penetration,
- Multiple, promiscuous, multi-component efflux pumps,
- Target inhibition profile
- Target resistance
- Chemotype specific resistance – modifiers, degraders
- Kinetics for each of these processes are all simultaneously operative
- Then add in human ADME…

The Spectrum of Activity of Polymyxins is Ideal; However, Nephrotoxicity (Should) Limits Clinical Use

Serum Creatinine Safety Population[a]	Colistin n=21 nN1(%)
≥ 0.5 mg/dL increase any time on study (including on or post IV therapy)	8/16 (50.0)
≥ 0.5 mg/dL while on IV therapy	6/16 (37.5)
Full Recovery or improvement[b]	3/6

[a] Patients starting CRRT prior to baseline were excluded from the analysis, as were all post-baseline serum creatinine measurements collected after start of CRRT.

[b] Full recovery defined as last post-baseline serum creatinine value < 0.5 mg/dL above the baseline value. Improvement defined as last post-baseline serum creatinine value > 0.3 mg/dL less than peak serum creatinine but not < 0.5 mg/dL above the baseline value

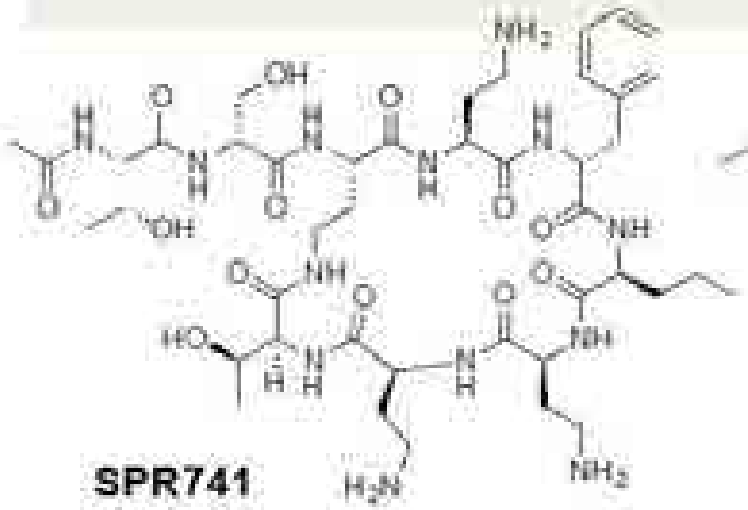
Colistin 300-mg loading dose; 5 mg/kg/d, divided q8h or q12h as 60-minute infusion

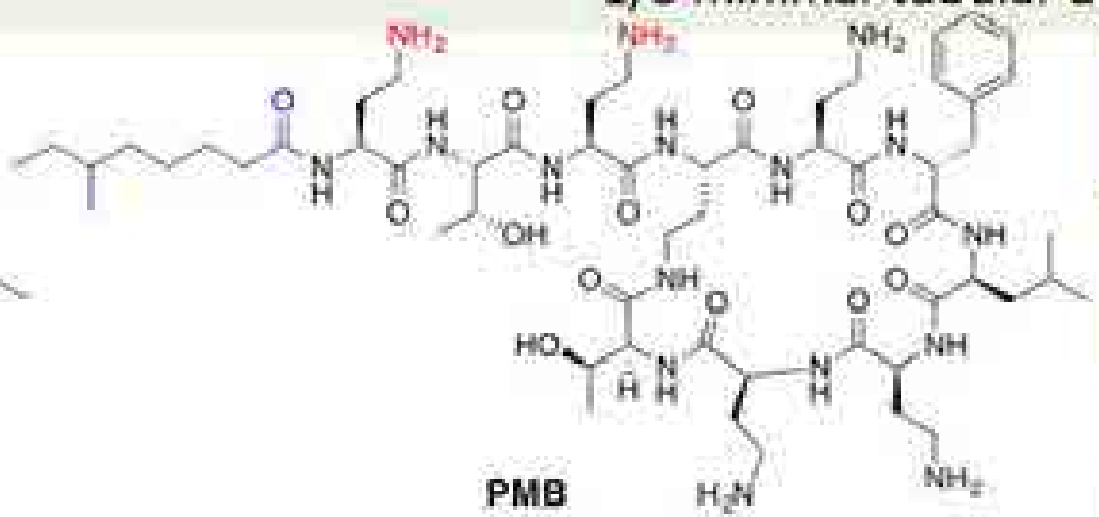
Source: Achaogen presentation, CARE trial data

SPR741: Nonclinical Studies Establish Go for Clinical Evaluation

- 7-day repeat dose (TID, 1 hour infusion) non-GLP monkey study

Compound	Dose (mg/kg/day)	BUN (increase)	SrCr (increase)	Renal histopathology	Cmax (µg/mL)	$AUC_{(0\text{-}24)}$ (µg*hr/mL)
PMB	12	2X	3X	1/3 minimal tubular degen 2/3 mild tubular degen	17	261
SPR741	60	No change	No change	2/3 normal 1/3 minimal tubular degen	66	489





Organism	MIC (µg/mL)	
	PMB	SPR741
E. coli	0.25	64
K. pneumoniae	0.5	>128
P. aeruginosa	1	32
A. baumannii	0.5	128

SPR741: Nonclinical Studies Establish Go for Clinical Evaluation

- 14-day repeat dose (TID, by 1 hour infusion) GLP monkey (4 dose groups) and rat (3 dose groups, ramp dosing) studies

Species	NOAEL Cmax (µg/mL)	NOAEL $AUC_{(0\text{-}24)}$ (µg*hr/mL)	Effect Level Cmax (µg/mL)	Effect Level $AUC_{(0\text{-}24)}$ (µg*hr/mL)	Effect Level Findings
Rat	3	8	7	20	Minimal-to-mild increase in BUN w/ associated histopathological findings
Monkey	47	363	78	672	Minimal-to-mild increase in BUN and serum creatinine with associated histopathological findings

SPR741: Favorable Clinical Safety Profile Predicted by Nonclinical Studies

Human SPR741 Dose (mg, TID)	Cmax (μg/mL)	$AUC_{(0\text{-}24)}$ (μg*hr/mL)	Stopping rules met? >2-fold increase in SrCr over baseline
50	3	28	None
150	11	88	None
400 (19 mg/kg/d)	27	232	None
600	93	528	None

- Administered 1.8 g/day for 14 consecutive days of a polymyxin
- Colistin at 5 mg/kg/day related with 40-50% increase in serum creatinine

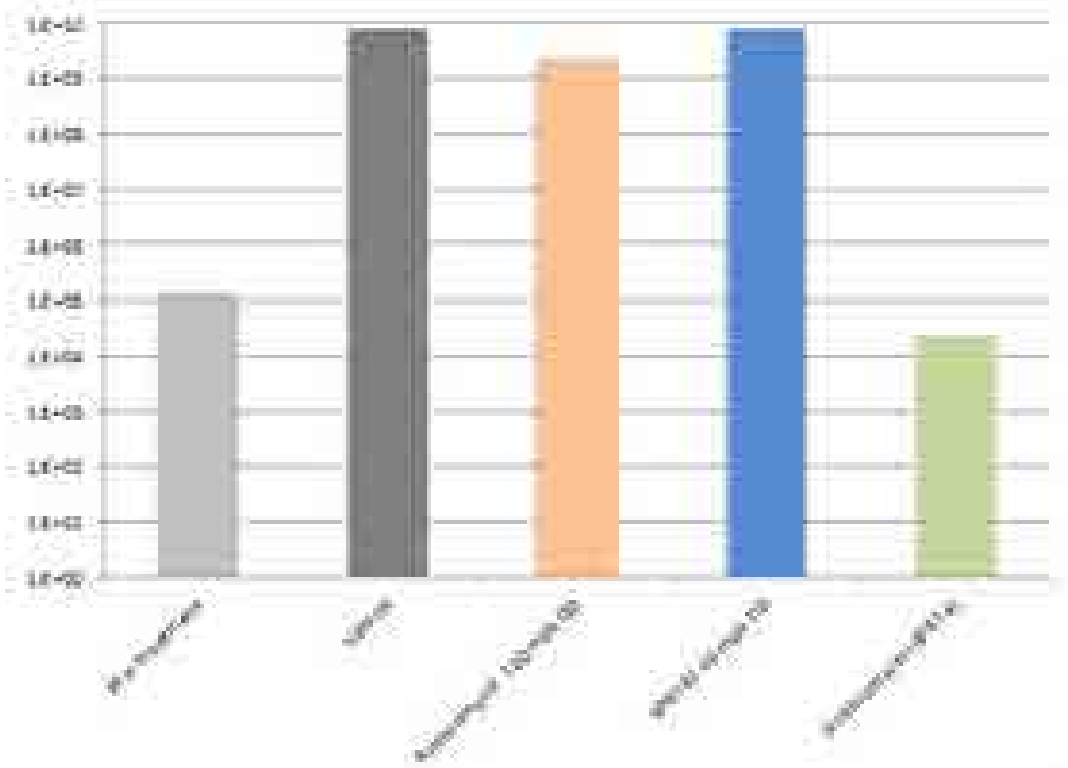
Species	NOAEL Cmax (μg/mL)	NOAEL $AUC_{(0\text{-}24)}$ (μg*hr/mL)	Effect Level Cmax (μg/mL)	Effect Level $AUC_{(0\text{-}24)}$ (μg*hr/mL)	Effect Level Findings
Monkey	47	363	78	672	Minimal-to-mild increase in BUN and SrCr w/ associated histopathology

Case Study in Potentiation: SPR741+Azithromycin

Opportunity

- Broad spectrum activity
- Robust *in vivo* translation (thigh, lung, UTI)
- Divergent clearance pathways and target organs of toxicity

	UTI (425)	
	MIC_{50}	MIC_{90}
Azithromycin	>16	>16
Azithromycin + SPR741	0.12	0.5



Case Study in Potentiation: SPR741+Azithromycin

Challenges

- Uncharacterized incidence of macrolide-R in Gram-negative bacteria. It is high, especially in MDR and *Acinetobacter*
- Poor exposure in urinary tract
- Not suitable in bacteremic patients (10% of UTI patients)
- High rates of phlebitis
- Approved only for short durations of therapy
- Difficulty in adoption

Case Study in Potentiation: SPR741+Azithromycin

- Demonstrated *in vitro* and *in vivo potentiation* of over a dozen partner agents across a wide variety of MDR bacteria, including Enterobacteriaceae, *A. baumannii*
- Excellent pre-clinical and clinical safety profile
- First polymyxin molecule to complete and proceed beyond Phase 1
- Robust CMC package with multiple routes to API
- Composition of matter IP protected through 2035

Summary/Conclusions

- Identify and front load your killer experiment
  - Tox, resistance, *in vivo* translation, PK/PD
  - "If an experiment isn't worth doing, it isn't worth doing well"
- New modalities are difficult
  - Old learnings and data won't necessarily apply
  - But, we must prevail – incremental improvements will only get us so far
  - New approaches are needed
- Polymyxins can be safe(r)!
  - We must look past intrinsic bias

Acknowledgements

All the wonderful folks at Spero and our exceptional collaborators


TAXIS Pharmaceuticals
New Solutions for Antibiotics to Treat Life-Threatening
Multidrug Resistant Bacterial Infections
Health Secretary (UK) Jeremy Hunt: "Antimicrobial resistance is perhaps our biggest global health threat - it could nullify the progress of over a century of modern medicine and kill millions."

TAXISTANCE™
Novel Drug Development Platform

Focused on the disruption of the foundation of bacterial cell wall architecture to address elemental drug resistance mechanisms:

1) **Efflux Pump Inhibition (EPI)**
   Platform technology targeting the most problematic Gram-negative pathogens

2) **FtsZ modulation blocks post-mitotic septum formation***
   Narrow spectrum, Oral anti-MRSA/StrepA

3) **MreB modulation undermines cell shape integrity, polar protein localization and chromosome segregation**

** Qualified Infectious Disease Product (QIDP) designation granted by FDA*

Efflux Pump Inhibition (EPI): An Antibiotic Drug Development Platform

- **Wide Range of Antibiotic Classes Impacted**
  - EPIs are potent synergistic agents with 28 antibiotics (so far)
  - Macrolides, Cephalosporins, Monobactams, Sulfanomides, Tetracyclines, Polypeptides; Antimycobacterials, Polypeptides and Fluoroquinolones

- **Durable, validated *in vivo* efficacy in murine septicemia and thigh models of wild type *P. aeruginosa* infection**

- **Pathogen-specific and Broad Spectrum EPIs**
  - Targeting *P. aeruginosa*, *K. pneumoniae*, *A. Baumannii* and *E. coli*

TAXIS

TXY842

A Broad-Spectrum EPI Potentiates a Macrolide against Multiple Gram-Negative Pathogens

E. coli ATCC 25922		*P. aeruginosa* ATCC 27853		*A. baumannii* ATCC 19606		*K. pneumoniae* ATCC 13883	
MIC (µg/mL)							
Macrolide Antibiotic alone	Macrolide + TXY842	Macrolide Antibiotic Alone	Macrolide + TXY842	Macrolide Antibiotic Alone	Macrolide + TXY842	Macrolide Antibiotic alone	Macrolide + TXY842
64	0.125 (512X)	64	0.25 (256X)	32	0.25 (128X)	128	0.125 (1024X)

MIC = Minimum Inhibitory Concentration

The amount of drug needed to inhibit bacterial growth (Lower is Better)

X Multiplier = Addition of EPI to Macrolide results in more potency (Higher is Better)

Significantly reduced dose of Macrolide required for effectiveness, thereby reducing risk of antibiotic resistance emergence

TYY842 delivered at 6.25 µg/mL

TXY9155

A Pathogen-specific EPI Selectively Potentiates a Cephalosporin against *P. aeruginosa*

P. aeruginosa ATCC 27853		*A. baumannii* ATCC 19606		*K. pneumonia* ATCC 13883	
MIC (µg/mL)					
Cephalosporin Antibiotic alone	Cephalosporin + TXY9155	Cephalosporin Antibiotic alone	Cephalosporin + TXY9155	Cephalosporin Antibiotic alone	Cephalosporin + TXY9155
32	1 (32X)	32	32 (1X)	1	1 (1X)

MIC = Minimum Inhibitory Concentration

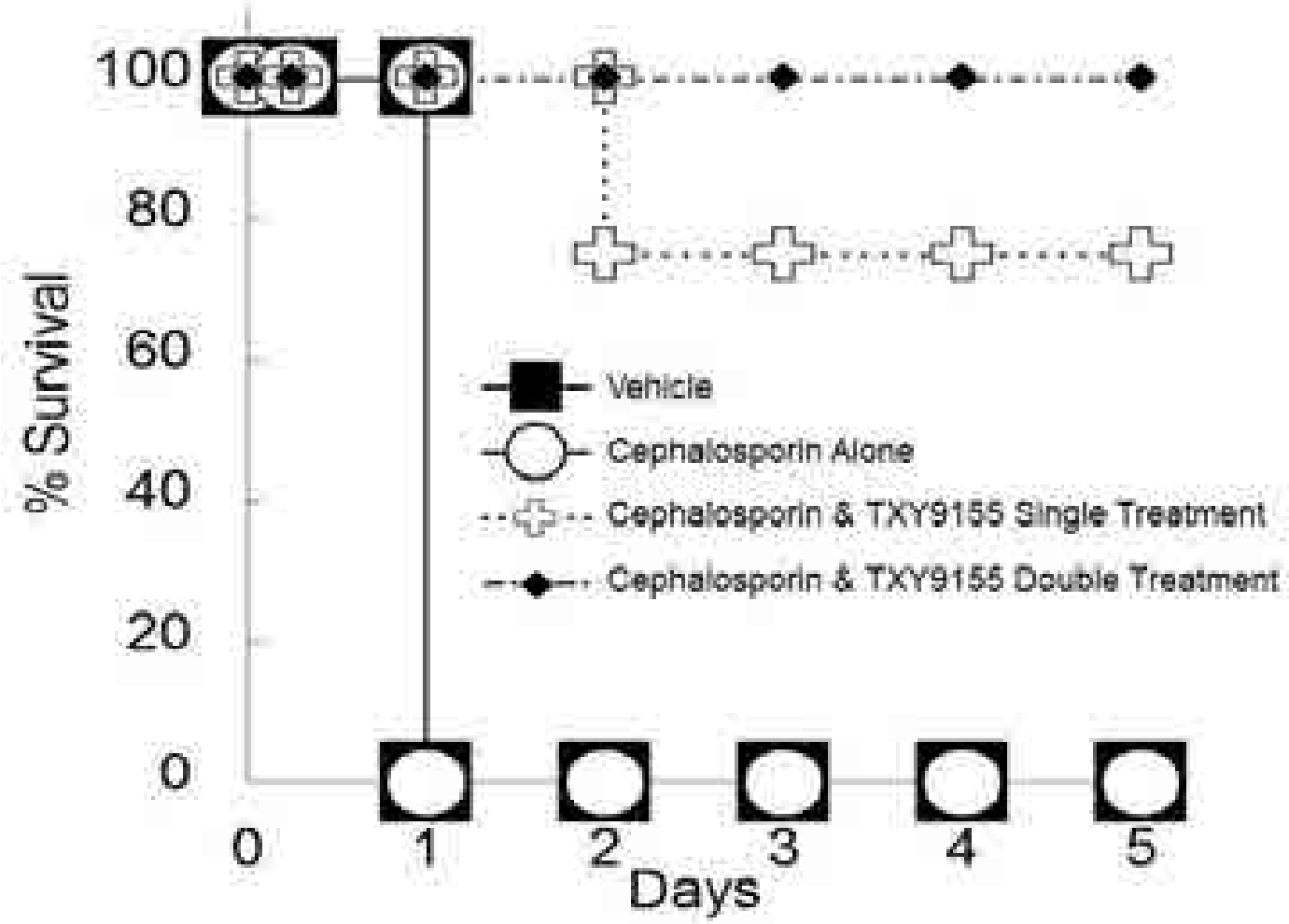
The amount of drug needed to inhibit bacterial growth (Lower is Better)

X Multiplier = Addition of EPI to Cephalosporin results in more potency (Higher is Better)

Significantly reduced dose of Cephalosporin required for effectiveness, thereby reducing risk of antibiotic resistance emergence

TYY842 delivered at **6.25 µg/mL**

Efficacy Studies of TXY9155 in Combination with a Cephalosporin in a Murine Septicemia Model of *P. aeruginosa* infection



Tremendous Potential with One Critical Obstacle

- **Generics** – Key Access, Watch Group, Reserve
  - Providing the global community with cost-effective access to life-saving drugs that already exist, but no longer work
- **Branded** – Lifecycle Management
  - Amoxicillin/Augmentin
- **R&D** – 'Do-overs'
  - Enable significant reduction of dose to overcome toxicity issues of past, current and future clinical candidates

Challenges

- First-in-Class
- Platform: Blessing & Curse
- Funding and Economics – The Elephant in the Room

Antibiotics as a Category

- **Ease of Translation - Bench to Bedside**
  - 28.1% approval success rate for anti-infectives compared to 16.9% for all New Chemical Entities (NCEs)
  - 37.7% approval success rate for anti-infectives that reach Phase III compared to 21.5% for all NCEs
- **Economic Incentives and Direct R&D Support**
  - GAIN (Generating Antibiotic Incentives Now) 2012 Legislation
    - Added market exclusivity for antibiotics (up to 5 years)
    - Priority Review
  - CARB-X
    - TAXIS recently filed applications
- **Market Dynamics will not Materially Change w/o Pull**

Health Outcomes & Economics

- **Life Expectancy pre-Antibiotics was ½ What it is Now:**
  - Infectious disease management and control is the foundation of modern medicine
  - As advancements in Cardiovascular and Oncology disease management drove the ascent of life expectancy, we forgot about Antibiotics

- **DRGs**
  - Life-saving Antibiotics are reimbursed at Pennies on the Dollar compared to CA Therapeutics
  - We spend 100s of thousands of dollars on medicines that 'may' extend life by…. Months?….. but very little is spent on Antibiotics, without which the wonders of modern medicine become irrelevant – we won't live long enough to take advantage of these wonders!

THANK YOU!

TAXIS Pharmaceuticals

CONTACT

Gregory G. Mario

732-230-3074

Gmario@TAXISPharma.com

Health Secretary (UK) Jeremy Hunt: *"Antimicrobial resistance is perhaps our biggest global health threat - it could nullify the progress of over a century of modern medicine and kill millions."*

Development Overview

Focused on Discovery & Development of Novel Antibiotics to Address Growing Threat to Societal Health of MDR Pathogens:

- Licensed Rutgers University technology: Broad patent portfolio
- 11 Employees; 3,500 sq.ft. Chemistry & Biology laboratories, Monmouth Junction, NJ, USA
- NCEs and Enhancement of Existing Classes; Gram(+) and Gram(-) Drug Candidates

***Psuedomonas, Klebsiella, E. Coli & Acinetobacter* Drug Development:**

Efflux Pump Inhibition (EPI): 3 Distinct Classes of Novel Compounds Resurrect Activity of Generic Antibiotics

- Durable, validated *in vivo* efficacy in *P. aeruginosa* murine septicemia model of infection
- *In vitro* potency enhancement up to 256X in presence of EPIs; 1-log reduction in adjuvants' FOR
- Broad patent estate
- MOA documented as Efflux Pump Inhibition; not associated w/ membrane disruption
- Multiple publication submissions to high profile journals & NIH/NIAID grant apps
- Characterization of PK, Safety Pharmacology & Lead Optimization by H1, 2019

Anti-MRSA (+StrepA) Drug Development – Lead Candidate: TXA709:

- 91% Oral Bioavailability; Synergistic with Beta-Lactams
- No Cross-Resistance with Marketed Drugs
- FDA granted TXA709 QIDP designation; Completed GMP/GLP preclinical toxicology
- Target markets: inpatient IV w/oral stepdown for sepsis and outpatient oral for cSSSI
- 7Kg supply of GMP material in hand; progressing toward Phase I trial in Q3'18

The Team

MANAGEMENT TEAM & DIRECTORS

Gregory Mario, MBA – President & CEO
S. David Kimball, Ph.D. – Prev. CSO, Hydra Biosciences
Edmond J. LaVoie, PhD – Prof. & Chair of Medicinal Chemistry, Rutgers School of Pharmacy
Ernest Mario, Ph.D. – Board Member for Celgene and former CEO and Vice Chairman of GSK
Gail McIntyre, Ph.D. – Prev. SVP at Furiex and PPD; TXA709 Development Team leader

EXTENDED TEAM

Keith Bostian, Ph.D. – Institute for Life Sciences Entrepreneurship, Kean College
Robert Bonomo, MD – Case Western, Louis Stokes VA
Chris Cimarusti, Ph.D. – Prev. SVP Pharmaceutical Dev., BMS
Henry Chambers, MD – Infectious Disease, UCSF
Timothy D. Costello, Ph.D. – CMC Manager
Zemer Gitai, Ph.D. – Princeton University
David Hooper, MD – Infectious Disease, Mass. General
James Kahn, MD – Prev. JNJ Executive Infectious Disease Research
Dean L. Shinabarger, Ph.D. – CEO, Micromyx
Lynn Silver, Ph.D. – Molecular and Microbiology
Vincent Tam, Pharm.D., - University of Houston, Clinical Pharmacodynamics
Michelle Usher – TXA709 Regulatory Affairs Manager

Session 2

Panel Discussion &
Audience Q&A

E-Mail Questions to

Duke.Abx@Duke.edu

@DukeMargolis

Understanding the Development Challenges Associated with Emerging Non-Traditional Antibiotics

Duke-Margolis Center for Health Policy

Break for Lunch 12:30 – 1:25 PM

Session 3: Developing agents that are studied in combination with existing antimicrobials to enhance elimination of bacteria

E-Mail Questions to

Duke.Abx@Duke.edu

@DukeMargolis

Lysins: Alternative Antimicrobials to Improve Clinical Outcomes of Serious Bacterial Infections

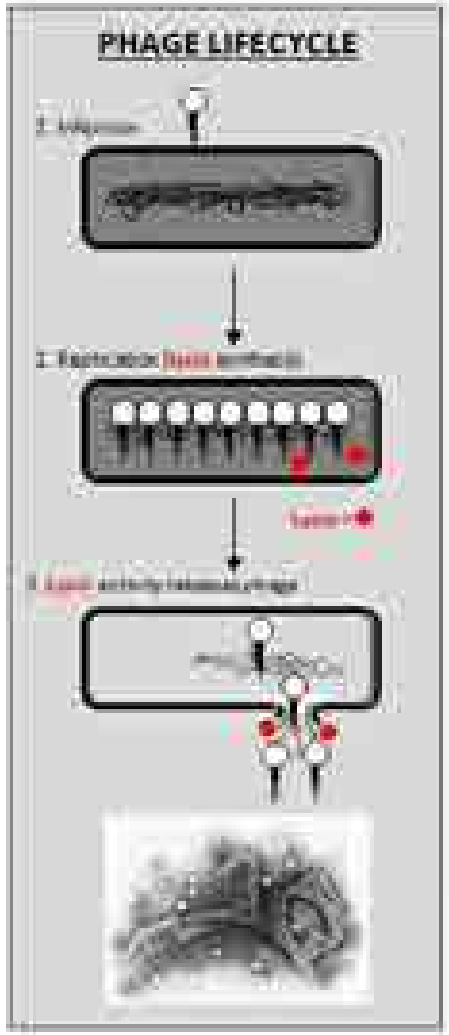
Dara Cassino, MD
EVP of Research and Development | CMO
Contrafect Corporation

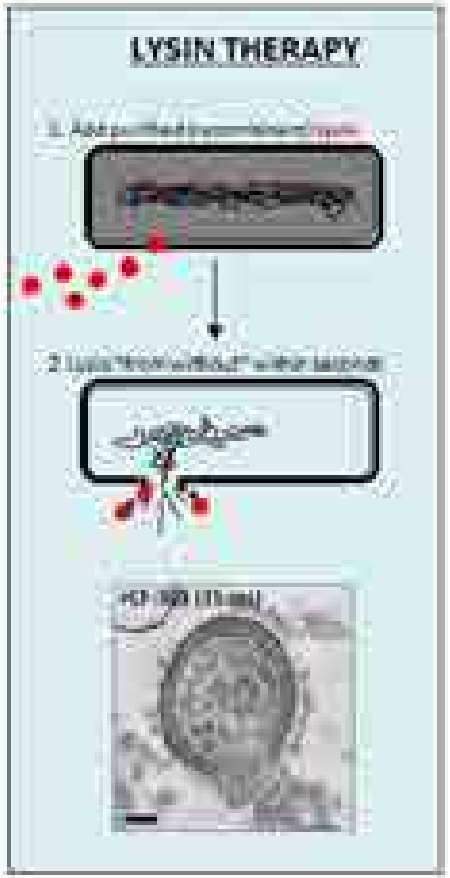
14 JUNE 2018

Forward Looking Statements

This presentation contains, and our officers and representatives may from time to time make, "forward-looking statements" within the meaning of the U.S. federal securities laws. Forward-looking statements can be identified by words such as "projects," "may," "will," "could," "would," "should," "believe," "expect," "target", "anticipate," "estimate," "intend," "plan," "proposed", "potential" or similar references to future periods. Examples of forward-looking statements in this presentation include statements made regarding ContraFect Corporation's ("ContraFect") therapeutic product candidates, including their ability to treat life-threatening, drug resistant infections, CF-301 properties and activity including but not limited to the ability of CF-301 used in addition to SOC antibiotics to significantly improve clinical success rates compared to SOC antibiotics alone, synergy with conventional antibiotics and clearance of biofilms, CF-301's value proposition and product attributes, expectations regarding clinical outcomes and efficacy of CF-301, in vitro and in vivo study results, CF-301 Phase 2 study design, anticipated timing of topline study results, timing of the completion of clinical trials or ability to achieve Phase 2 study endpoints. Forward-looking statements are statements that are not historical facts, nor assurances of future performance. Instead, they are based on ContraFect's current beliefs, expectations and assumptions regarding the future of its business, future plans, proposals, strategies, projections, anticipated events and trends, the economy and other future conditions. Because forward-looking statements relate to the future, they are subject to inherent risks, uncertainties and changes in circumstances that are difficult to predict and many of which are beyond ContraFect's control, including those detailed in ContraFect's filings with the Securities and Exchange Commission. Actual results may differ from those set forth in the forward-looking statements. Important factors that could cause actual results to differ include, among others, the occurrence of any adverse events related to the discovery, development and commercialization of ContraFect's product candidates such as unfavorable clinical trial results, insufficient supplies of drug products, the lack of regulatory approval, or the unsuccessful attainment or maintenance of patent protection. Any forward-looking statement made by ContraFect in this presentation is based only on information currently available and speaks only as of the date on which it is made. No representation or warranty is made as to the completeness or accuracy of the information provided in this presentation. Except as required by applicable law, ContraFect expressly disclaims any obligations to publicly update any forward-looking statements, whether written or oral, that may be made from time to time, whether as a result of new information, future developments or otherwise. Audiences are cautioned that forward-looking statements or similar information are not guarantees of future performance and, accordingly, are expressly cautioned not to put undue reliance on forward-looking statements or similar information due to the inherent uncertainty therein.

Lysins: Novel Alternatives to Conventional Antibiotics





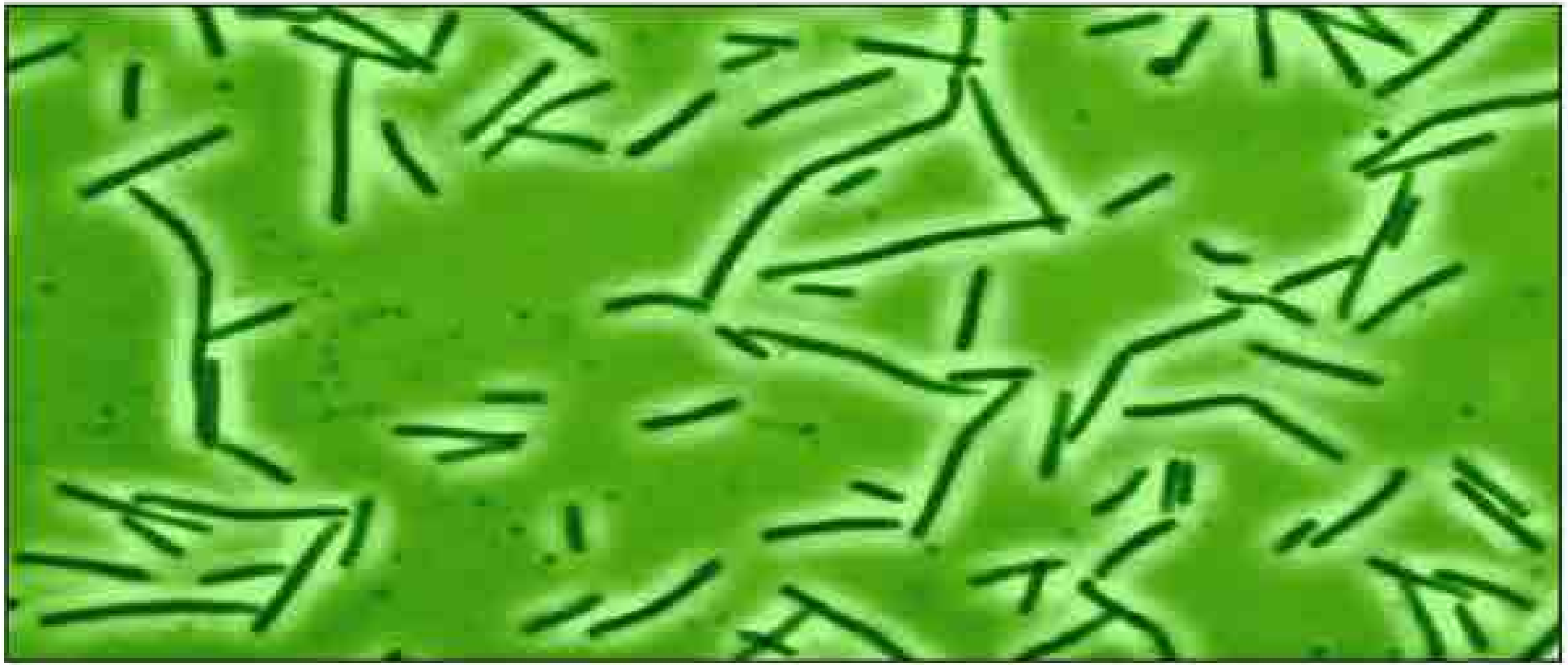
Lysins: Phage-derived, Recombinant Therapeutic Proteins

- Novel MOA: Peptidoglycan Hydrolysis leading to Osmotic Lysis
- Potent and Rapidly Bactericidal (Measured in vitro by MIC and Time Kill Assays)
- Targeted, Species-specific Killing
- Highly Potent Eradication of Biofilms (Measured by MBEC and EM)
- Low Propensity For Resistance and No Antibiotic Cross-resistance
- Synergy with Conventional Antistaphylococcal Antibiotics
- Suppression of Emergence of Antibiotic Resistance in vitro and ex vivo
- Marked Post-antibiotic Effect

CF-301: Lead Lysin Candidate now in Phase 2

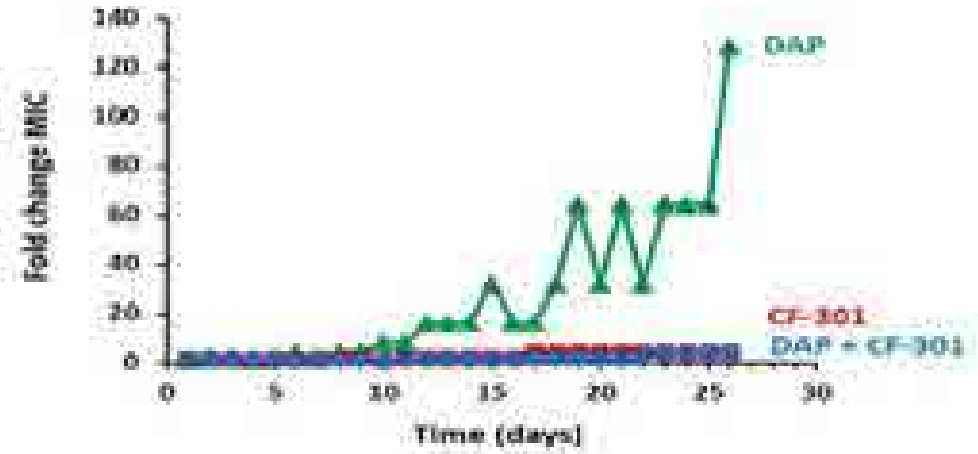
- 26 kDA modular bacterial cell wall hydrolase
- Highly active against *Staphylococcus aureus* (including antibiotic resistant strains), all other Staph species and some Strep species
- Complimentary to and synergistic with conventional antibiotics
- Well tolerated with predictable PK in Phase 1
- Being studied in Phase 2 as a potential therapeutic to improve clinical cure rates for *S. aureus* bacteremia and endocarditis used in addition to conventional antistaphylococcal antibiotics

Lysins: Rapid, Targeted Bactericidal Action



CF-301: Low Propensity for Resistance

In vitro Serial Passage Resistance Studies - MRSA



- After 26 days of serial passage, CF-301 MIC remained stable (increased ≤2 fold)
- CF-301 suppresses resistance to daptomycin (DAP), vancomycin or oxacillin

Source: Schuch et al JID 2014:209

CF-301: A Potent Anti-Staphylococcal Biofilm Agent

Biofilm: A Major Medical Problem

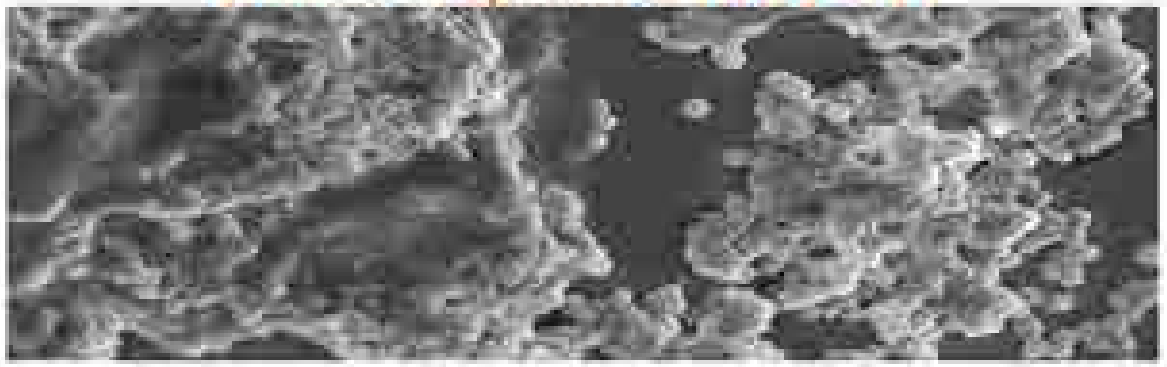
- Biofilms harbor and protect bacteria from immune defenses
- Conventional antibiotics can't clear or penetrate biofilms
- Biofilms can increase antibiotic resistance 1,000-fold

Mature MRSA biofilms are highly susceptible to CF-301 in vitro and resistant to Daptomycin (DAP)

- CF-301 $MBEC_{90}$* = 0.25 ug/ml
- DAP $MBEC_{90}$* >1,024 ug/ml

CF-301 Clears In Vitro Biofilm On A MRSA-Infected Catheter in 15 minutes

Before Exposure to CF-301



15 min Exposure to CF-301

*minimum biofilm-eradicating

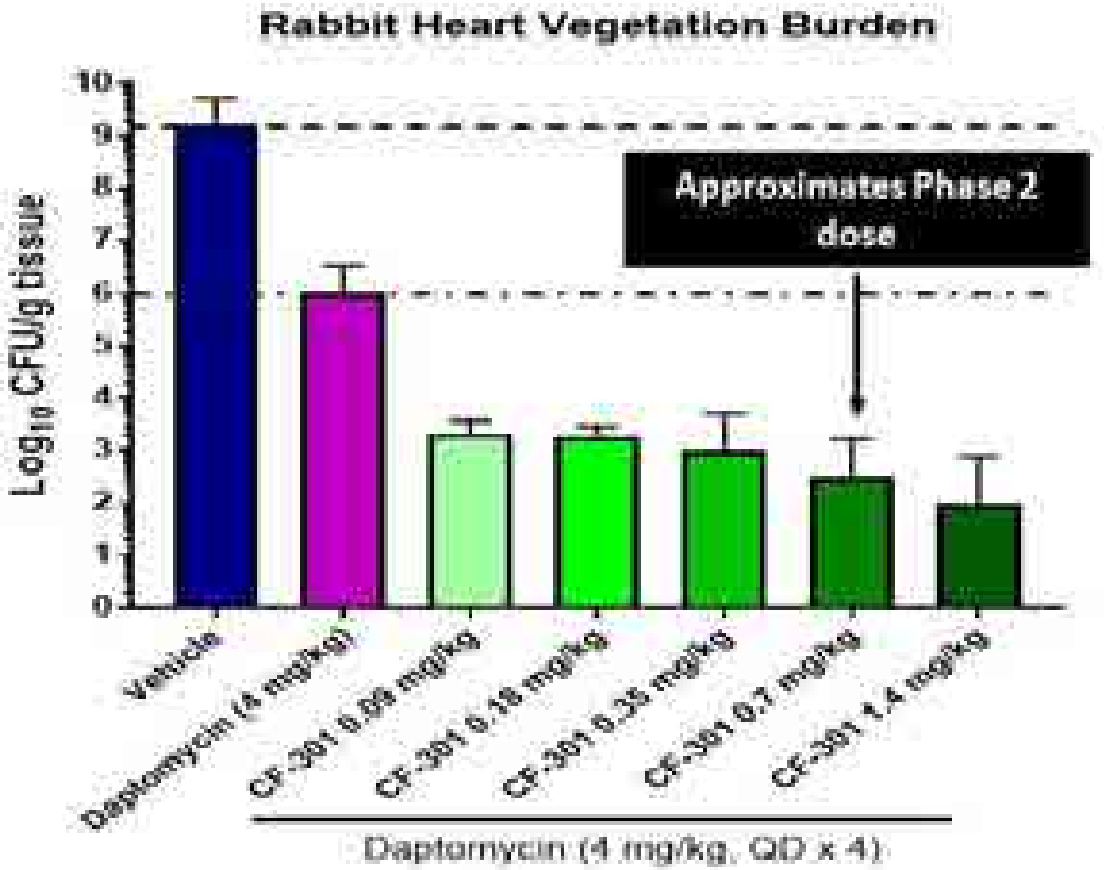
Source: Schuch, et al, AAC 2017

CF-301 Enhances DAP Activity in Rabbit Endocarditis Model

Results from single dose of CF-301 plus daptomycin dosed daily for 4 days

- ~6-log reduction in CFUs at all CF-301 doses vs. vehicle ($p \leq 0.001$)
- $\geq$ 3 log reduction in CFUs at all CF-301 doses tested vs. DAP alone ($p \leq 0.002$)
- Efficacy maintained at the lowest CF-301 dose tested (0.09 mg/kg) ($p \leq 0.001$)

Similar efficacy demonstrated with broad range of timing of CF-301 dose relative to initial dose of SOC



Source: Schuch et al. Oral Presentation, CDMRP/MDRP Meeting, April 2017

CF 301: Phase 1 Trial Demonstrated Safety and Tolerability

Single escalating IV dose, double-blind, placebo-controlled

- 20 healthy volunteer; 4 dosing cohorts (0.04, 0.12, 0.25, 0.40 mg/kg)

Well tolerated; no clinical adverse safety signals

- No serious adverse events (AEs)
- No CF-301-related hypersensitivity AEs
- 5 non-serious AEs were mild, transient and resolved by end of study
  - CF-301 - headache, contact dermatitis, allergic rhinitis
  - Placebo - viral upper respiratory tract infection, viral infection

9 of 13 CF-301 subjects developed anti-drug antibodies

- Complete or near complete resolution by Day 180
- Not correlated with markers of allergic immune response

Well-behaved pharmacokinetic (PK) profile

- Estimated effective exposures at 0.25 mg/kg dose

CF-301: Ongoing Phase 2 Clinical Trial

Study population

- Adults with complicated *Staph aureus* bacteremia, including endocarditis, caused by MRSA or MSSA, receiving standard of care antibiotic therapy

Study design

- International, multi-center, randomized, double-blind, placebo-controlled clinical trial
- Superiority design compares CF-301 + SOC vs. Placebo + SOC
- 115 patients randomized 3:2 to receive single 2-hour IV infusion CF-301 or placebo

Endpoints

- Primary endpoint: early clinical response (Day 14)
- Safety, tolerability and pharmacokinetics
- Additional clinical, microbiological and health resource utilization measures

Key milestones

- First patient randomized in May 2017
- Topline data expected in 4Q18

Ato*Bio

Duke-Margolis Center for Health Policy Symposium: Understanding the Development Challenges Associated with Emerging Non-Traditional Antibiotics

June 14, 2018

Atox Bio

Session 3: Developing agents that are studied in combination with existing antimicrobials to enhance elimination of bacteria

Immunomodulatory Therapy

Wayne M Danner, MD
Chief Medical Officer, Atox Bio

June 14, 2018

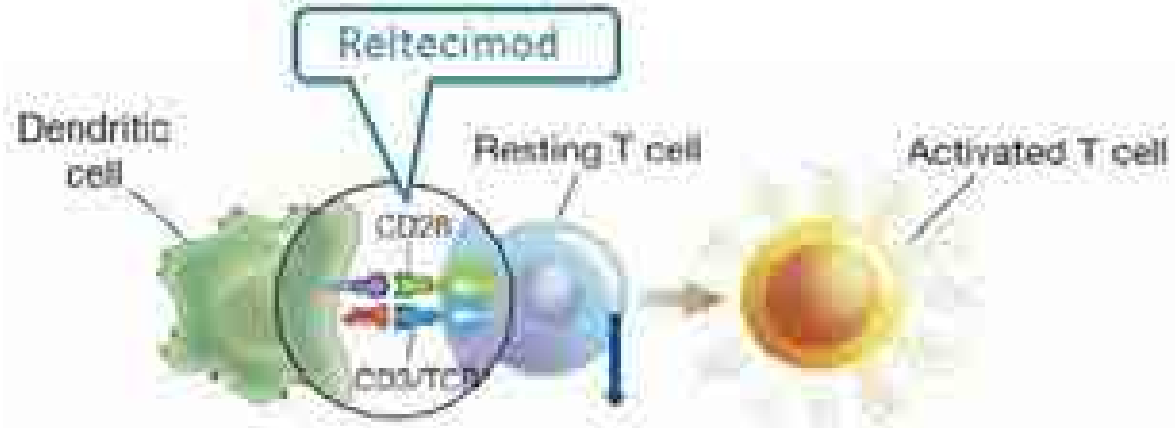
Atox Bio At a Glance –
Acute Inflammation Therapies for Critically Ill Patients

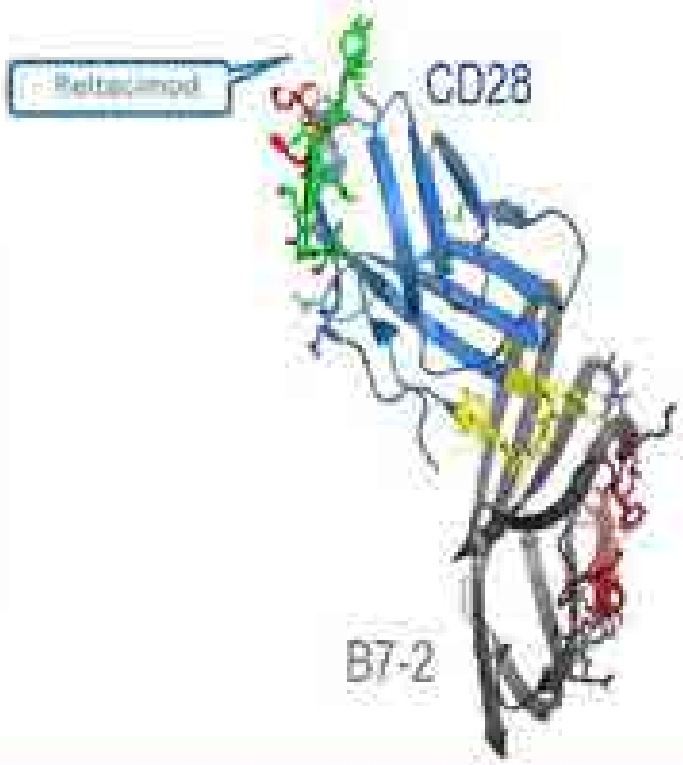
- **Overview**
  - Late stage company developing Reltecimod, an immunomodulator for critically ill patients
  - Host oriented approach to treating morbidity associated with severe acute inflammation
  - Ongoing pivotal Phase 3 study in Necrotizing Soft Tissue Infections (NSTI; "Flesh Eating Bacteria")
  - Abdominal Sepsis induced Acute Kidney Injury (AKI) Phase 2 study begun in April 2018
- **Ongoing Phase 3 Study in NSTI with Reltecimod**
  - First product to be specifically developed for NSTI
  - Phase 2 data demonstrated clear efficacy; no serious adverse events
  - FDA and EMA orphan drug status; FDA fast track designation
- **Financing**
  - Recent financing: $30M in December 2017
  - $25M BARDA contract
  - Funded through data readout

ARIX BIOSCIENCE
ADAMS STREET PARTNERS
SR-one
OrbiMed
LUNDBECKFONDVENTURES
BARDA

Reltecimod – A Novel Immunomodulator to Treat Severe Inflammation

- Short peptide that binds to the CD28 dimer interface to attenuate the formation of the immunological synapse with B7-2 (CD86)
- Modulates, but does not inhibit the immune response to attenuate the excessive acute inflammation
- Different from antibiotics – Reltecimod is pathogen agnostic
- No risk of resistance development



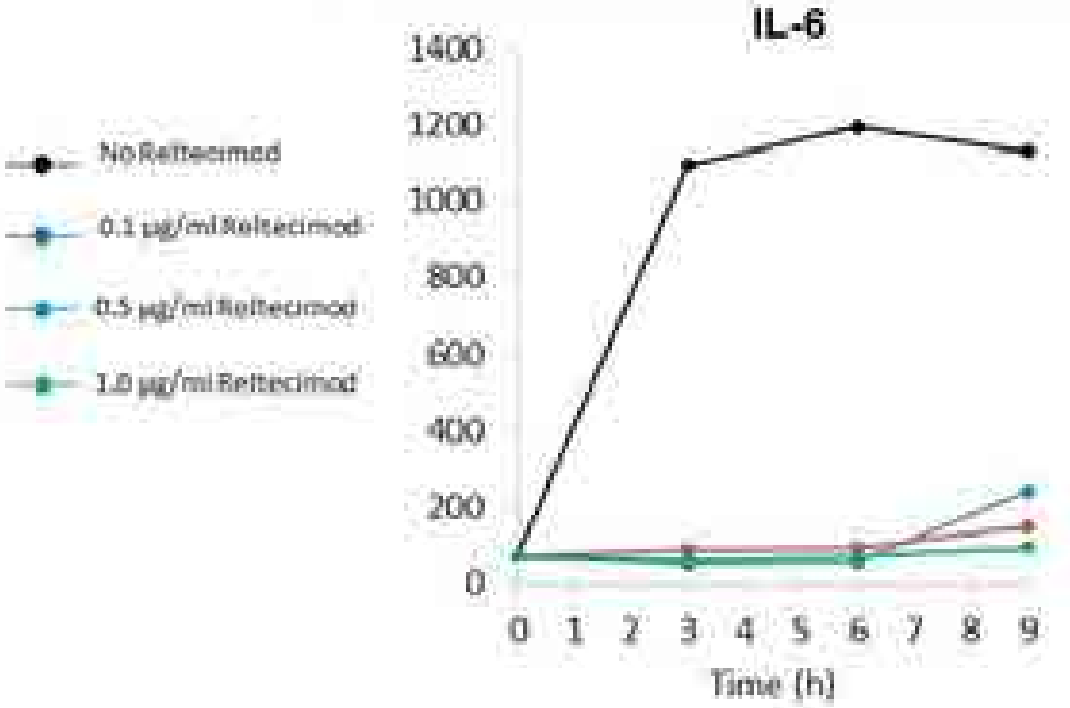


AtoxBio

Modulation of Cytokine Response

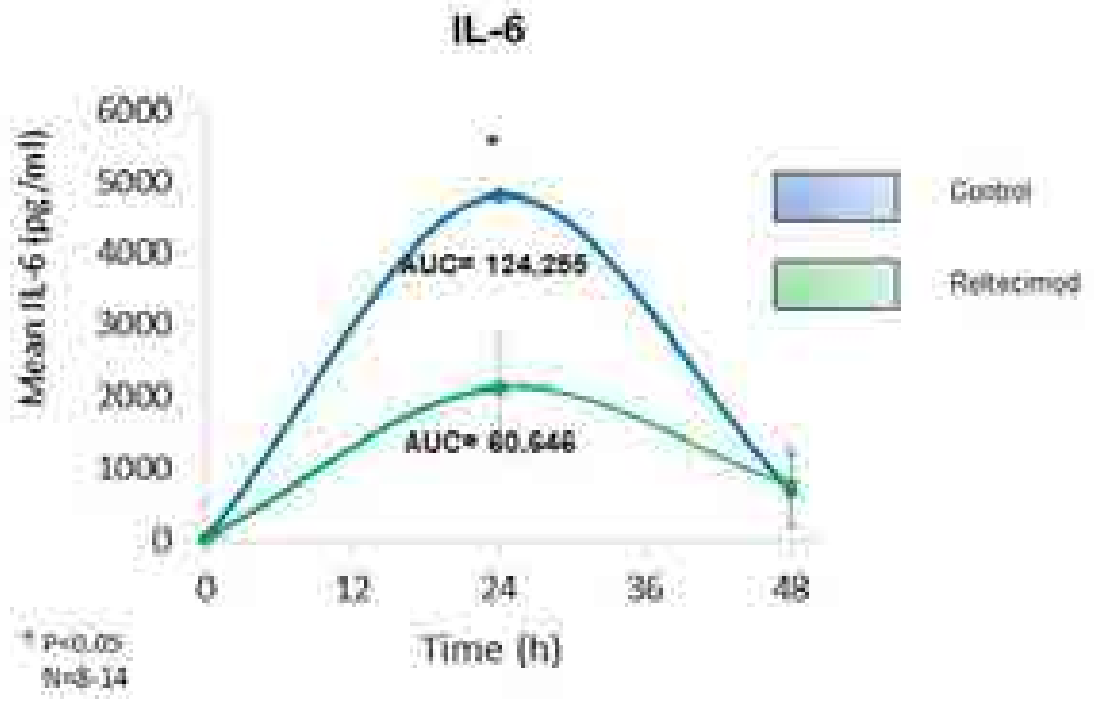
In vitro:

Short exposure to Reltecimod is sufficient to attenuate SEB induced cytokine response in human PBMCs



Animals:

Reltecimod attenuates but does not inhibit IL-6 cytokine expression in a CLP model



Reltecimod administered at 2 hours post infection; outcome measured at 24 and 48 hours

AtoxBio

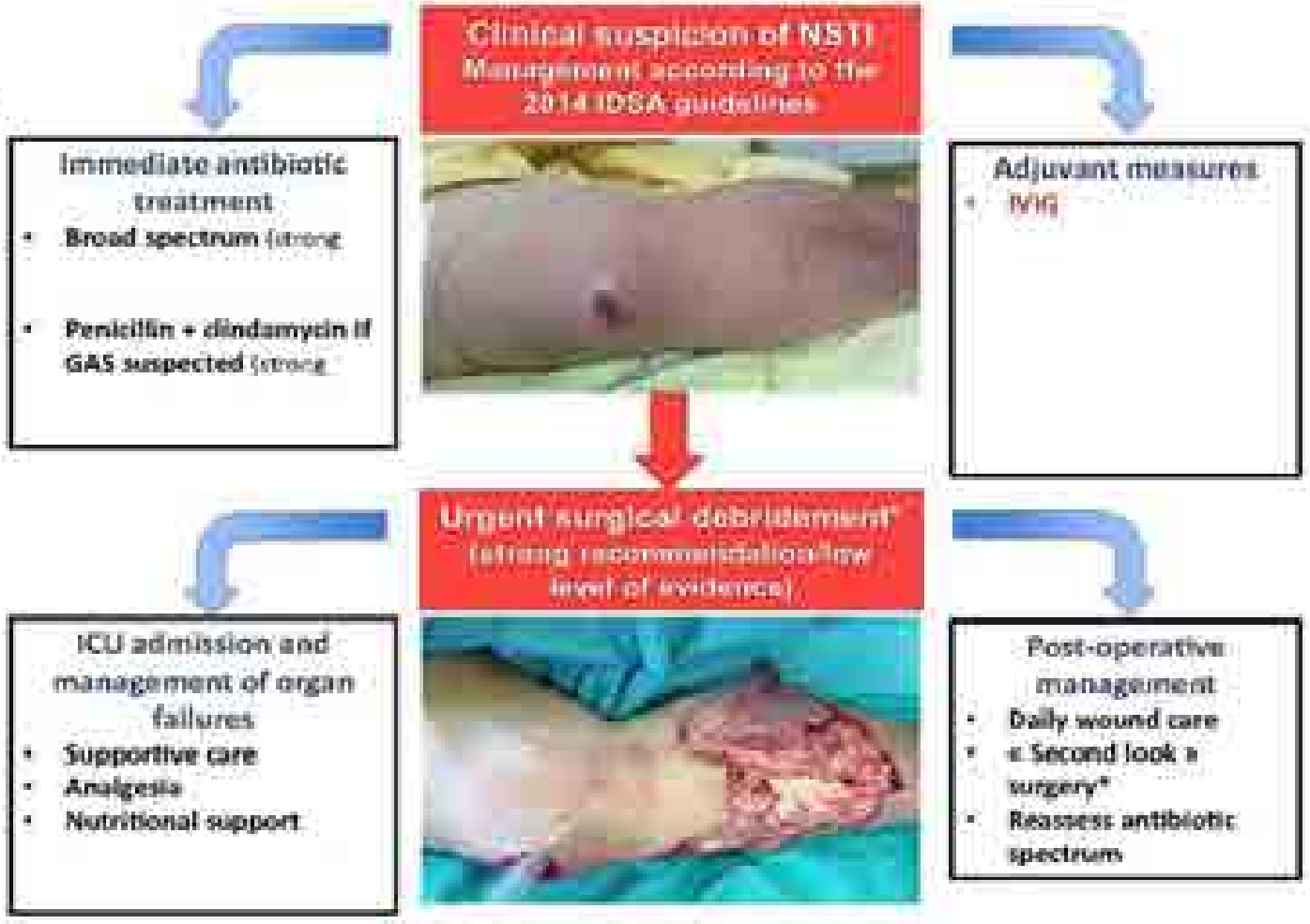
Severe Acute Inflammation Could Lead to Organ Failure

Organ failure causes nearly 50% of all ICU deaths

AtoxBio

Necrotizing Soft Tissue Infections – No Approved Pharmacologic Treatment

- What is NSTI?
  - Rapidly-progressing infections involving significant necrosis and tissue destruction coupled with systemic organ dysfunction
- Significant Treatment Limitations:
  - Significant morbidity
    - Multi organ dysfunction/failure: extended ICU stay, acute kidney injury, extended hospital stay
  - Poor patient quality of life
    - Highly invasive surgery
    - Undesirable and large number of debridements: impaired mobility, severe disfiguration, long rehabilitation, amputations (~10%)
  - Mortality 15-20%
  - Currently no approved pharmacologic treatments
  - Significant unmet need



AtoxBio

NSTI Phase 2 (ATB-201): Study Design

- First randomized, double blind, placebo controlled study in patients with NSTI

40 patients (3 arms)

10 Placebo, 15 Reltecimod 0.25 mg/kg,
15 Reltecimod 0.5 mg/kg

Single dose of Reltecimod (6 hr)

7 level 1 US trauma sites

Baseline Severity	0.50 mg/kg	0.25 mg/kg	Placebo
SOFA	3.47	2.87	3.10
Shock (vasopressor support)	4 (27%)	1 (7%)	0 (0%)

- Endpoints evaluated both the systemic and local manifestations of NSTI: resolution of organ dysfunction, ICU stay, days on ventilator and number of debridements

ATB-201: Significant Treatment Effect on Resolution of Organ Dysfunction

- Tested using SOFA (Sequential Organ Failure Assessment) score evaluating 6 major organ systems:
  - **Respiratory** - PaO2/FiO2
  - **Cardiovascular** - Mean Arterial Pressure OR administration of vasopressors
  - **Renal** - Serum Creatinine or urinary output
  - **Coagulation** - Platelets
  - **CNS** - Glasgow Coma Scale
  - **Liver** – Bilirubin
- SOFA score tracks patient status during ICU stay. Has demonstrated to be a good indicator of prognosis (both short-term and longer term)

Day 14 SOFA≤1 Reflects Medical Wellness and Lack of Organ Dysfunction

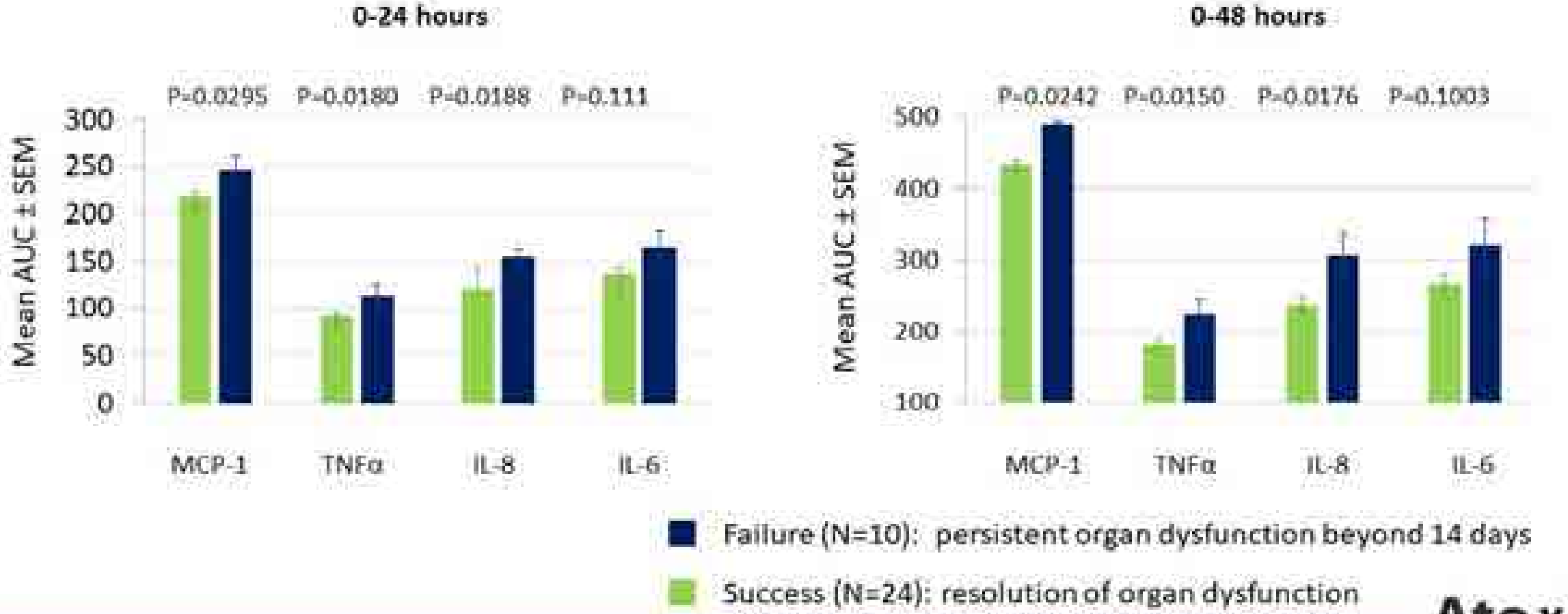
	Placebo	0.25 mg/kg	0.5 mg/kg
Patients with Day 14 SOFA≤1	4/10 (40%)	10/14 (71.4%)	13/14 (92.9%)
	p=0.0162		
Mean Day 14 SOFA score	2.7	1.1	0.7

Bulger, E.M., Maier, R.V., Sperry, J., Joshi, M., Henry, S., Moore, F.A. et al. JAMA Surg. 2014;149(6):528-536

AtoxBio

Lower Cytokine Exposure is Correlated to Persistent Organ Dysfunction in Patients with NSTI; Phase 2 (ATB-201) Study

Patients defined as success by SOFA (N=24), had ~20% reduction in TAUC values in 3/4 tested cytokines (p<0.03) as compared to patients defined as failure (N=10) when evaluated either at 0-24 or 0-48 hours post-surgery



ATB-201: Consistent Response Across Multiple Clinically Relevant End Points

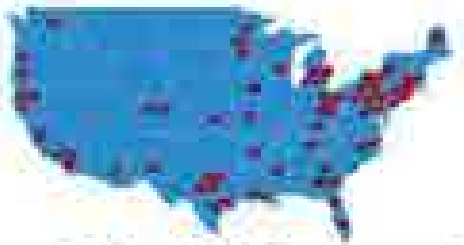
	Placebo	0.25 mg/kg	0.5 mg/kg
Days in ICU	8.9	4.9	5.4
Days on Ventilator	5.2	3.1	2.7
% of patients with only 1 debridement	20	26	33
% of patients with >3 debridement	30	20	13
% Mortality	20	6.7	6.7

- No drug related serious adverse effects

NSTI Phase 3 ACCUTE Pivotal Trial (ATB-202) – Study Design

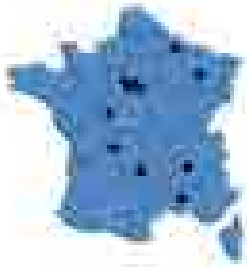
290 patients (1:1) – 60% enrolled

Single dose of Reltecimod (6 hr)



68 level 1 US trauma sites

Primary Endpoint (NICCE)	Co-Primary Endpoint
1. Alive at day 28 2. <=3 Debridements 3. No amputation after first debridement 4. Organ dysfunction (mSOFA at day 14 <=1) 5. Decrease of ≥3 score points in mSOFA at day 14	1. Alive at day 28 2. <=3 Debridements 3. No amputation after first debridement
p-value ≤ 0.01	p-value ≤ 0.05



10-12 French sites to be initiated in August 2018

EMA accepted NICCE alone as primary endpoint with p-value ≤0.05

- Organ dysfunction at entry criteria: baseline mSOFA >=3 (at least one organ with a score of >=2*)
- Major secondary end point – complete recovery from Acute Kidney Injury (study powered to achieve statistical significance on this end point)

* Consistent with new 2016 SCCM/ESICM Sepsis-3 definition

AKI Phase 2 (ATB-203) – Study Design

120 patients (1:1)

Abdominal sepsis induced AKI

Single dose of Reltecimod (6 hr)

~50 level 1 US trauma sites

First sites initiated in April 2018

- To compare the rates of complete recovery (alive, free of dialysis and return of serum creatinine to <150% of reference baseline at Day 14)
  - Primary endpoint: Complete recovery (75% treated vs 50% placebo) at Day 14
  - One sided p-value of 0.05-allows for variance of treatment difference down to 22% with 80% power for positive study
- Blinded review to assess AKI stage at entry and recovery
- Study initiated and first patient enrolled

Unique Drug Development Challenges

- Small foreign biotech
- Transition original biothreat development plan (focus on animal rule) to move drug into clinic
- Identify unique patient population/clinical indication with unmet medical need
  - Avoid pitfalls encountered by other development programs that focused on broader heterogenous sepsis patient populations
- Need to develop novel clinical endpoint
- Challenging patient enrollment
  - Sporadic acutely occurring orphan disease with minimal available epidemiological information
  - Unlike other orphan diseases no central patient registry/centers of excellence to access potential patients and predict patient enrollment
  - Limited number of investigative sites with clinical trial resources and access to target patient population to effectively conduct study
- Single pivotal trial for regulatory review and approval given orphan nature of clinical indication

Duke-Margolis Symposia
Vu Truong

June 14 2018

www.aridispharma.com

Forward-Looking Statements

These forward-looking statements relate to future events or future financial performance of the Company. All such forward-looking statements involve risks and uncertainties and are not guarantees of future performance. An investment in the securities of Arvinas is speculative in nature, involves a high degree of risk, and should not be made by an investor who cannot bear the economic risk of its investment for an indefinite period of time and who can now afford the loss of its entire investment. These include many important factors that affect our ability to achieve our stated objectives including, but not limited to:

- The timing of regulatory submissions;
- Our ability to obtain and maintain regulatory approval of our existing product candidates and any other product candidates we may develop, and the labeling under any approval we may obtain;
- Approvals for clinical trials may be delayed or withheld by regulatory agencies;
- Pre-clinical and clinical studies will not be successful or confirm positive results or meet expectations or meet regulatory requirements or meet performance thresholds for commercial success;
- The timing and costs of clinical trials, the timing and costs of other expenses;
- Our ability to obtain funding from third parties;
- Management and employee operations and execution risks;
- Loss of key personnel;
- Competition;
- Market acceptance of products;
- Intellectual property risks;
- Assumptions regarding the size of the available market, benefits of our products, product pricing, timing of product launches;
- The uncertainty of future financial results;
- Risks associated with this offering;
- Our ability to attract collaborators and partners;
- Our reliance on third party organizations.

We operate in a very competitive and rapidly changing environment. New risks emerge from time to time. It is not possible for our management to predict all risks, nor can we assess the impact of all factors on our business or the extent to which any factor, or combination of factors, may cause actual results to differ materially from those contained in any forward-looking statements we may make. In light of these risks, uncertainties and assumptions, the forward-looking events and circumstances discussed in this presentation may not occur and actual results could differ materially and adversely from those anticipated or implied in the forward-looking statements.

Except as required by law, neither we nor any other person assumes responsibility for the accuracy and completeness of the forward-looking statements. We undertake no obligation to update publicly any forward-looking statements for any reason after the date of this presentation to conform these statements to actual results or to changes in our expectations.

This presentation is strictly confidential, is for informational purposes only and may not be relied upon in connection with the purchase or sale of any security. You may not disclose any of the information contained herein to any other parties without our prior express written permission.

We are an "emerging growth company" as defined under the Securities Act of 1933, as amended (the "Act") and, as such, this presentation and the accompanying oral presentation may be construed as communications permitted pursuant to Section 5(d) of the Act and Section 105(b) of the Jumpstart Our Business Startup Act of 2012. Any offering of securities will only be made by means of a registration statement (including a prospectus) filed with the Securities and Exchange Commission ("SEC"), after such registration statement becomes effective. No such registration statement has become effective as of the date of this presentation. This presentation does not constitute an offer to sell or the solicitation of an offer to buy any securities in any jurisdiction. In the event we conduct an offering, before you invest you should read the prospectus in the registration statement and other documents we file with the SEC for more complete information about us and the offering. When available, you may review these documents for free by visiting EDGAR on the SEC website at http://www.sec.gov.

Paradigm shift in development & treatment of anti-infectives

	Current Approach		Near Future
1)	Empirical broad-spectrum antibiotics	Rapid Diagnostics → 	Diagnostic-driven, narrow spectrum anti-infectives
2)	Non-inferiority clinical trial design	→	Superiority clinical trial design

Paradigm shift in infectious diseases treatment

Empirical broad-spectrum antibiotics

Diagnostic-driven, *targeted* monoclonal antibody (mAb)

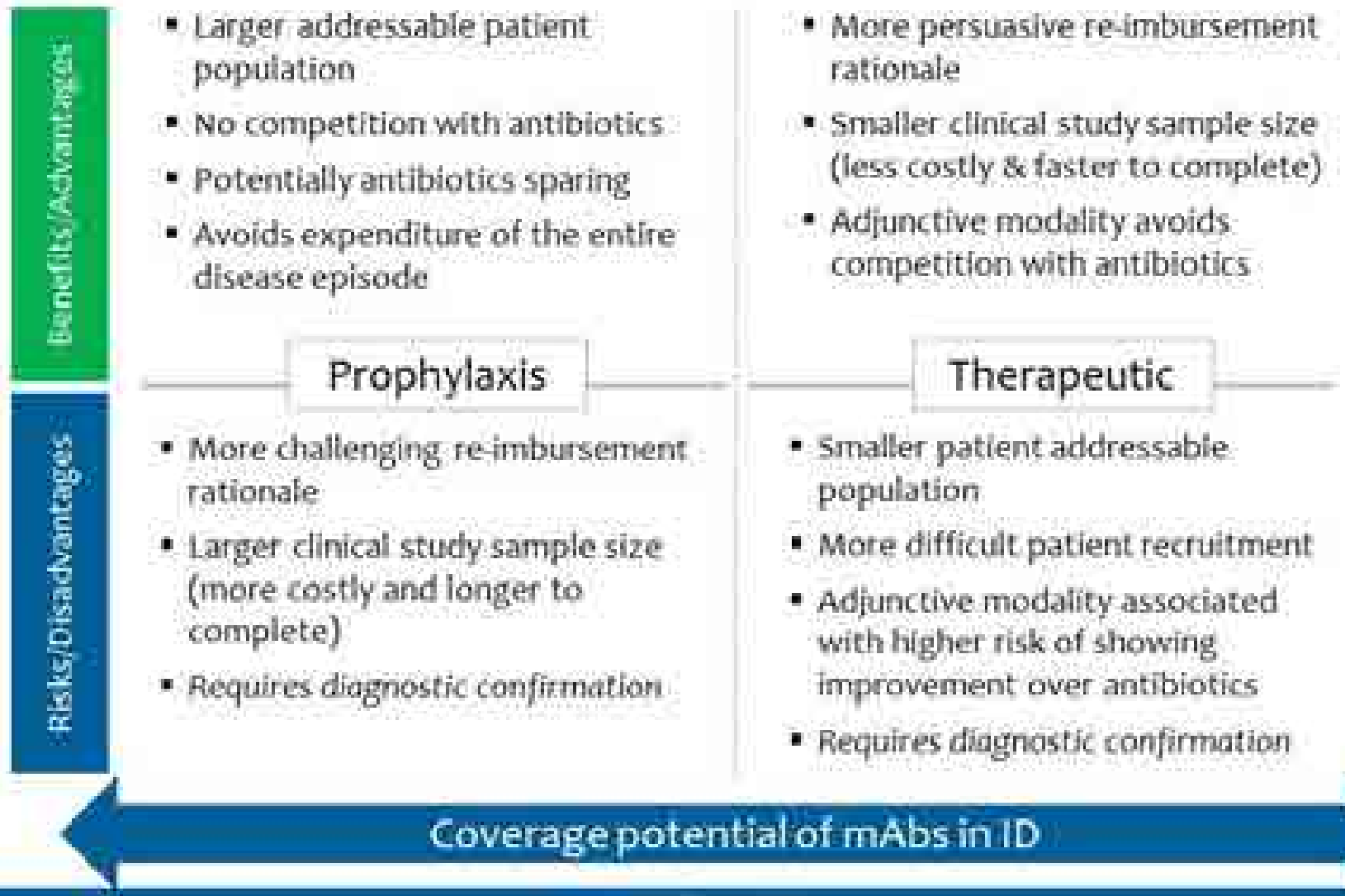
Challenges:

- Growing antibiotic resistance
- Variable safety; Short duration
- Lack of product differentiation
- Antibiotics perturb microbiome

Solutions offered by mAbs:

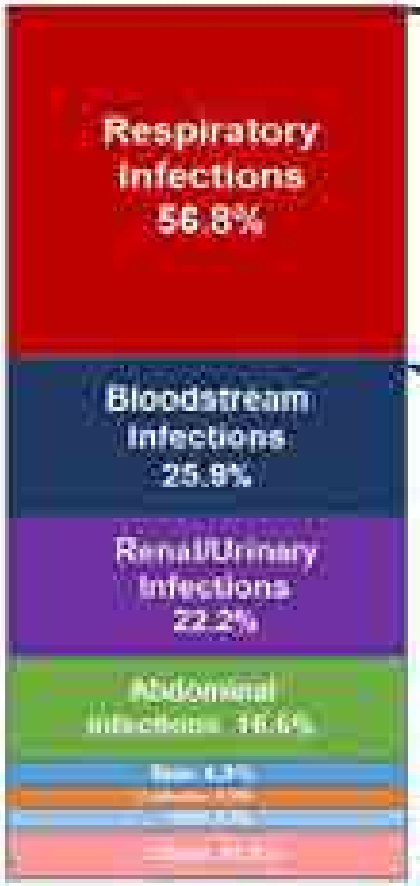
- Optimized by nature to fight infection
- Strong safety; Long durability of action
- Highly differentiated; precision medicine
- Avoids negative impact on microbiome

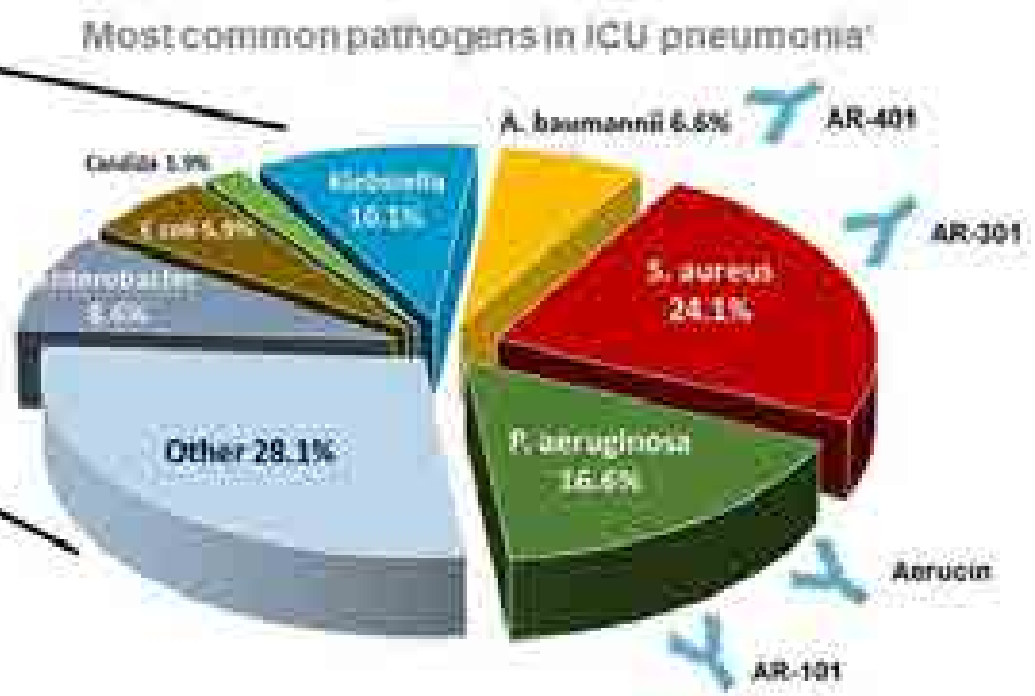
Therapeutic vs. Prophylaxis Uses of mAbs in ID



Infections in the Intensive Care Units (ICU)

Aridis has a portfolio of human mAbs to treat respiratory infections



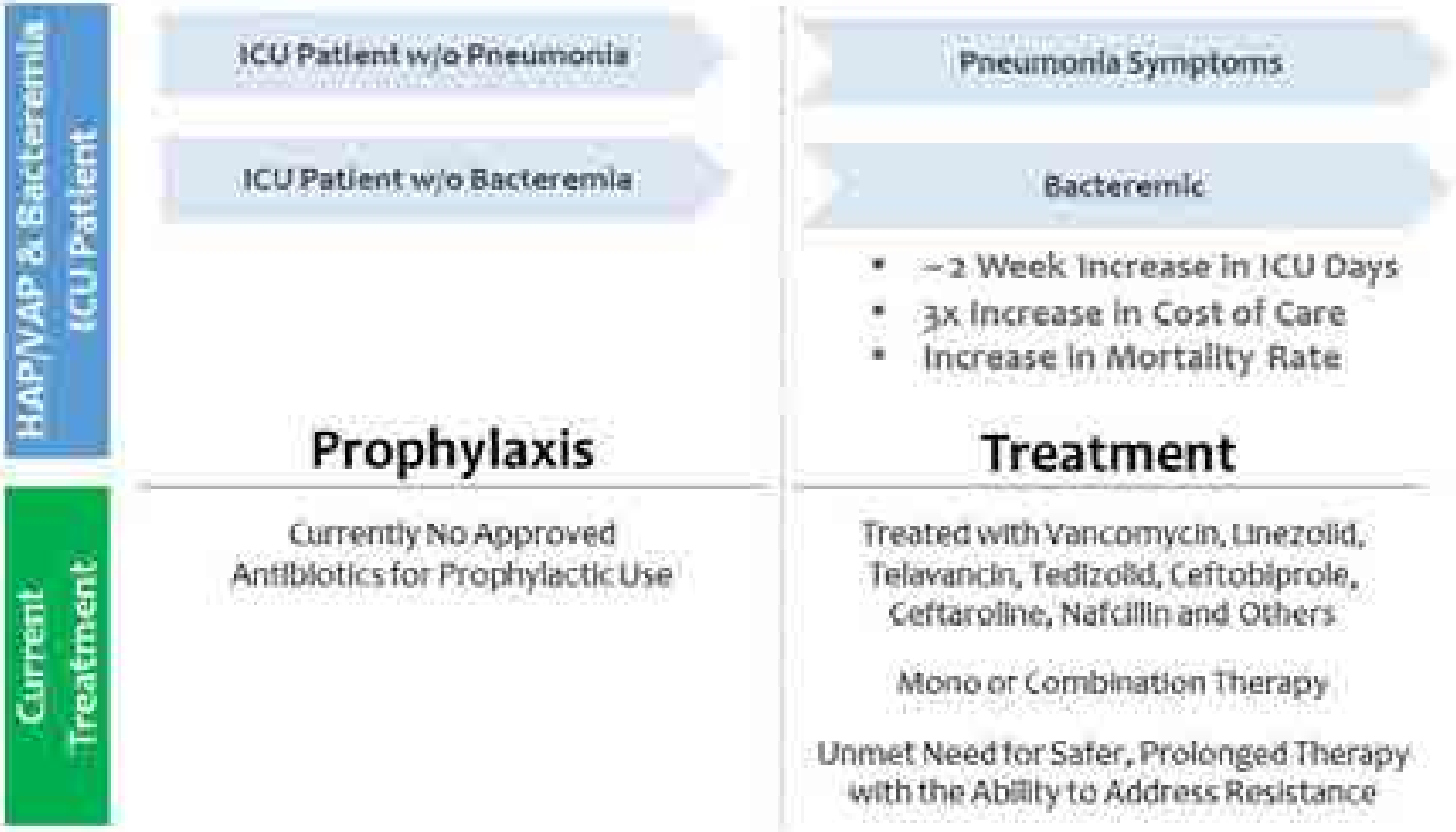


Total US HAP/VAP/HCAP population ~645,000*

North America data)

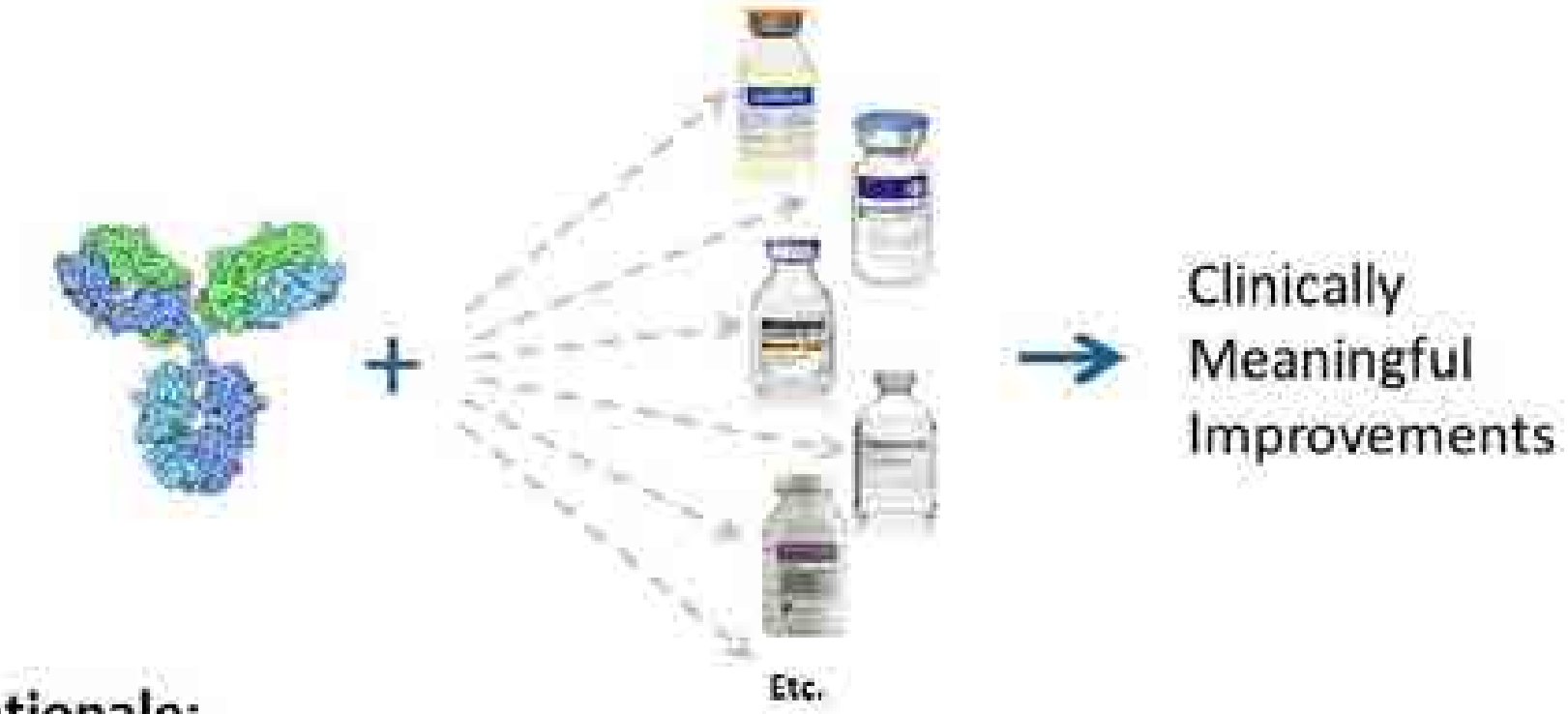
*NHSN CDC Report 2006-2010. Antimicrobial-resistant pathogens associated with HAI. Edwards JR et al Infect Control Hosp Epidemiol. 2013

Aridis is focusing on therapeutic treatment using mAbs in critical care setting



Clinical Strategy

Use Adjunctive Modality to Differentiate and Show Superiority vs. Antibiotics Alone

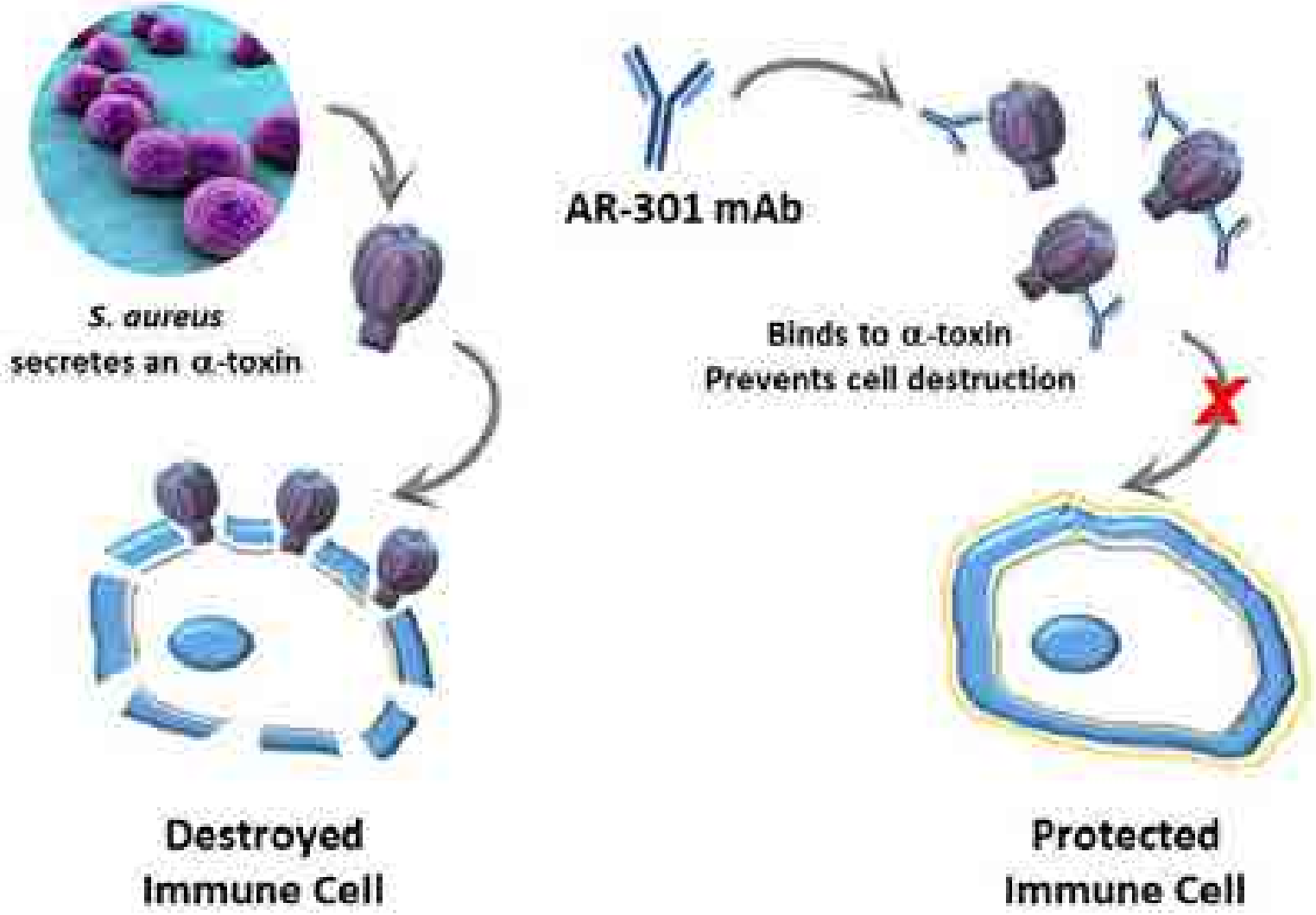


Rationale:

- Differences in MOA & PK/PD may result in complementarity in effects
- Use superiority trial design to clearly demonstrate clinical benefits
- Provides opportunity for outcome-based & value-based pricing
- Provides for product differentication

AR-301 Mechanism of Action: Targets *S. aureus* α-Toxin

Toxin inhibition represents a proven mechanism of action for mAbs



Recently Completed AR-301 Phase 2a Trial

Design (ClinicalTrials.gov ID NCT01589185)	▪ Randomized, double-blind, placebo-controlled, single ascending dose of AR-301 ▪ 31 sites across EU and U.S.
Number of Patients	▪ 48 patients with HAP or VAP caused by *S. aureus*
Groups (all groups received standard of care "SOC" antibiotics)	▪ SOC [antibiotics alone] + Placebo (n=16) ▪ SOC + AR-301 (1 mg/kg) (n=6) ▪ SOC + AR-301 (3 mg/kg) (n=8) ▪ SOC + AR-301 (10 mg/kg) (n=10) ▪ SOC + AR-301 (20 mg/kg) (n=8)
Primary Endpoint	✓ Safety and pharmacokinetics
Secondary Endpoints	✓ Time to removal of ventilator (VAP patients) ✓ Microbiological cure ✓ Shorter time to eradication ✓ Days in ICU ✓ Hospitalization days ▪ All-cause mortality ▪ Clinical cure rate

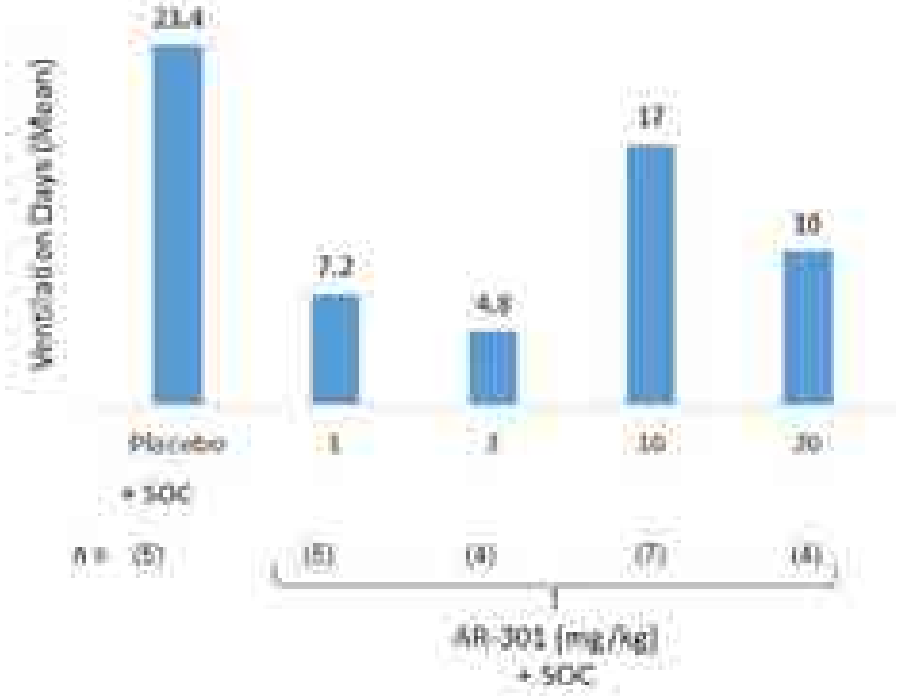
✓ = Data trend in favor of adjunctive treatment benefit

▪ = No trend

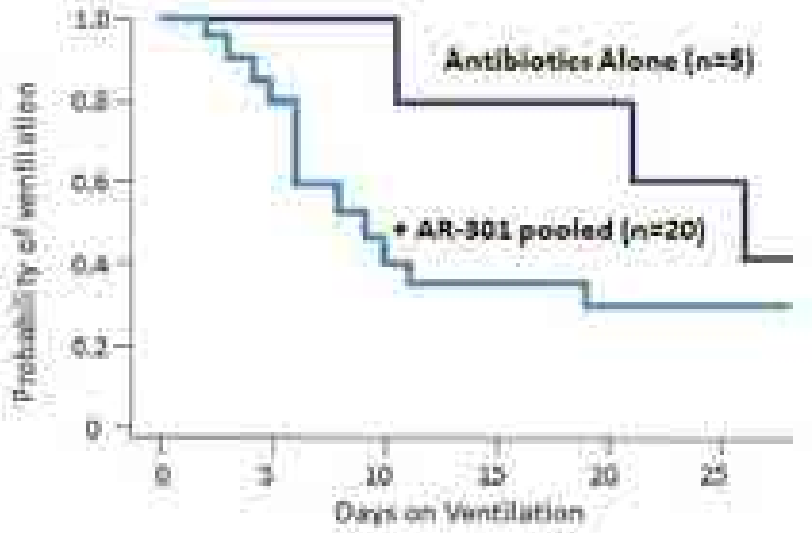
AR-301 Phase 2 Efficacy: Time on Mechanical Ventilation

Statistically Significant Reduction in Ventilation Days with Adjunctive AR-301 Treatment

Ventilation Days in VAP Patients (Microbiologically confirmed Intend to Treat population); $p < 0.01$ for Placebo vs. AR-301 (pooled)

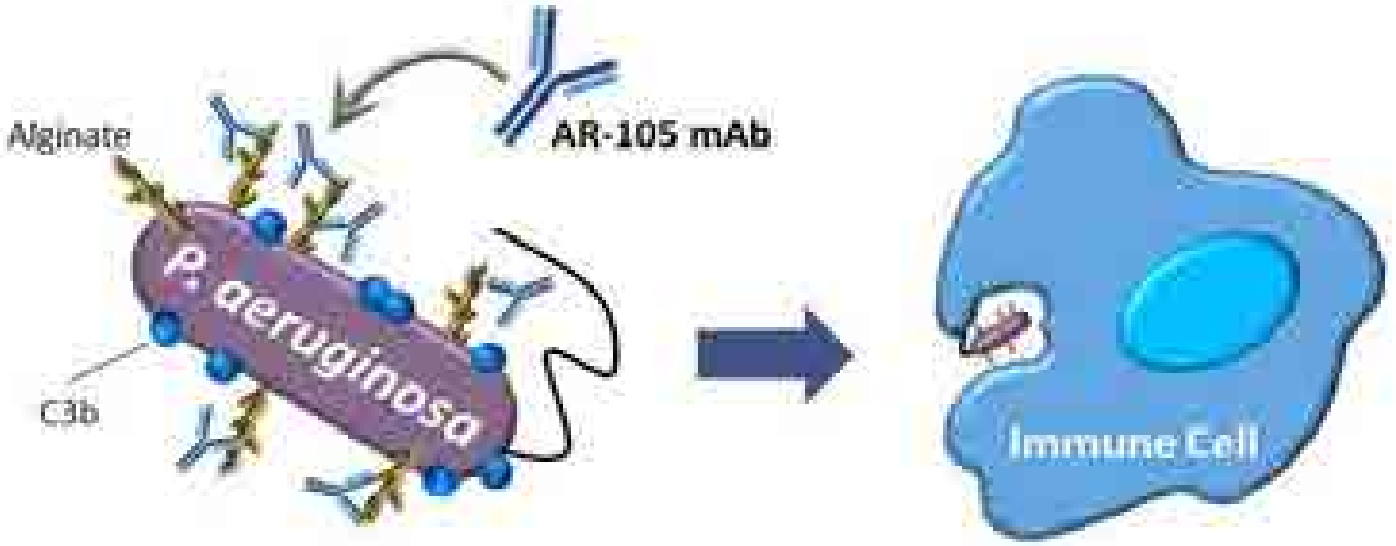


Lower Probability of Ventilation Requirement for VAP patients (exploratory analysis)



Mechanism of Action: AR-105 Facilitates Immune Killing

Pseudomonas aeruginosa



AR-105 mAb binds to *P. aeruginosa* alginate;
Activates complement system (C3b)

Improves immune recognition;
Enhances bacterial engulfment/killing

Ongoing Global Phase 2 Trial of AR-105

Design (ClinicalTrials.gov ID NCT03027609)	• Randomized, double-blind, placebo-controlled, single dose
Number of Patients	• Up to 240 patients with VAP caused by Gram (-) *P. aeruginosa*
Clinical centers	• Up to 130 sites, up to 23 countries (U.S., EU, Asia)
Groups (all groups received standard of care "SOC" antibiotics)	• Placebo: antibiotics alone (up to 120 patients) • Antibiotics + 20 mg/kg (up to 120 patients)
Primary Endpoint	• Clinical cure rate
Secondary Endpoints	• Time to removal of ventilator • Microbiological cure • All-cause mortality • Time to clinical resolution • Days in ICU • Hospitalization days • Antibiotics utilization

Thank you

Vu Truong
CEO
Aridis Pharmaceuticals
5941 Optical Court
San Jose, CA 95138
(408) 385-1742
truongv@aridispharma.com

Session 3

Panel Discussion &
Audience Q&A

E-Mail Questions to

Duke.Abx@Duke.edu

@DukeMargolis

Session 4: Preventing infections using non-traditional antibiotic agents

E-Mail Questions to

Duke.Abx@Duke.edu

@DukeMargolis

Novel Monoclonal Antibody Therapies for Serious Infections

The "Ideal" Anti-infective?

- Targets only the pathogen of interest
- Minimal (if any) potential for resistance development
- Few (if any) target organs of toxicity
- Well-established manufacturing and quality characteristics
- Single dose PK
- Not an antibiotic
- Safety profile allows potential for pre-emptive therapy, assuming at-risk subjects can be identified

Challenges for mAbs in ID

- Novel approach or appearance of novelty
- Novel mechanisms of action, e.g., targeting virulence factors
- How much targeting is too much? Species vs. strains vs. clones
- Cost of goods → Pressure on price and potency
- All the 'normal' challenges of anti-infective development
- All the 'normal' challenges of prevention development
  - What is the real risk of disease incidence? → Study size/power
  - What are the real costs of disease? → Number needed to treat
- Combination product development

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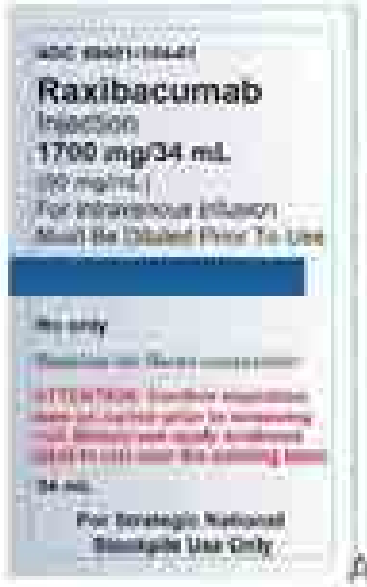
Monoclonal Antibodies as Therapeutics

- First approved in 1986
- Today over 45 approved mAbs with global sales >70 billion USD
- 4 approved for infectious disease indications:

RSV prevention
1998



Anthrax treatment
2012/2016

ZINPLAVA™
(bezlotoxumab) Injection 25mg/mL

CDI
2016

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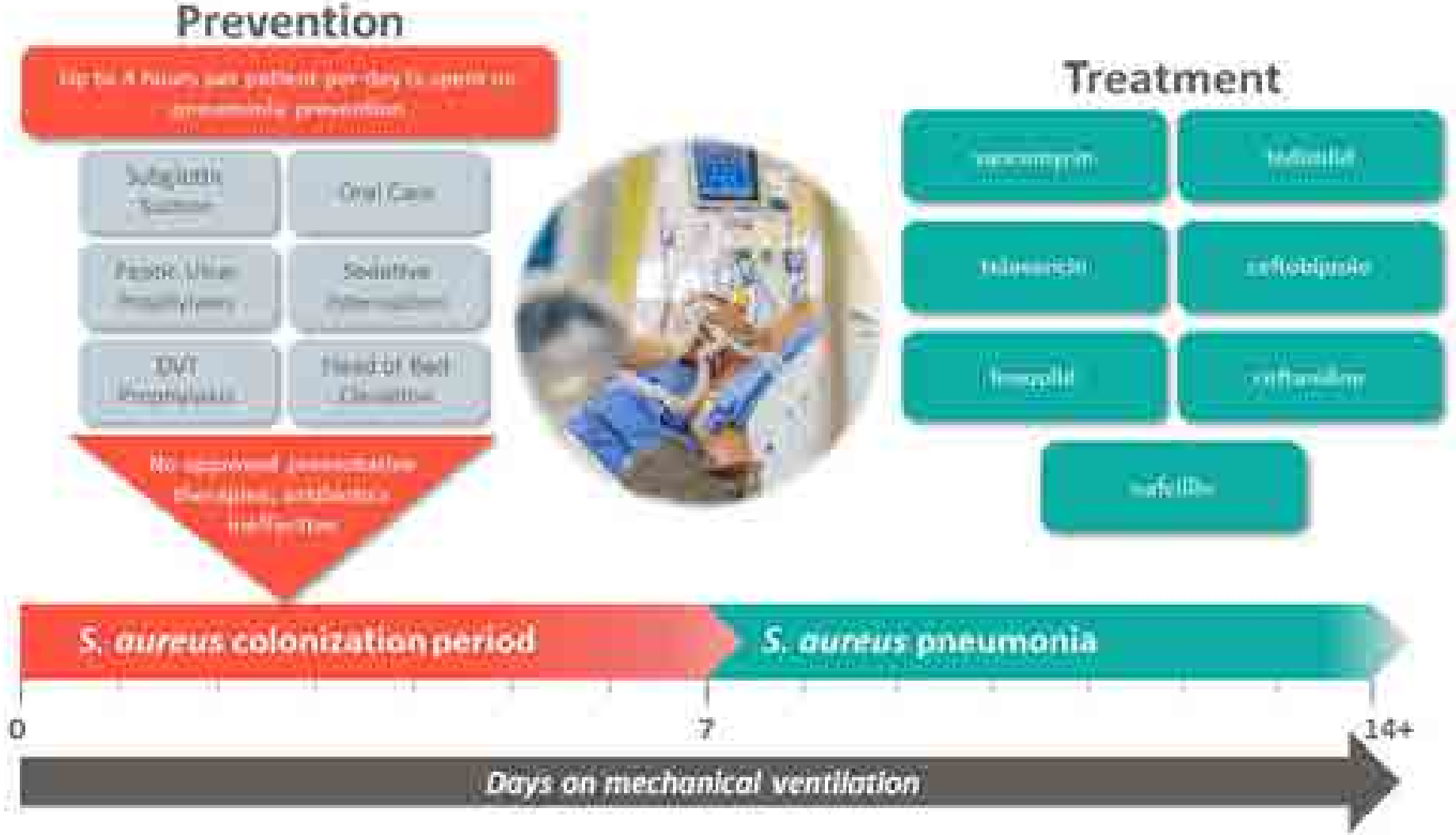
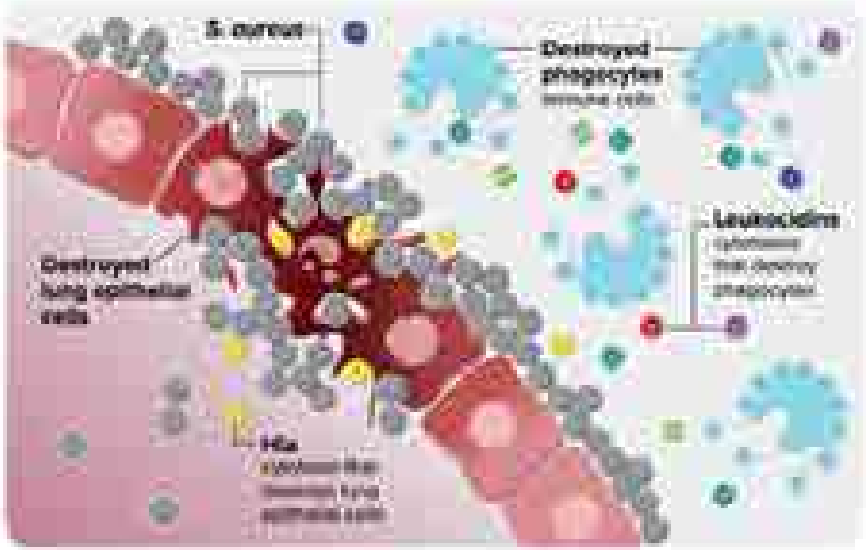
There are no approved drugs to proactively prevent pneumonia in mechanically ventilated patients



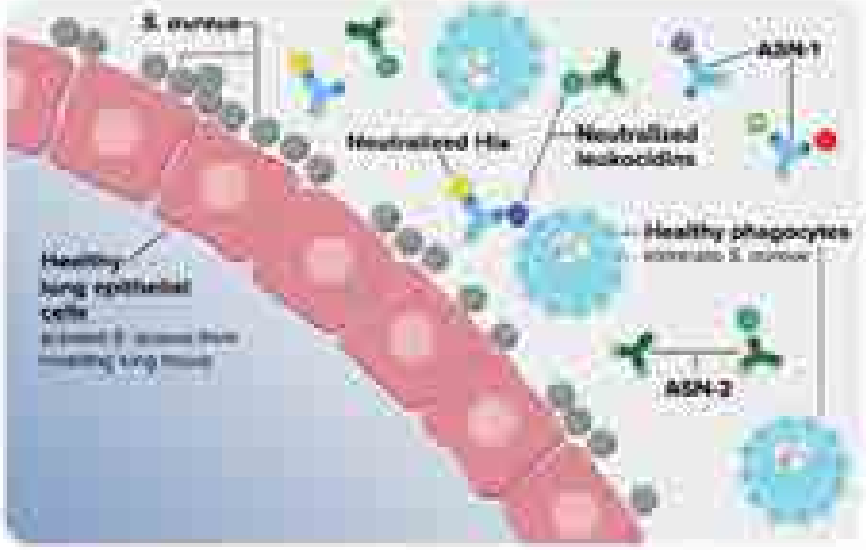
ASN100 is the only therapy in development that neutralizes all six cytotoxins critical to *S. aureus* pneumonia pathogenesis

ASN100 protects both lung epithelial cells and phagocytes from *S. aureus* cytotoxin-induced damage, potentially preventing *S. aureus* bacteria from invading lung tissue and allowing phagocytes to eliminate *S. aureus*

Pathogenesis of *S. aureus* Pneumonia



ASN100: Mechanism of Action



Hla HlgAB HlgCB PVL LukED LukGH

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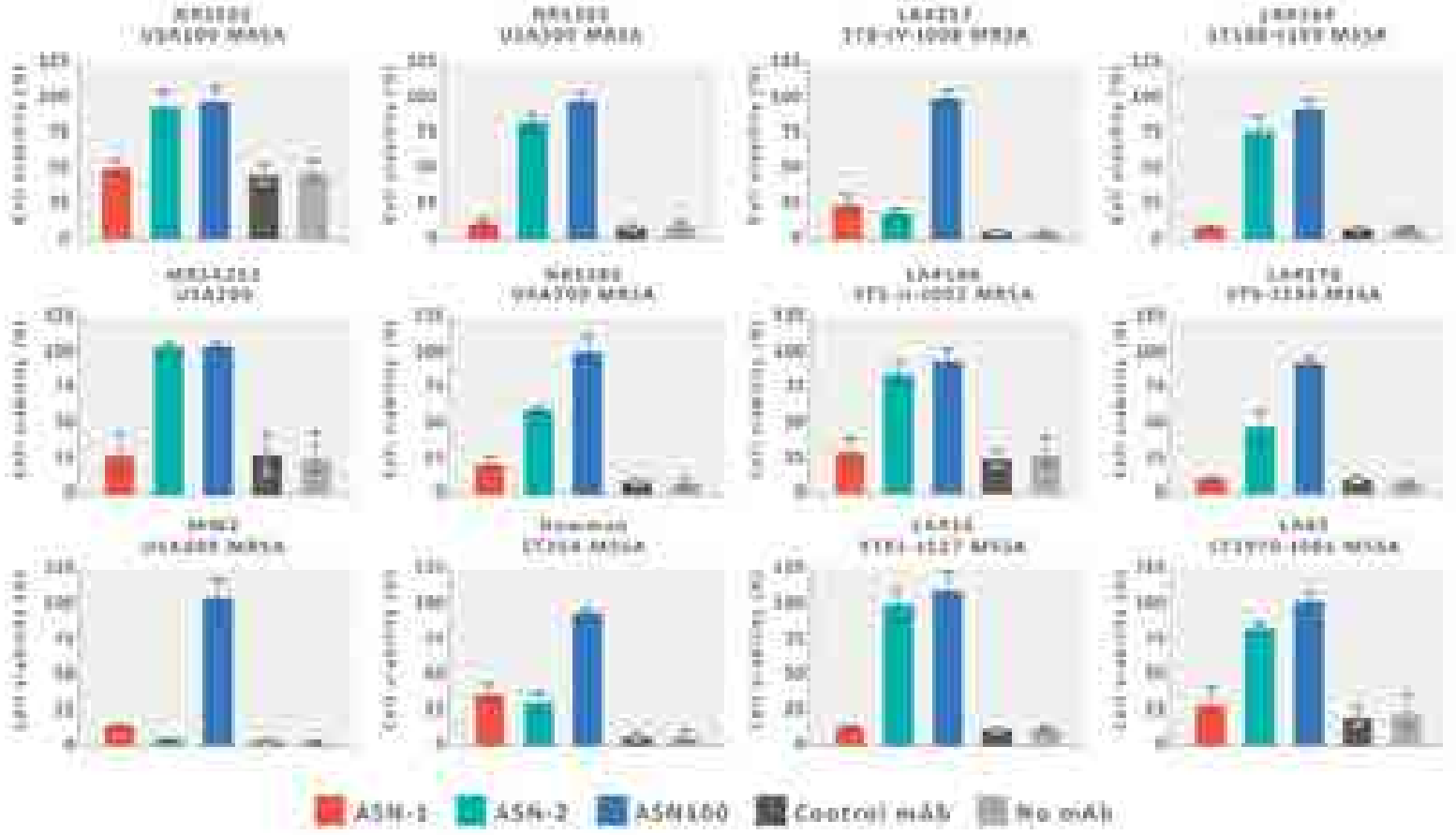
ASN100 protected human phagocytes against leukocidins from a diverse set of *S. aureus* isolates in *in vitro* studies



- ASN100 was highly effective in maintaining human PMN (neutrophil) viability
- For *pvl* (lukSF) positive strains, toxin neutralization was generally dependent on both ASN-1 and ASN-2, while ASN-2 alone was often able to provide protection against *pvl* negative strains

Phase 2 superiority trial with results expected in 2018

Double-blind, placebo controlled superiority trial designed to detect a statistically significant 50% reduction in the occurrence of *S. aureus* pneumonia in high-risk, mechanically ventilated patients

Enrollment
- Mechanically ventilated
- No pneumonia
- Concomitant antibiotics allowed

Randomization
- Heavily colonized
- No pneumonia
- 1:1 randomization
- Stratified by concomitant antibiotic use
- **Single dose** ASN100 or placebo

Efficacy Assessment
- Primary: *S. aureus* pneumonia
- Secondary: Duration of ventilation, ICU length of stay, all-cause mortality (28 days)

- Planned enrollment: 654 patients in the United States, Europe, and multiple additional countries
- Power analysis for statistical significance planned after ~1/3 of patients have been treated (expected 2H'18)
- Top-line results expected in 2H'18
- Fast Track Designation for the prevention of *Staphylococcus aureus* pneumonia in mechanically ventilated patients at high risk for *S. aureus* pneumonia

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ASN100: A Precision Therapy for an Unmet Medical Need

Hundreds of thousands of patients at risk for *S. aureus* pneumonia in the US each year

Ventilated Patients in US each year, >90% on antibiotics

~20% of ventilated patients are heavily-colonized[1] (High risk)

ASN100

A single dose to prevent progression to pneumonia, a disease that costs hospitals $50,000 or more per patient

- Mortality: 30%
- 20 excess days in hospital (6 in ICU)

[1] Stutik, 2014

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Targeted immunotherapy with mAbs offers a promising alternative therapeutic approach for serious infections

Potential advantages:

- Selective, precise effect on novel targets
- Fully human
- Preserve healthy microbiome
- No propagation of antibiotic resistance
- 3-week half life expected for fully human mAbs
- Pre-emptive therapy supporting antimicrobial stewardship
- Broadly potentiate activity of antibiotics at sub-therapeutic doses

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Rebiotix:

Non-Traditional Antibiotics Program

June 2018

Rebiotix
Microbiota Restoration Therapy

REBIOTIX: MICROBIOME PIONEER AND LEADER

At Rebiotix, we are revolutionizing the treatment of debilitating diseases by harnessing the power of the human gut microbiome to greatly improve lives

- Founded in 2011 to bring the first microbiome therapeutic product to market
- Developed proprietary microbiome-based drug platform to rehabilitate the human gut microbiome
- Demonstrated efficacy in preventing recurrent *Clostridium difficile* infection (CDI) in three Phase 2 trials
- Enrolling Phase 3 trial of lead product RBX2660
  - Fast Track, Orphan, Breakthrough Therapy designation
- Expanded into oral formulation & novel disease targets

Rebiotix is the most clinically successful microbiome company

Rebiotix

INCREDIBLE IMPORTANCE OF THE HUMAN MICROBIOME

Human Gut Microbiome:

- Most diverse and dense microbial community in the body
- Plays an important role in the immune system
- Can be damaged (Dysbiosis)
  - Antibiotics, viruses, stress or environmental factors
- Dysbiosis can lead to *C. difficile* infections (CDI)
  - #1 healthcare-associated infection (HAI) in the US

- Restoring a healthy microbiome can effectively prevent recurrent CDI

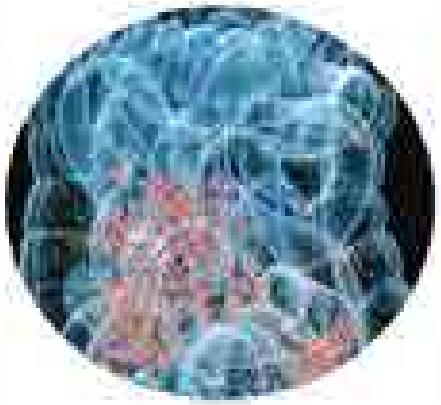
Can microbiome restoration act to treat or prevent other infections?

Rebiotix

REBIOTIX MICROBIOTA RESTORATION THERAPY™ (MRT)

Mimics a Normal, Healthy Human Gut Microbiome

HUMAN GUT MICROBIOME	REBIOTIX MRT SOLUTION
High diversity and high microbial population	High diversity and high microbial population per dose
Dominated by four major bacterial phyla including **spore & non–spore-forming** microbes	Drug processing preserves normal donor phyla including spore- & non–spore-forming microbes
Key non-spore-forming genus ***Bacteroides*** constitutes ~30% of bactena in healthy gut*	Consistent *Bacteroides* per dose
Non–spore-forming *Bacteroides* decimated in *C. diff* patients	Direct evidence that Bacteroidia are restored in RBX2660-treated patients



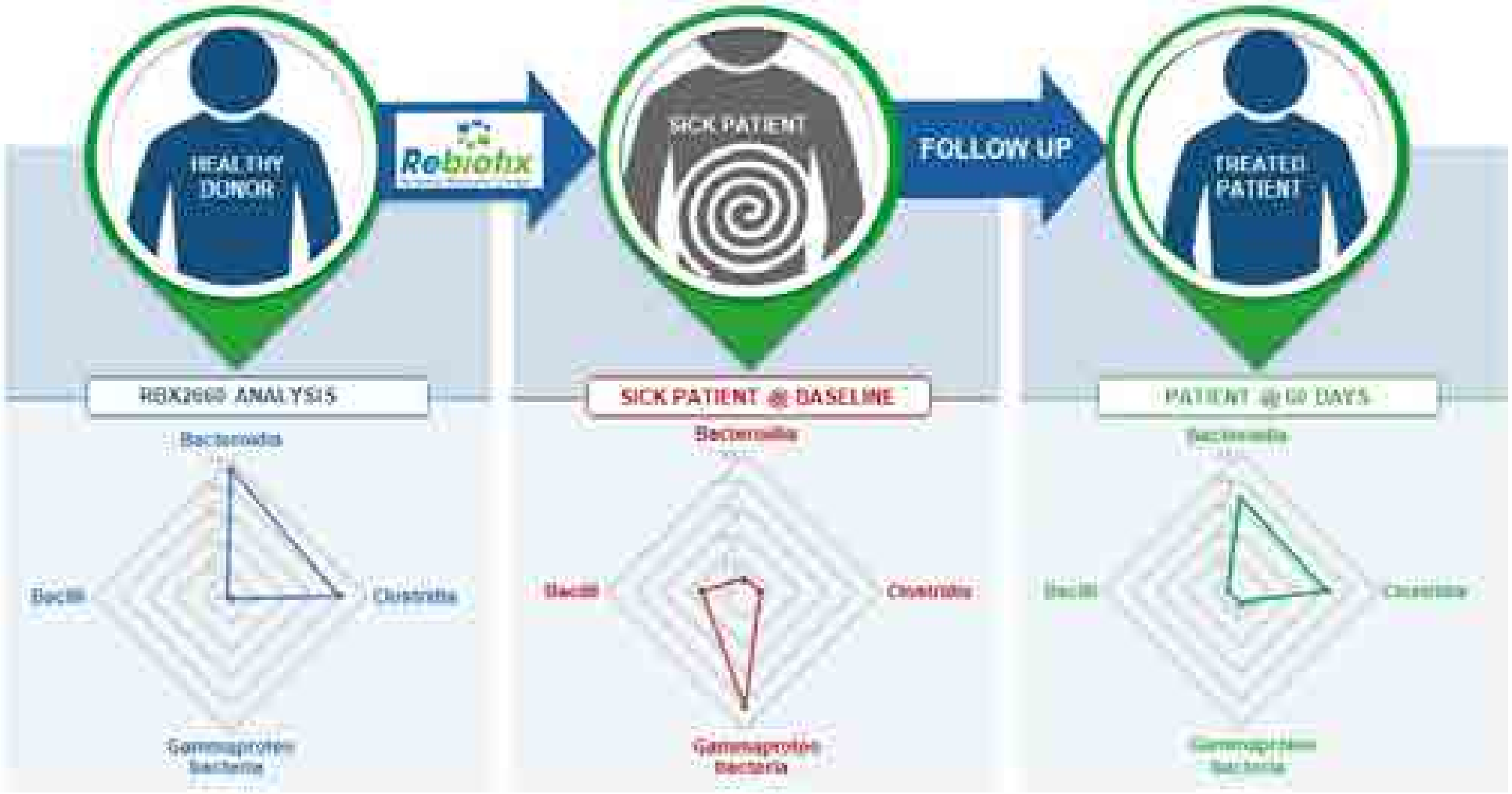
Lead product candidate RBX2660 – liquid microbiota suspension

*Sears CL (2005) Anaerobe 11(5):247-51

Rebiotix

REBIOTIX DEMONSTRATED SIGNIFICANT IMPACT ON DYSBIOSIS

Patients are analyzed at baseline & over follow-up



RBX2660 CLINICAL DEVELOPMENT PROGRAM SUMMARY

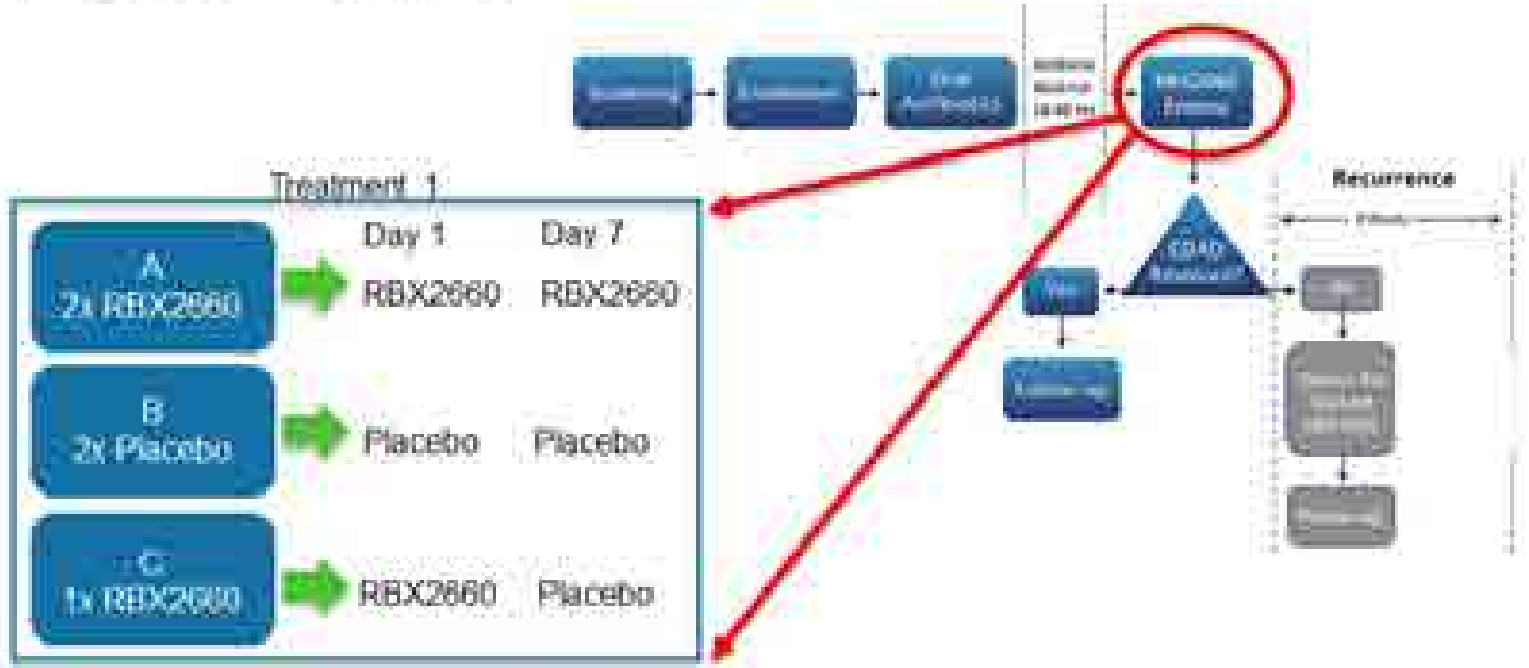
Study Design Criteria	PUNCH™ CD (Phase 2)	PUNCH™ CD2 (Phase 2b)	PUNCH™ Open Label (Ph2)	PUNCH™ CD3 (Phase 3)
Consistent Patient Population: Multi-recurrent CDI	✓	✓	✓	✓
Consistent endpoint: Freedom from Recurrent CDI	✓	✓	✓	✓
Consistent Product: Same mfg process & release criteria	✓	✓	✓	✓
Controlled Trial	No	Yes	Yes	Yes
Total Patients (Active + Control)	N=34	N=127	N=242	enrolling
Treatment Success v. Control	87% v. n/a (multiple doses)	67% v 46% (p <0.05)	79% v. 52% (p<0.0001)	

Rebiotix

PUNCH™ CD2: GROUNDBREAKING MICROBIOME TRIAL

"GOLD STANDARD" PHASE 2B TRIAL DESIGN:

- Prospective, Randomized, Double-blind, Placebo-controlled
- 133 patients randomized: Three treatment arms
- Enrollment from Dec 2014 – Nov 2015



First ever multicenter, randomized, double-blind, placebo controlled IND study for microbiota based drug

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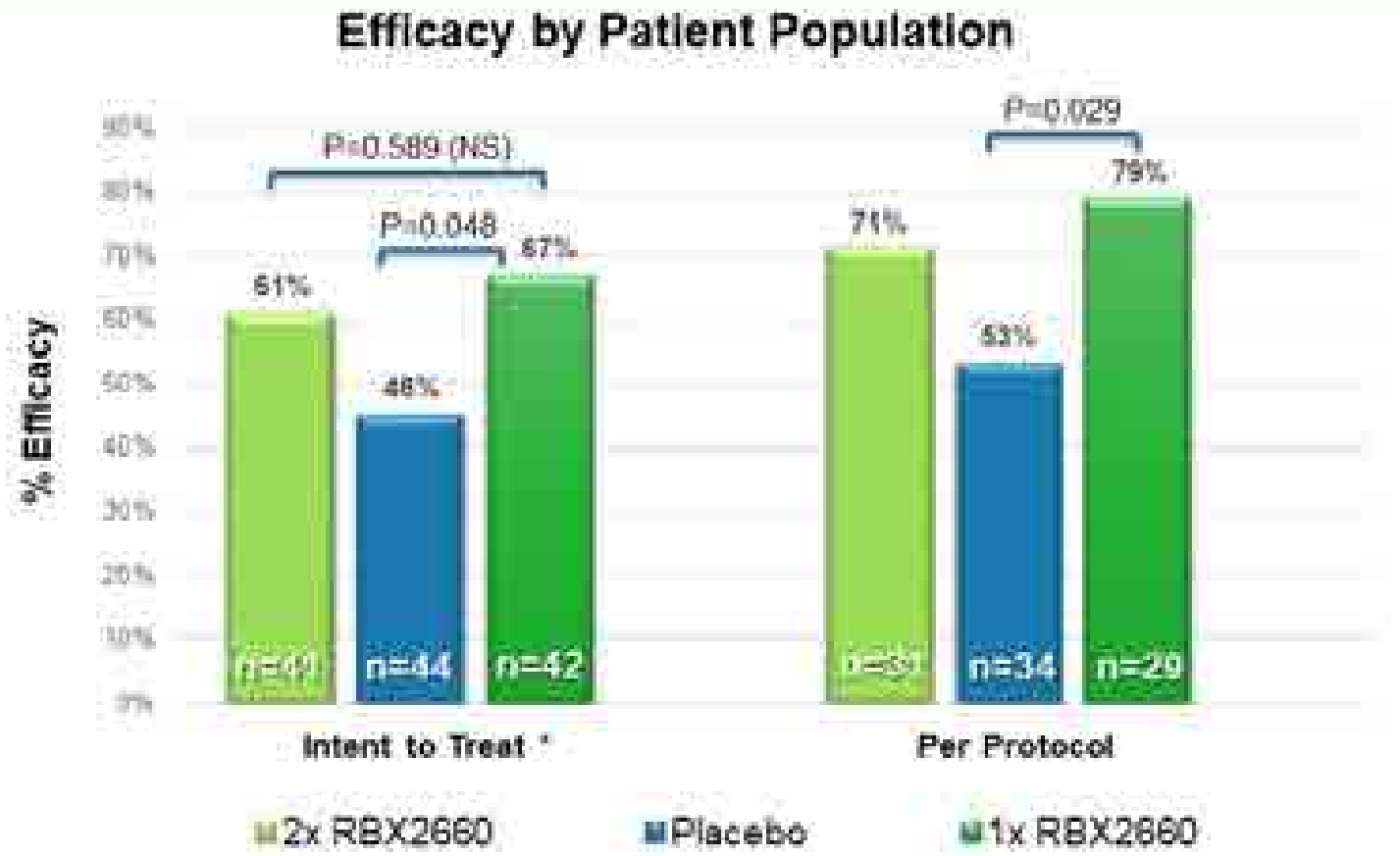
PUNCH™ CD2:
PHASE 2B RBX2660 STATISTICALLY SIGNIFICANT V. PLACEBO



- Two doses of RBX2660 were not different than one dose for all populations, P=0.589 - No escalating dose effect
- Treatment with single-dose RBX2660 significant vs. Placebo

* Excludes randomized subjects who were not treated

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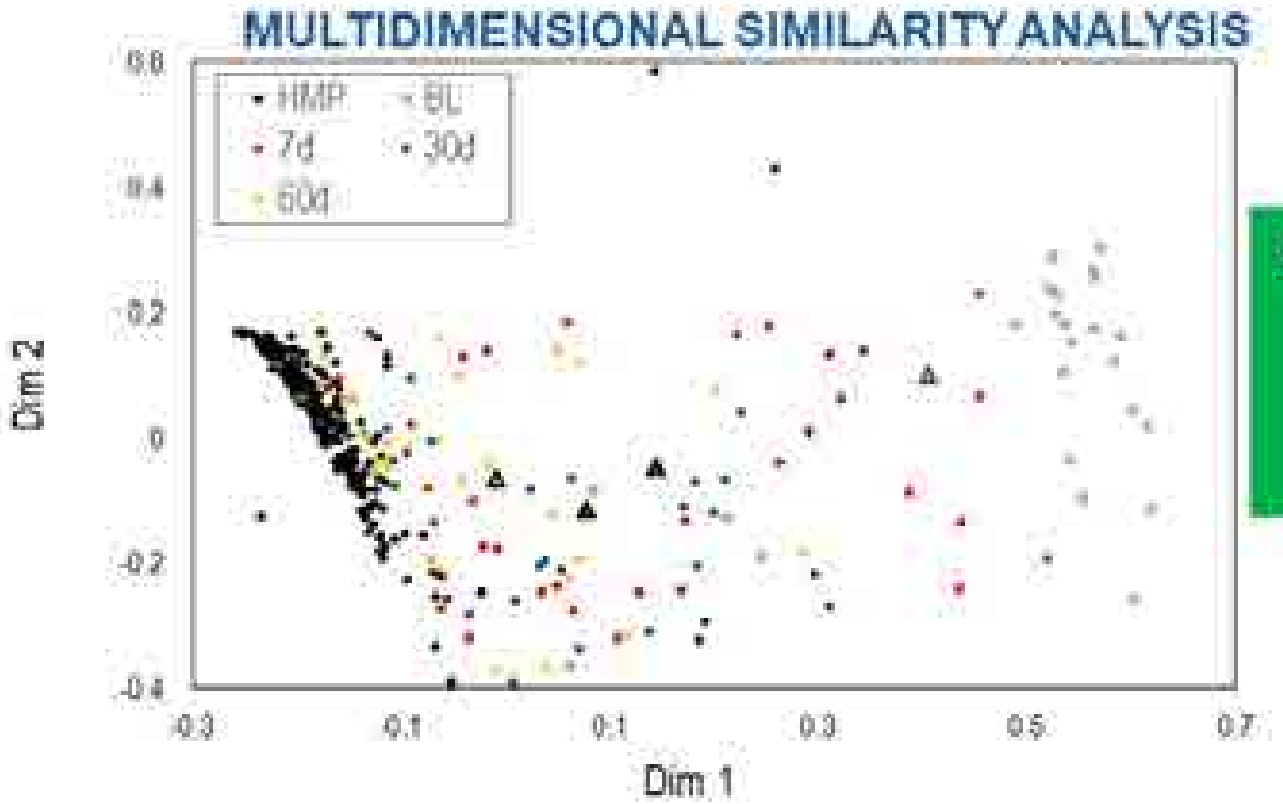
REBIOTIX MRT RESTORED A HEALTHIER MICROBIOME

- Over 200 patient samples collected and sequenced
- Patients were dysbiotic at study entry, dissimilar to a normal range for "healthy" individuals (HMP; Human Microbiome Project)



After treatment, patient microbiomes progressively shifted closer to HMP "normal"

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ANTIMICROBIAL RESISTANCE AND THE MICROBIOME

- Antibiotics facilitate antimicrobial resistance (AR) in the microbiome
- Microbiome functions as a reservoir of AR
  - AR genes from benign microbes can transfer horizontally to pathogens
- Can modulating the microbiome affect carriage of resistant organisms and resistance genes?

Scary prediction:

By 2050, 10 million people per year are projected to die from AR infections.

Images: Wellcome Trust (2014)

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COMMUNITY RESISTOME OVER TIME

At baseline – high level of resistance genes

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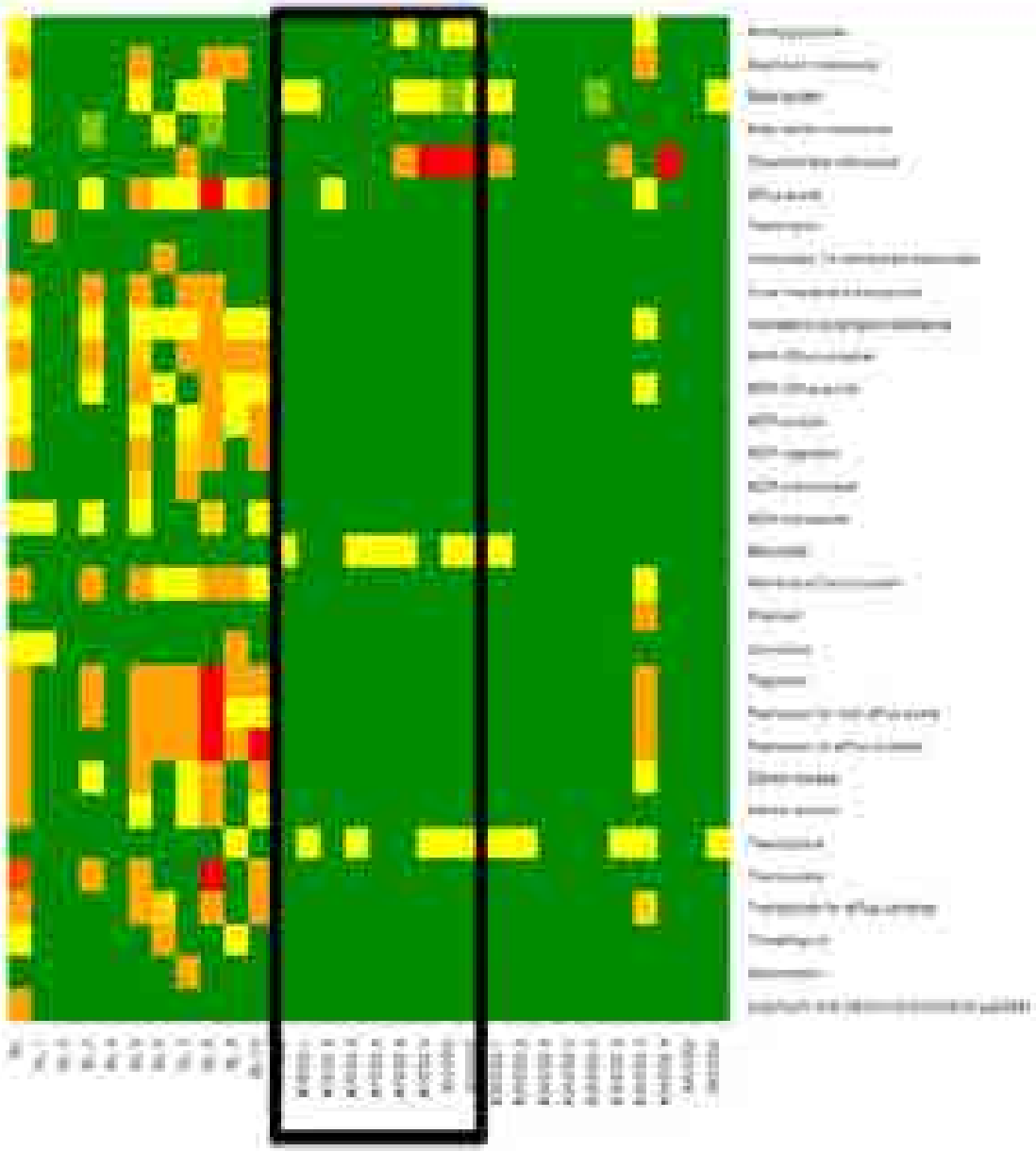
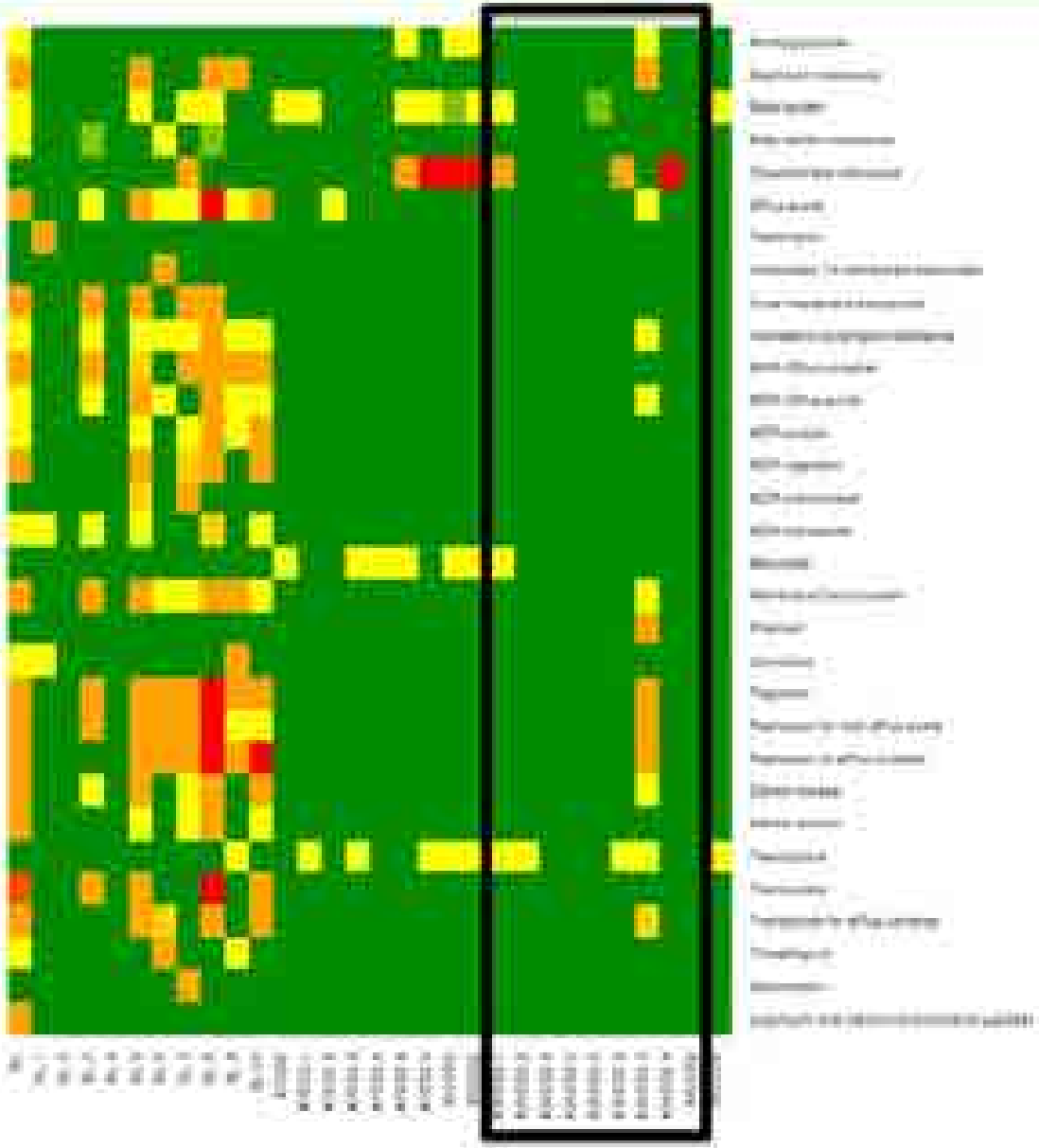
COMMUNITY RESISTOME OVER TIME

7 days post treatment



COMMUNITY RESISTOME OVER TIME

30 days post treatment



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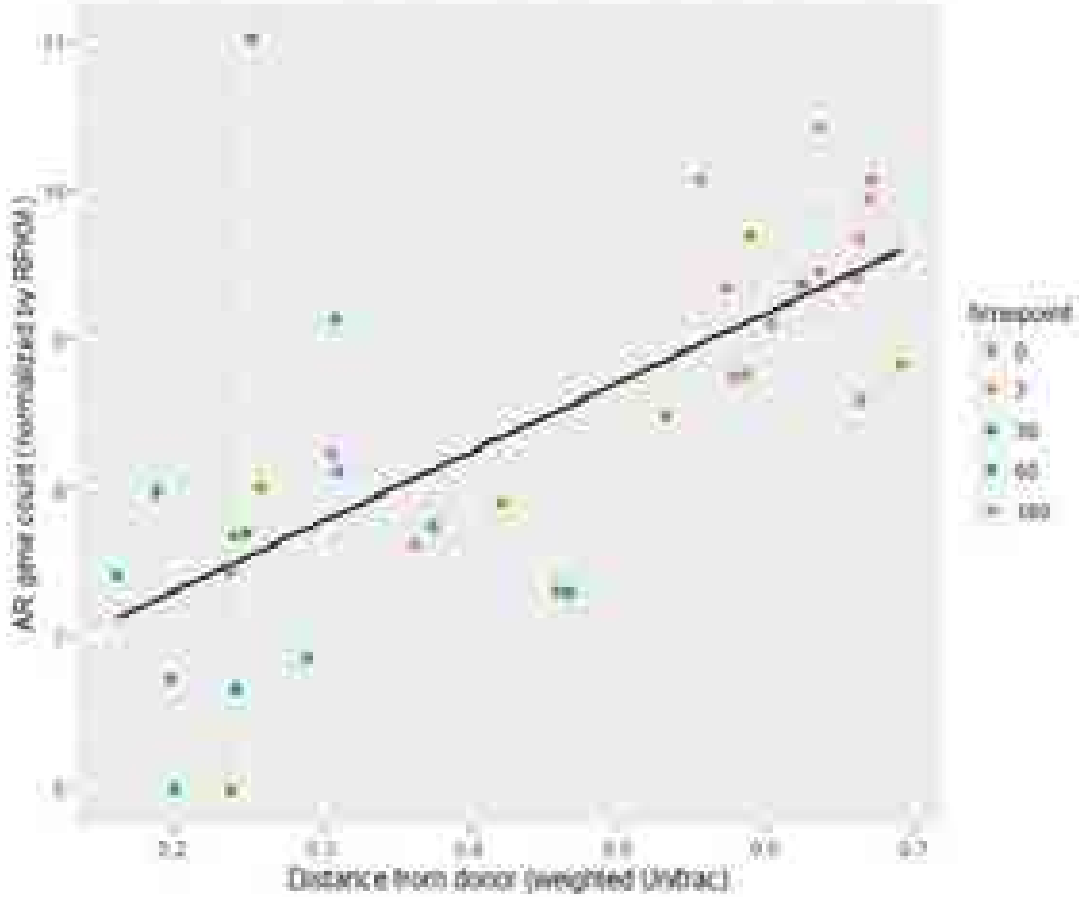
UNIFRAC DISTANCE PREDICTS RESISTANCE GENE ABUNDANCE

- The closer the recipient specimen taxonomy was to donor taxonomy, the fewer resistance genes were detected
- Follows the pattern of microbiome and metabolic profiles of successful patients



Test for correlation (lme)
p<<0.001***

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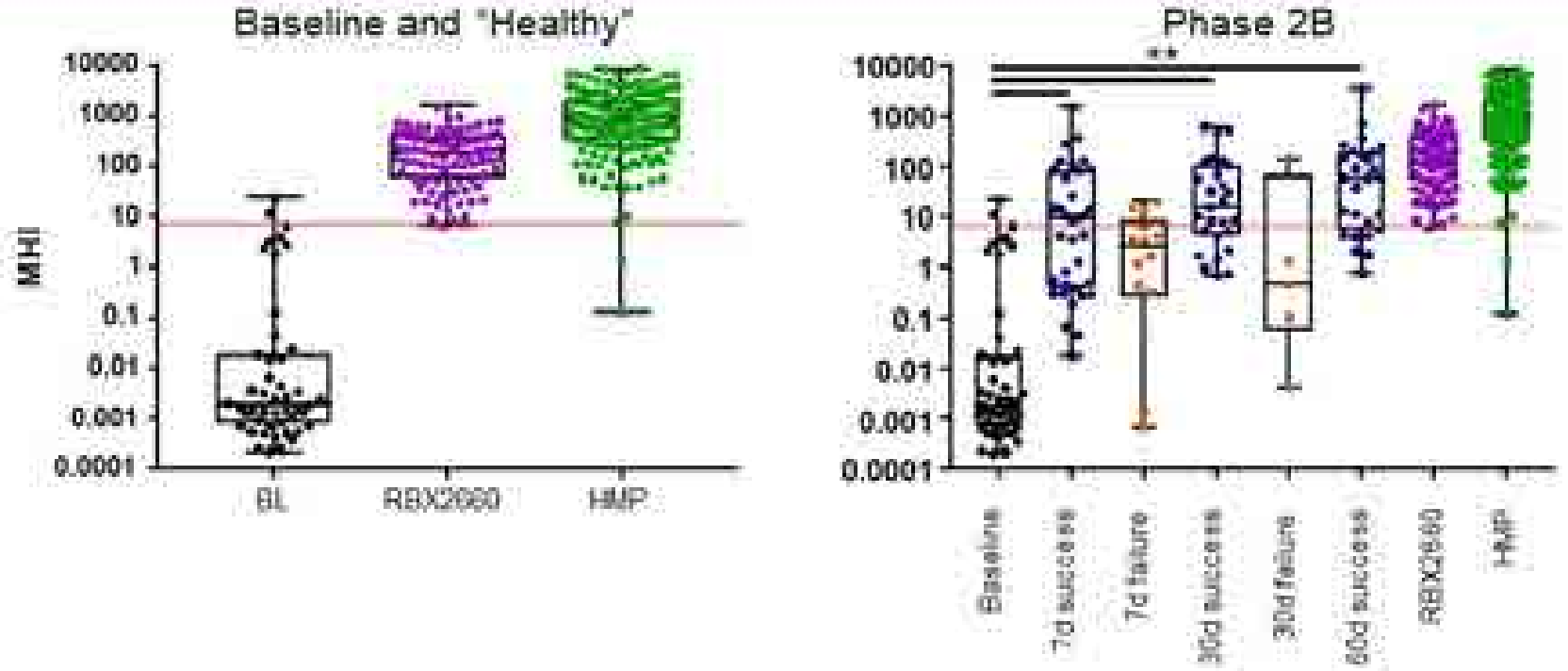
DEVELOPING A PROTOTYPE MICROBIOME HEALTH INDEX™ (MHI) TO MEASURE RESPONSE



- Prototype MHI is a single measure of collective changes in key taxa
- MHI threshold of health vs dysbiosis determined from Baseline and RBX2660
- Most of responders are above the threshold as early as 7 days, median MHI for failures never exceeds threshold

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PUNCH CD™ CONCLUSIONS AND NEXT STEPS

- When treated with RBX2660, significant reduction in CDI infections was shown in recurrent CDI patients over standard-of-care antibiotic therapies
- RBX2660, in the context of preventing CDI recurrence, may be the first therapy with potential to reverse the enrichment of antibiotic resistance
- Distance from RBX2660 composition can measure treatment success and is a predictor of AR abundance
  - Closer to donor, better treatment success and fewer AR genes
- Correlation was repeated with additional clinical data sets
  - Analysis of further study samples, provided by Rebiotix, are currently being evaluated at Washington University St. Louis CDC Epicenter
- New proof-of-concept clinical studies are underway to test MRT on other infections

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Thank you

Additional information, contact: Lee Jones

Ljones@Rebiotix.com

651-705-8772

Rebiotix

Engineering Antimicrobials™

AMICROBE

To prevent and treat infections

Purpose-built antimicrobials for surgery and trauma

Duke-Margolis

June 14, 2018

This work is supported in part by US Army Medical Research & Materiel Command through the Military Burn Research Program (W81XWH-15-2-0065) and by the Assistant Secretary of Defense for Health Affairs through the Peer Reviewed Medical Research Program (W81XWH-16-1-0561). Opinions, interpretations, conclusions and recommendations are those of Amicrobe and are not necessarily endorsed by DoD. CARB-X support is provided by Department of Health & Human Services Assistant Secretary for Preparedness & Response (BARDA) and Wellcome Trust through Boston University (4500002454).

What we do

Two lead product candidates for surgery and trauma:

PREVENT
Amicidin-α
Surgical Gel

DoD W81XWH-15-2-0065
DoD W81XWH-16-1-0561

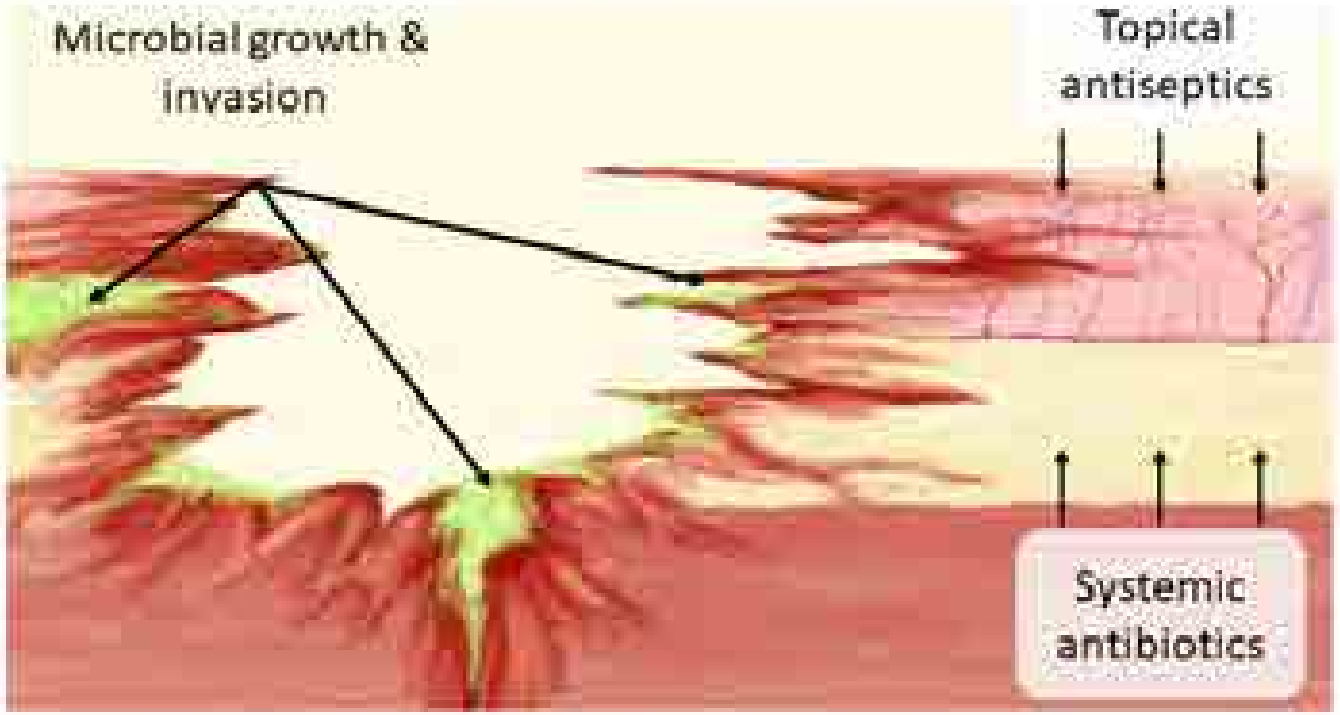
1. Broad microbicidal activity
2. Optimized physical properties
3. Safety

TREAT
Amicidin-β
Solution

DoD W81XWH-15-2-0065
CARB-X 4500002454

Why?

Because microbes like wound environments



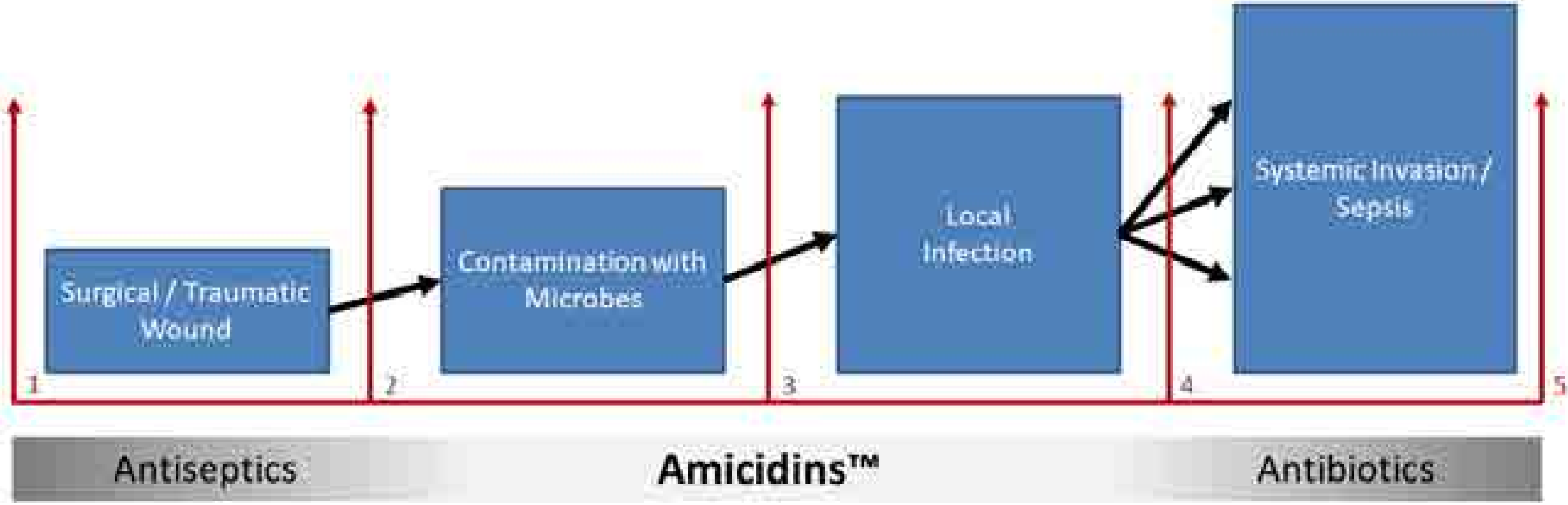
"...surgical infection, at the outset, is always local....since the microbes are, so to speak, within reach of the hand. The question then is simply, how to destroy them without harming the tissues?"

– The Treatment of Infected Wounds (1917)
Alexis Carrel and Georges Dehelly
(Dakin's Solution)

A new technology is needed

The progression of infection

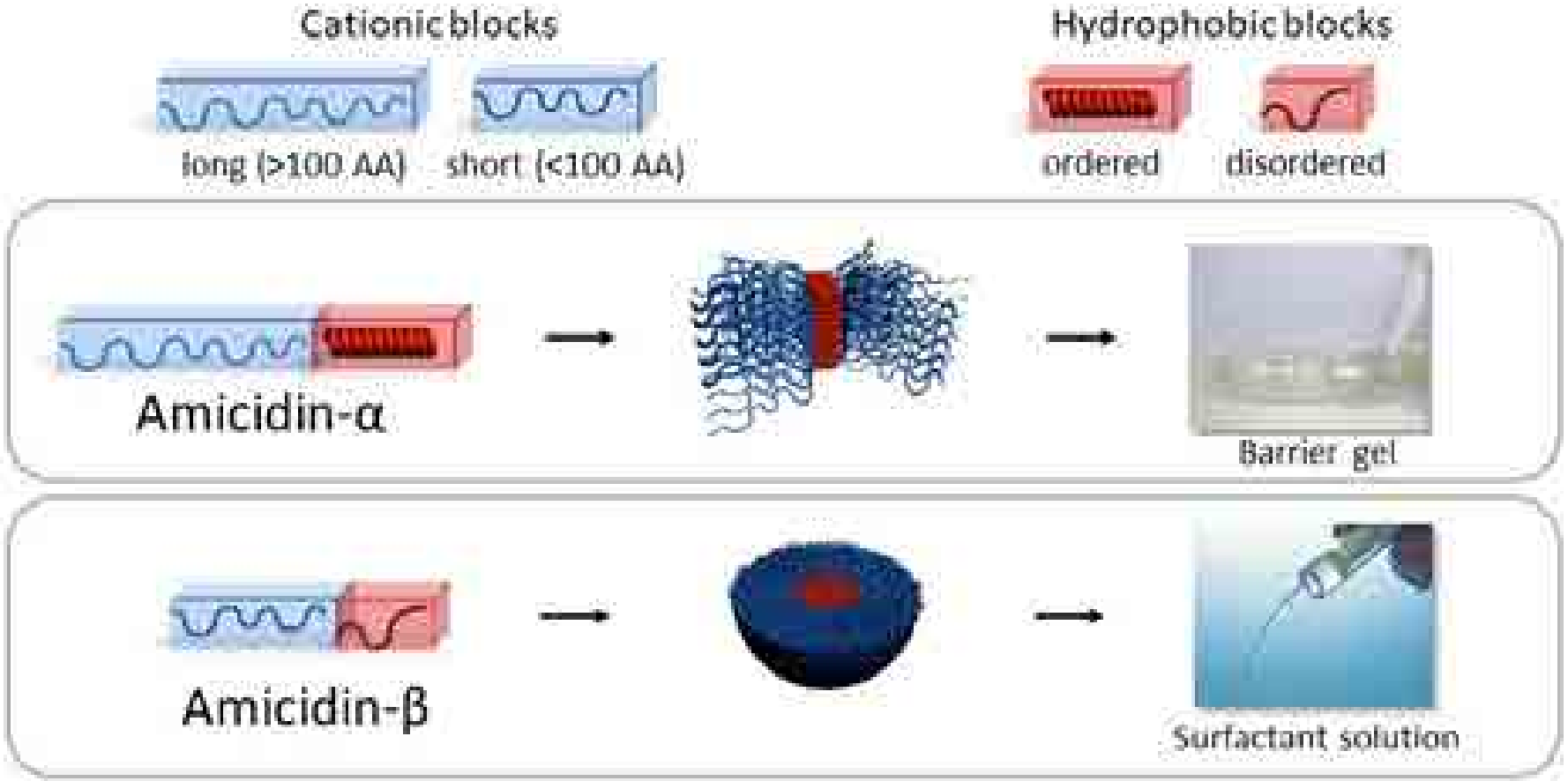
"Surgical infection, at the outset, is always local"
– Alexis Carrel & Georges Dehelly, 1917



To fill the gap between antiseptics and antibiotics

Amicidins are synthetic proteins (with a block architecture)

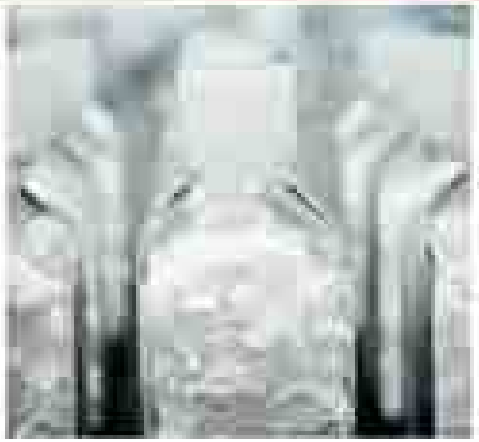
Purpose-built antimicrobials



Broad microbicidal activity and physical properties for enhanced intrawound performance

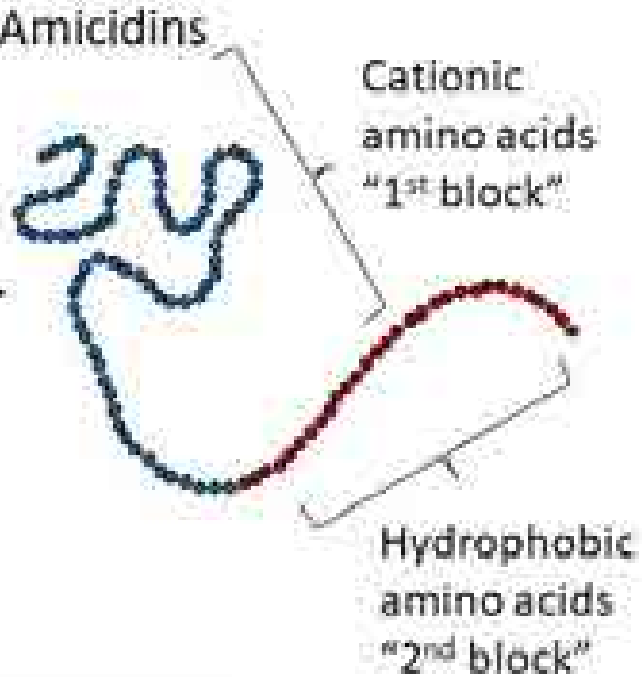
Manufactured with robust polymer methods

Scalable, cost-effective



One-pot polymerization

1. 1st Monomer
2. Initiator
3. Solvent
4. 2nd Monomer



To enable metric ton production

Broadly microbicidal against key pathogens

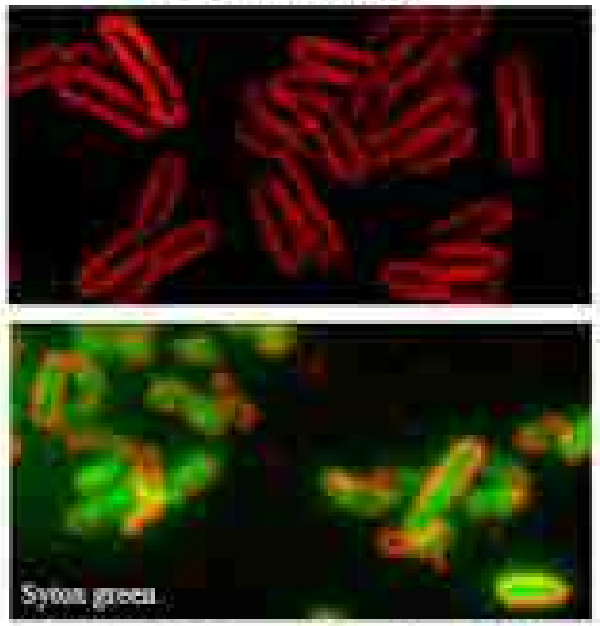
99.9-99.999% killing in 1 hr at 10-100 µg/mL

Partial List

S. aureus (incl. **MRSA**)
S. epidermidis
Vancomycin-resistant *E. faecium*
S. pyogenes
A. baumannii (incl. **Pan-resistant**)
P. aeruginosa (incl. **multidrug-resistant**)
E. coli (incl. **ESBL+**)
K. pneumoniae (incl. **KPC, ESBL+; CRE**)
P. mirabilis
MDR *B. fragilis*
C. albicans (incl. fluconazole-resistant)

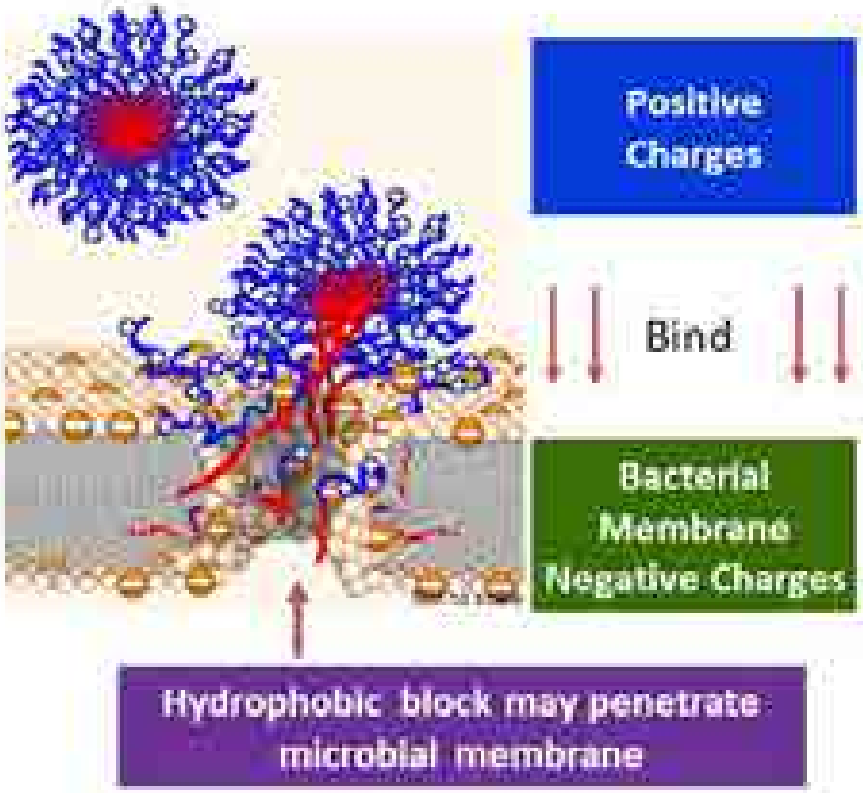
Bold = CDC 2013 Threats
MDR= multidrug resistant
CRE = carbapenem-resistant Enterobacteriaceae

*P. aeruginosa**



10 min; 100 µg/mL Amicidin-β

Microbicidal Action



Rapid multi-modal mechanism conserved in evolution; resistance unlikely

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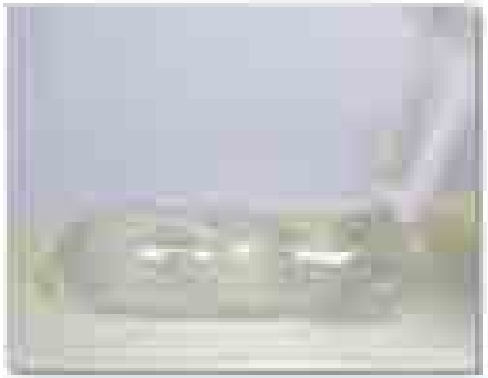
*Performed by Linnaeus Bioscience

PREVENT

Amicidin-α
Surgical Gel

"Active" microbicidal barrier

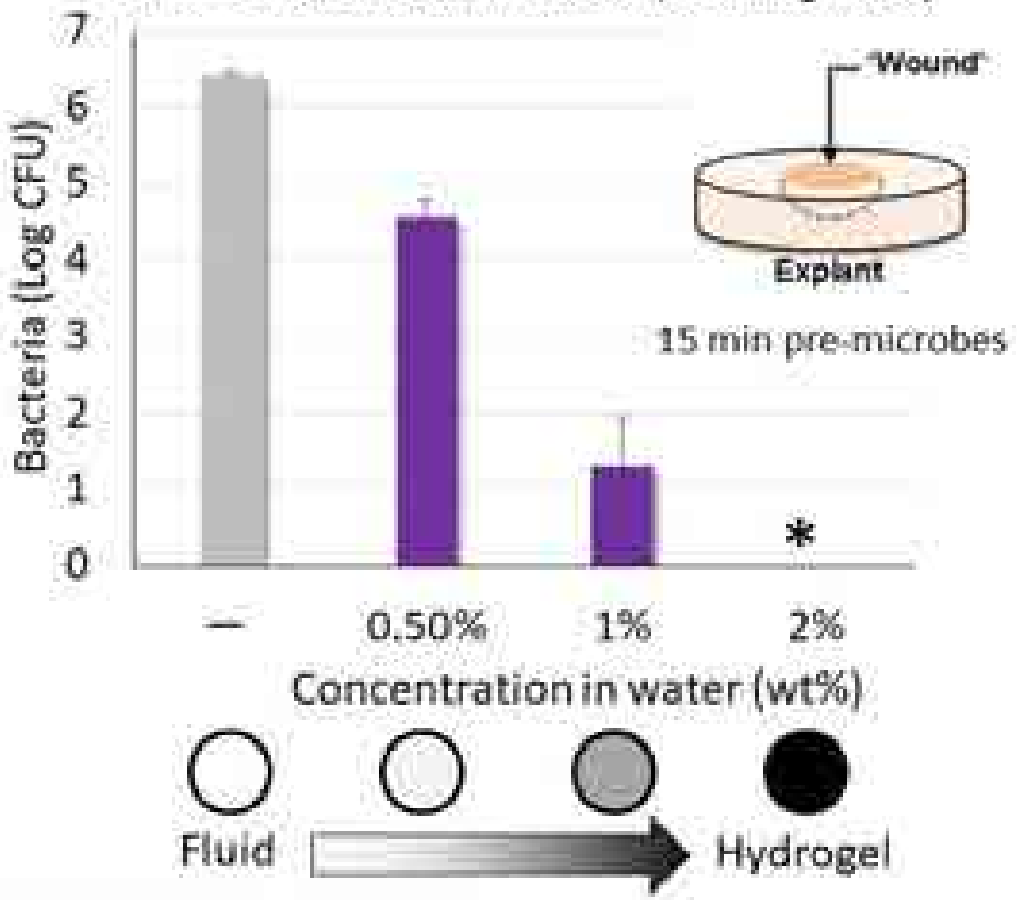
Intraoperative use to reduce incidence of surgical site infections



Key qualities:

1. Broad & rapid microbicidal activity
2. Tissue-coating, barrier properties
3. Shear-thinning for easy application & spreading
4. Transparency for visualization of coated tissues
5. Bioresorbability & easy removal by irrigation

***Ex vivo* Porcine Skin Model** *(P. aeruginosa)*



To prevent microbial contamination and block progression

AMICROBE

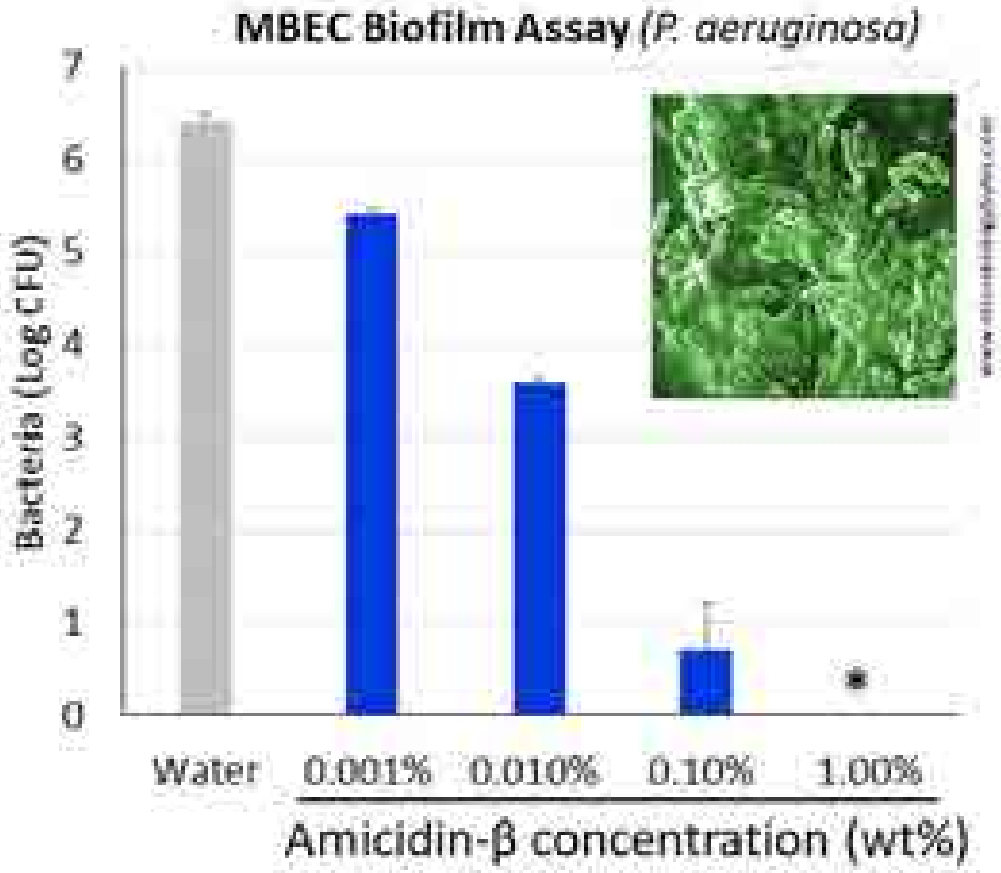
* = no microbes detected

TREAT

Amicidin-β Solution

Potent microbicidal solution (with surfactant activity)

Intraoperative and post-operative treatment of contaminated and infected wounds



Key qualities:

1. Broad & rapid microbicidal activity
2. Enhanced anti-biofilm activity & tissue debridement
3. Bioresorbability & easy removal by irrigation

To treat microbial contamination / local infections and block progression

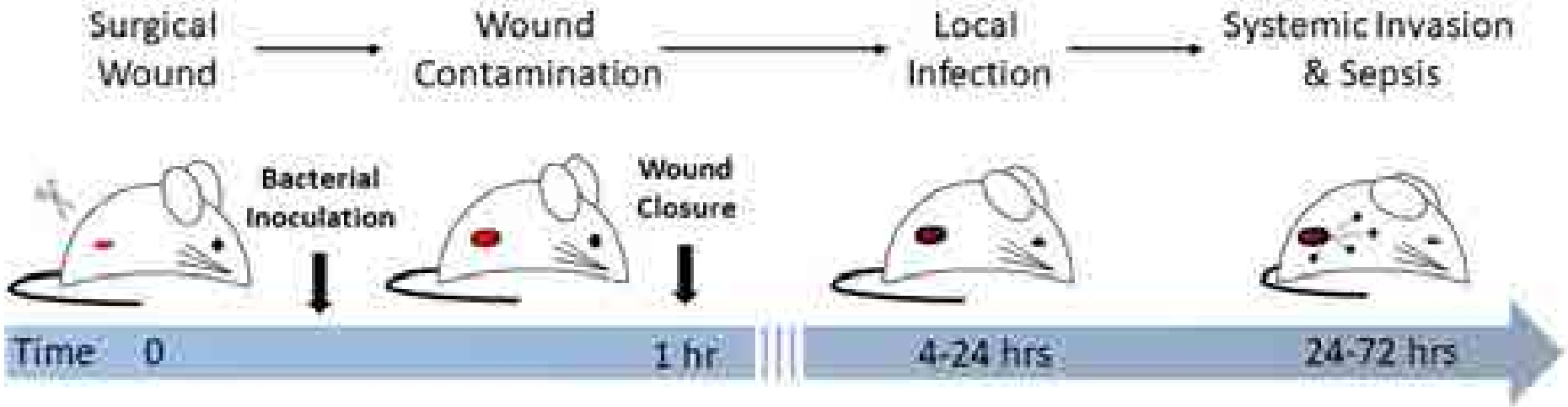
AMICROBE

* = no microbes detected

Interrupting the progression of infection

Rodent deep tissue orthopedic model with MRSA & P. aeruginosa

University of Cincinnati
DoD W81XWH-15-2-0065



- Incision made, femur exposed, stainless steel suture placed around bone
- Wounds inoculated for 15min, followed by saline rinse; closed at 1 hr
- Assessments include microbial counts, tissue histology, and physical exam

Progression depends on microbial number & virulence

PROVENT

Amicidin-α
Surgical Gel

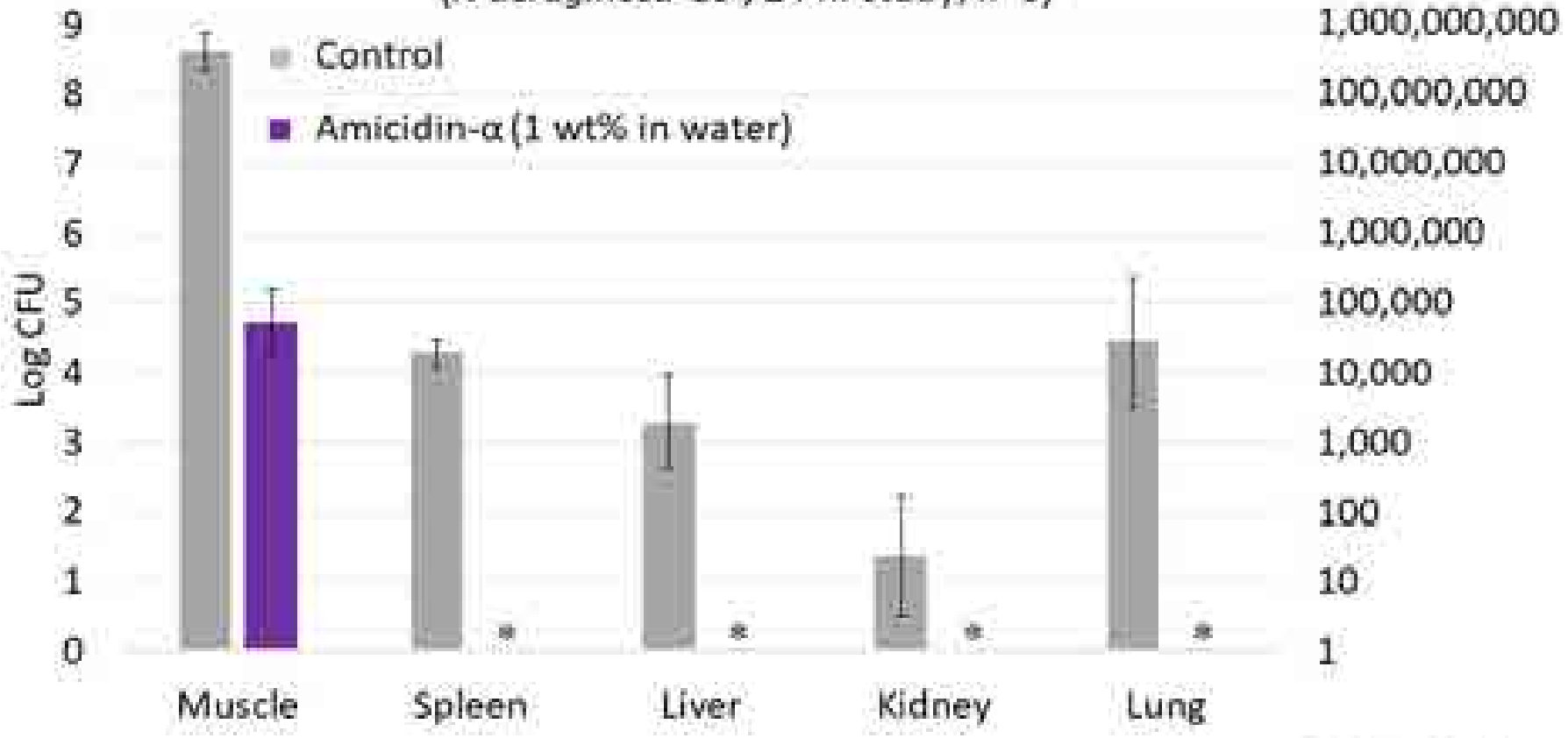
Limits contamination and blocks progression

Applied intraoperatively (post-incision and pre-closure)

University of Cincinnati
DoD W81XWH-15-2-0065

Rodent Deep Tissue Orthopedic Model

(*P. aeruginosa* 10^7; 24 hr study; n=6)



*= No microbes detected

AMICROBE

TREAT

Amicidin-β Solution

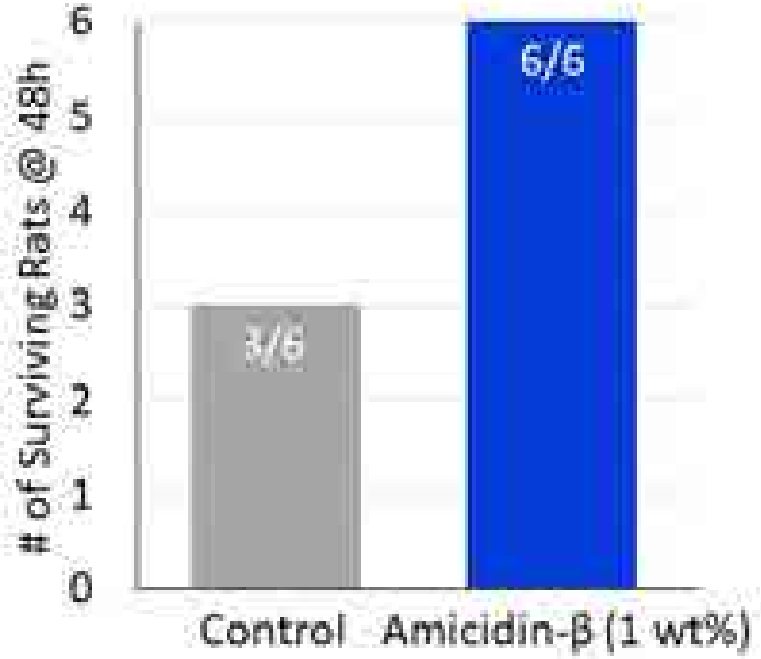
Treats contaminated / infected wounds

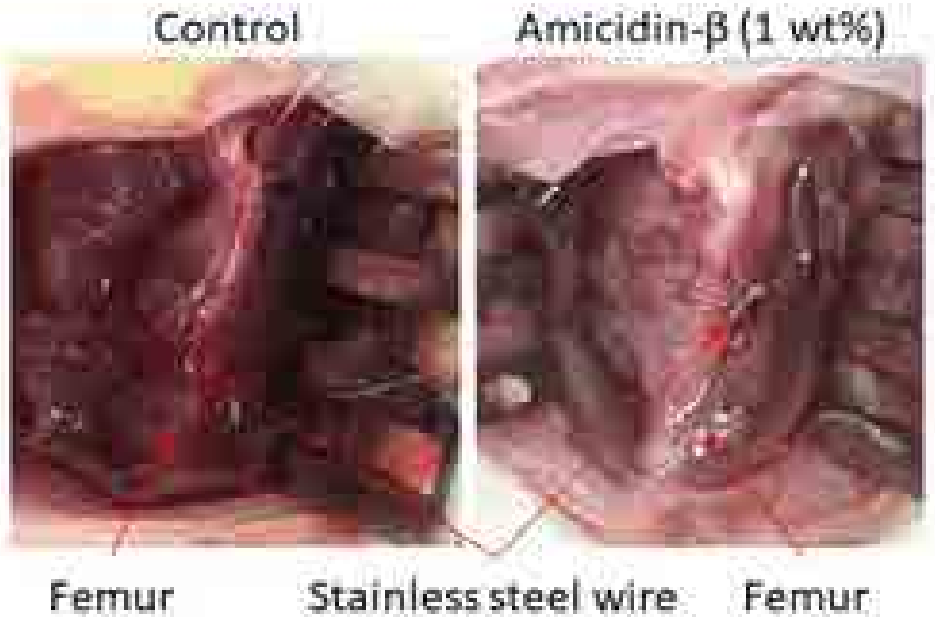
Applied post-contamination (intraoperatively and post-operatively)

University of Cincinnati
DoD W81XWH-15-2-0065

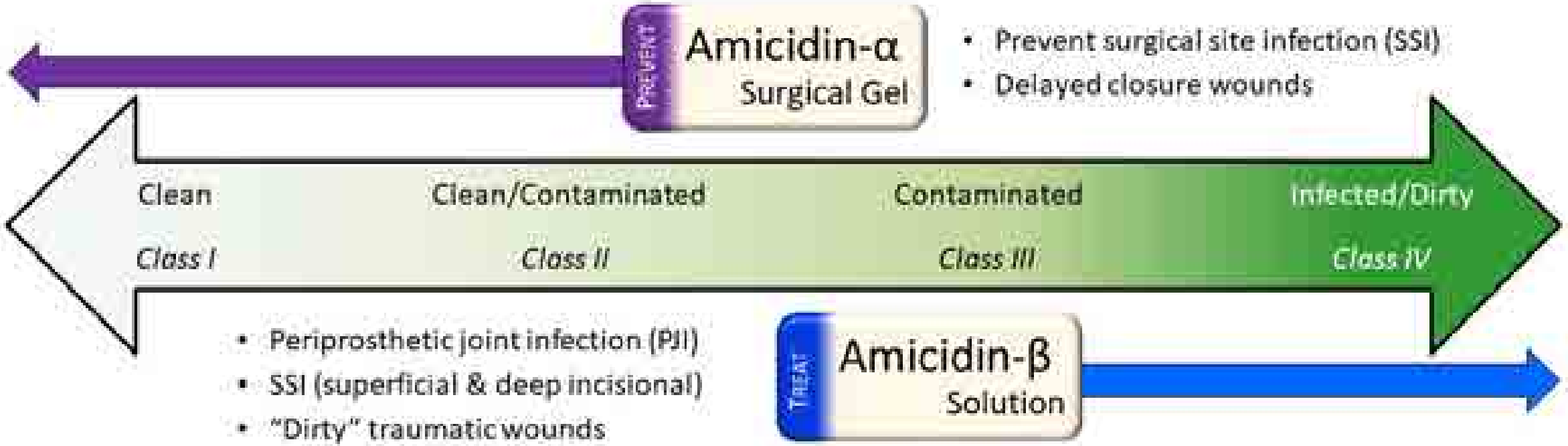
Rodent Deep Tissue Orthopedic Model

(*P. aeruginosa* 10^7; 48 hr study; n=6)





Purpose-built antimicrobials for surgery & trauma



To prevent and treat life-threatening infections

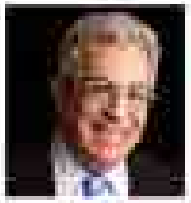
Amicrobe Senior Team

Michael P. Bevilacqua, M.D., Ph.D., *Founder, CSO, and CEO*

- Brigham and Women's Hospital, Harvard Medical & UCSD Medical Faculty
- Pew Scholar; Howard Hughes investigator
- Amgen Vice President; start-up experience

Timothy J. Deming, Ph.D., *Founder and Head of SAB*

- Prof. of Bioengineering and Chemistry, UCLA
- World-recognized leader in synthetic block copolypeptides



Joseph S. Solomkin, M.D., F.A.C.S., *Chief Medical Officer*

- Prof. of Surgery Emeritus, University of Cincinnati
- WHO & CDC task force member for surgical site infection prevention

Doug L. Looker, Ph.D., *VP, Preclinical Development & Manufacturing*

- 20+ years in large & small molecule manufacturing & development
- Substantial FDA experience, including five INDs and one NDA

Daniel J. Huang, *Vice President of Operations*

- Project and data management expertise; operations and finance
- Government contract negotiation and administration

Thank you again to the DoD and CARB-X

Topics for discussion

Clinical trial design to enable use in a broad range of surgical and trauma settings

Importance of surrogate markers in prevention studies

Session 4

Panel Discussion &
Audience Q&A

E-Mail Questions to

Duke.Abx@Duke.edu

@DukeMargolis

Session 5: Wrap-up panel to discuss remaining needs and next steps

E-Mail Questions to

Duke.Abx@Duke.edu

@DukeMargolis

Understanding the Development Challenges Associated with Emerging Non-Traditional Antibiotics

Duke-Margolis Center for Health Policy

JW Marriott • Washington, DC
June 14, 2018