

Clinical trial designs for non-traditional antibiotics

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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 $X \approx Y$
 - 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 CRE¹

- In 2012-13, colistin was the only alternative for CRE. A study of plazomicin vs. colistin-based SOC² 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**

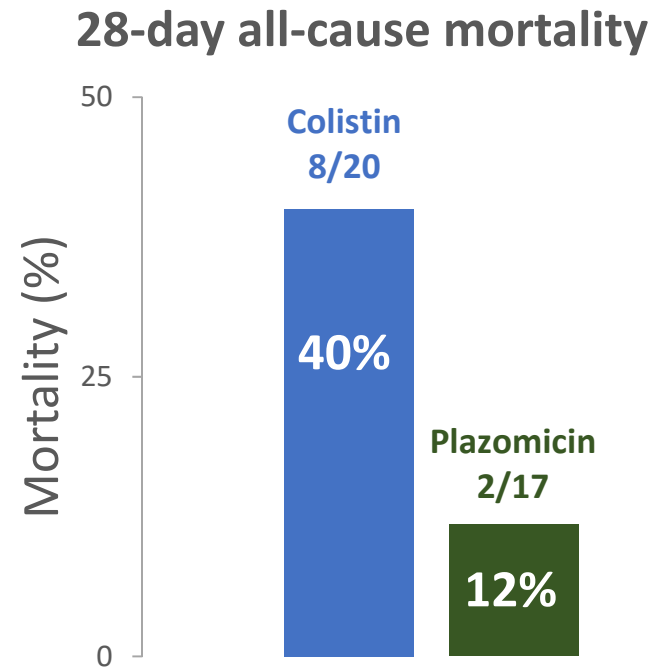


Figure adapted from slide 24 the Jan 2017 Achaogen corporate presentation. Downloaded 24 Feb 2017 from <http://files.shareholder.com/downloads/AMDA-2JY46Z/3956962155x0x922829/80C50E00-4B27-4F84-B13F-55DE31AABA28/AKAO-Corporate-Deck-January-2017.pdf>

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	<i>Yes</i>
2. Placebo is routinely acceptable	Yes	<i>No</i>	<i>No</i>
3. Transmissible resistance arises → new agents always needed	No	No	<i>Yes</i>
4. New agents are really for use...	Today	Today	<i>Tomorrow¹</i>

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-fight-superbugs/>).

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 **sndrome** 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

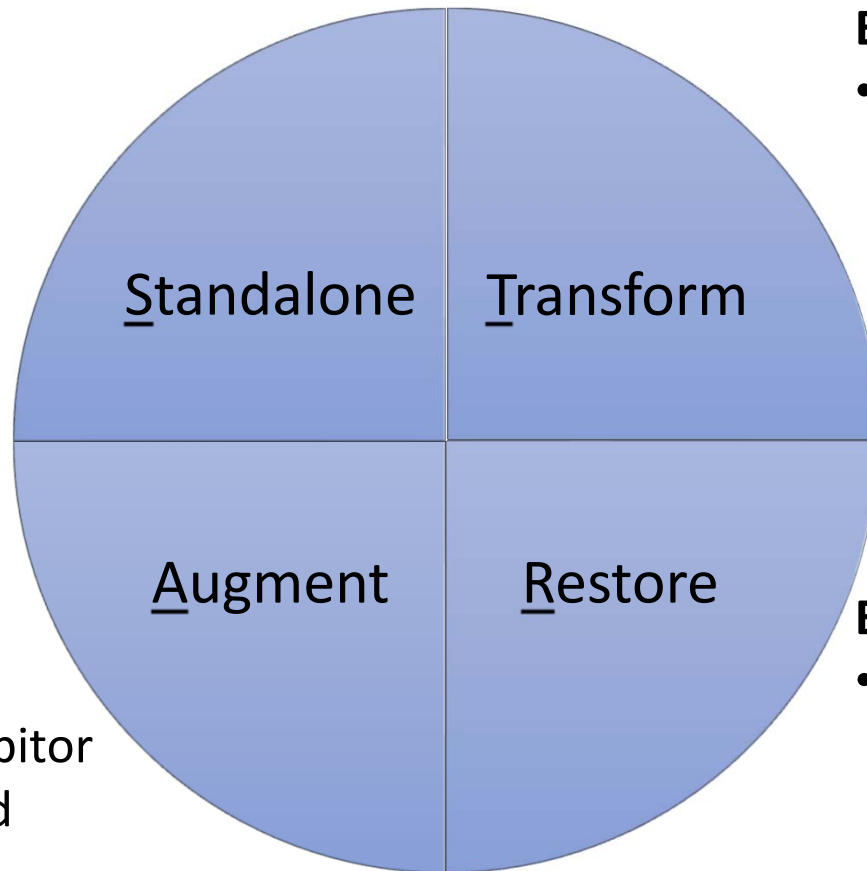
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STAR: Four treatment archetypes¹

Examples

- Phage
- Lysins
- Antisense



Example²

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

Example²

- Virulence factor inhibitor + approved antibiotic

Example²

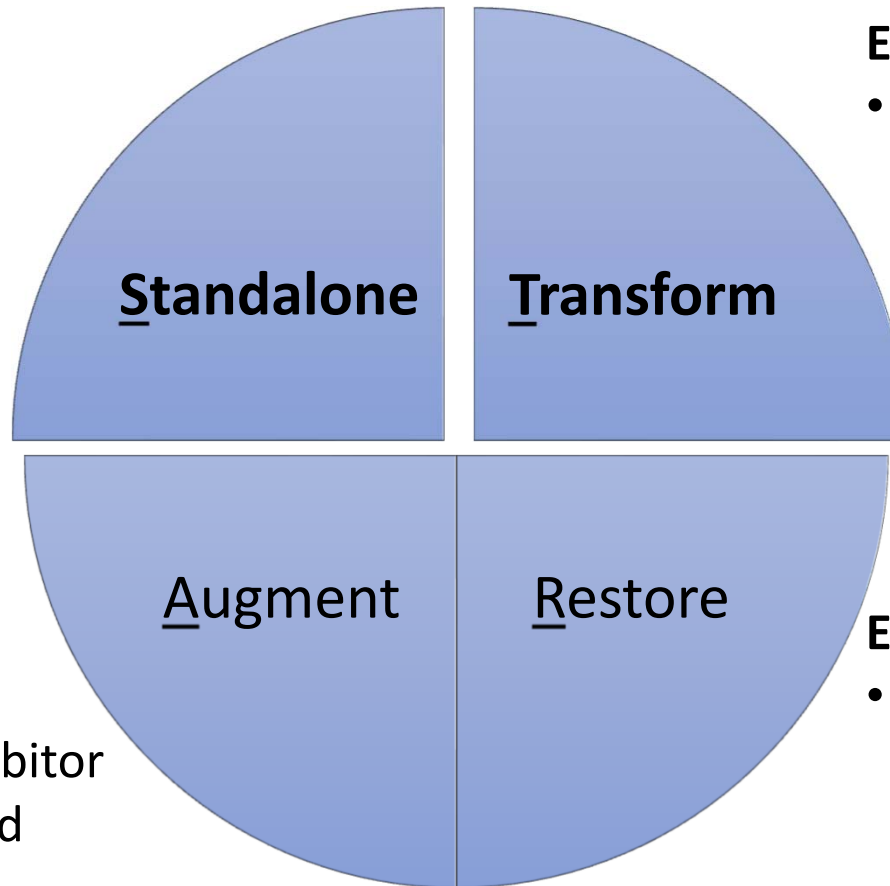
- BL-BLI (Beta-lactam beta-lactamase inhibitor) combinations

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

Examples

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- Lysins
- Antisense



Example*

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

Example*

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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, 2018-06-14 - Rex-Outterson - Duke-Margolis - Non-traditional antibiotic intro 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: ertapenem¹ 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

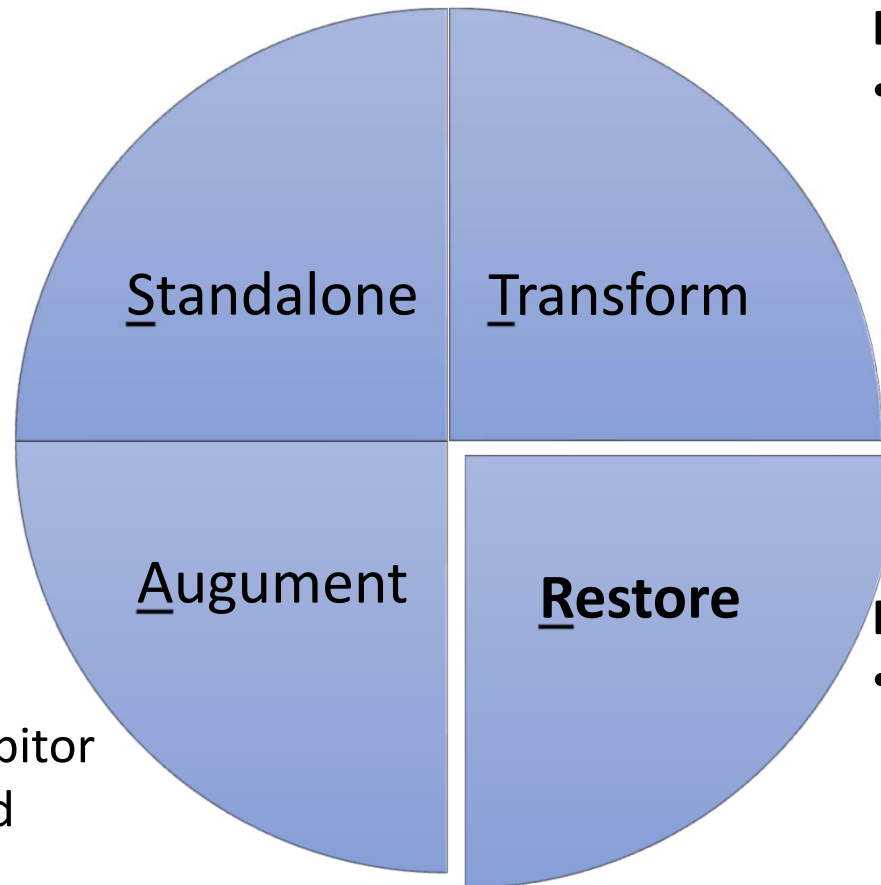
(Not Fully) Standalone problem

- 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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Example*

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

Example*

- Virulence factor inhibitor + approved antibiotic

Example*

- BL-BLI (Beta-lactam beta-lactamase inhibitor) combinations

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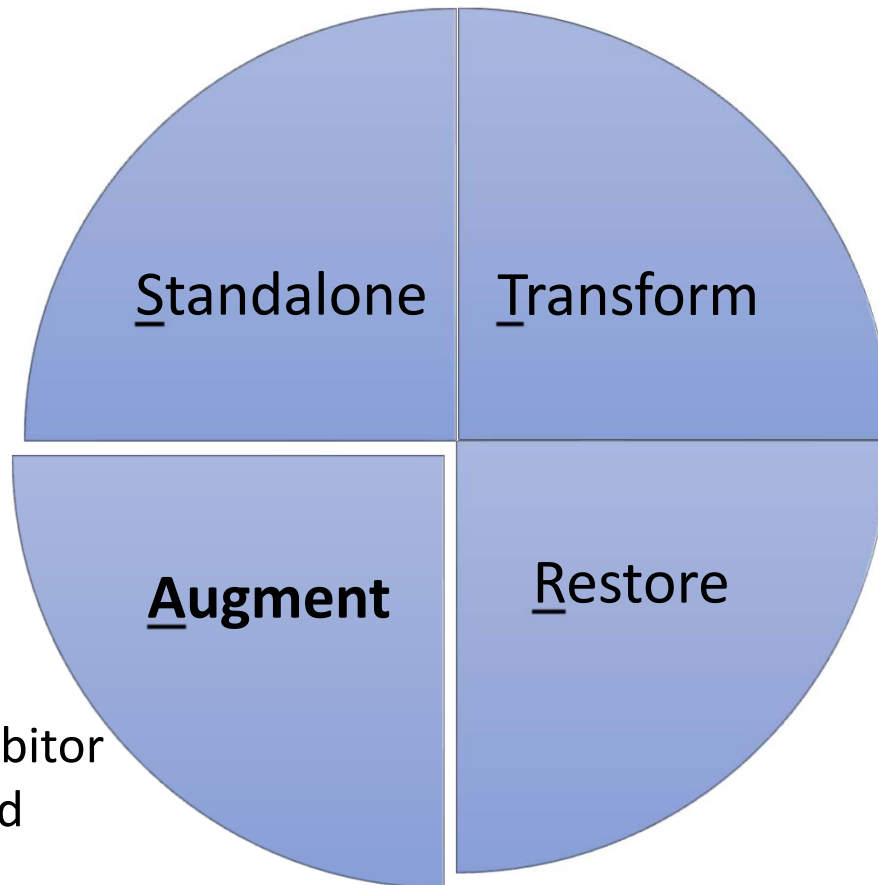
Restore an existing agent

- 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

Examples

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Example*

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Augment an existing therapy

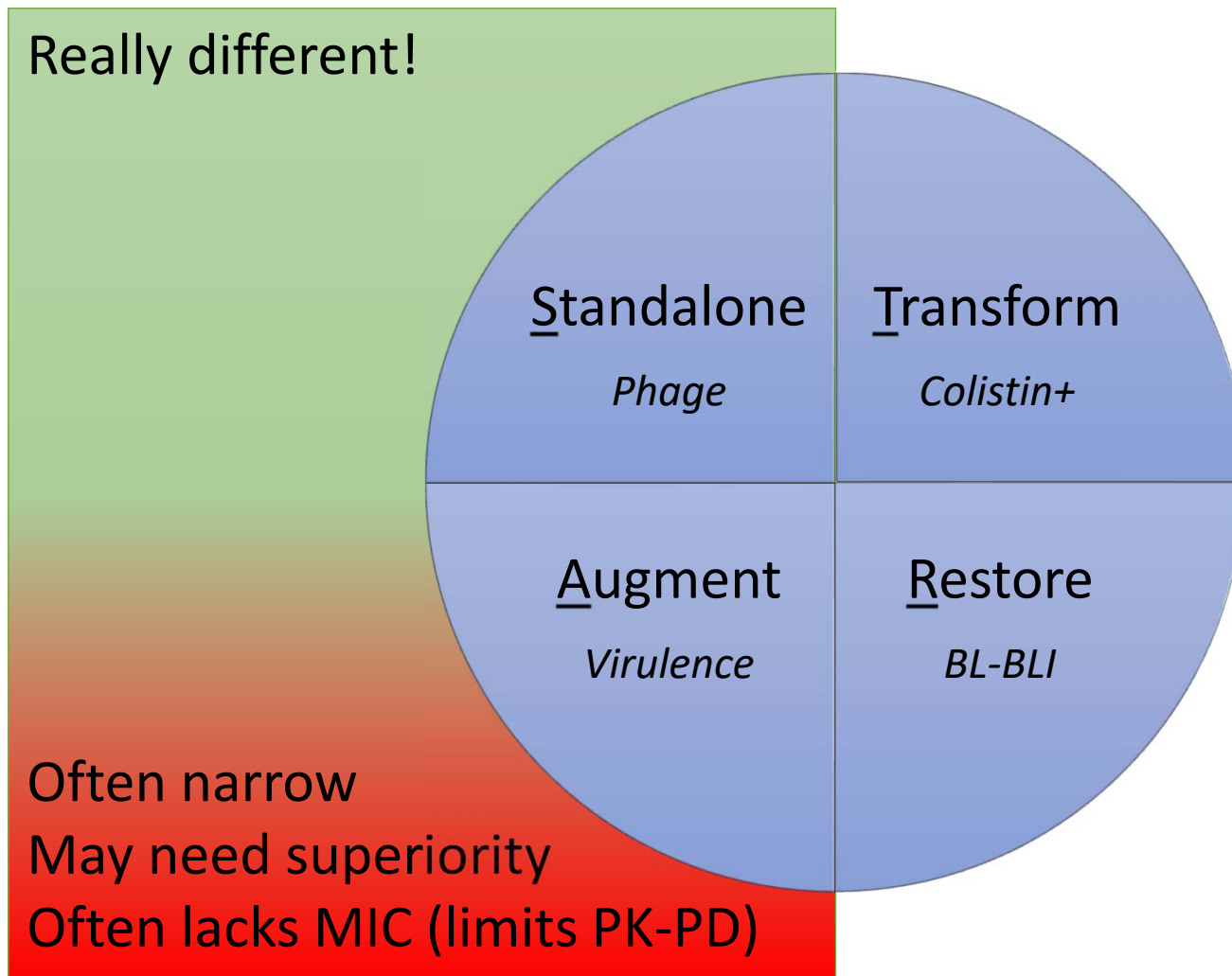
- Example: Virulence inhibitor or such
 - Usually lacks an MIC equivalent and has no discernible in vitro effect on the base therapy in the laboratory
 - Not sufficient alone: Must also give an active antibacterial (e.g., toxin inhibitor + a Fleming antibiotic)
- Distinctive hurdles
 - **Base therapy 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?

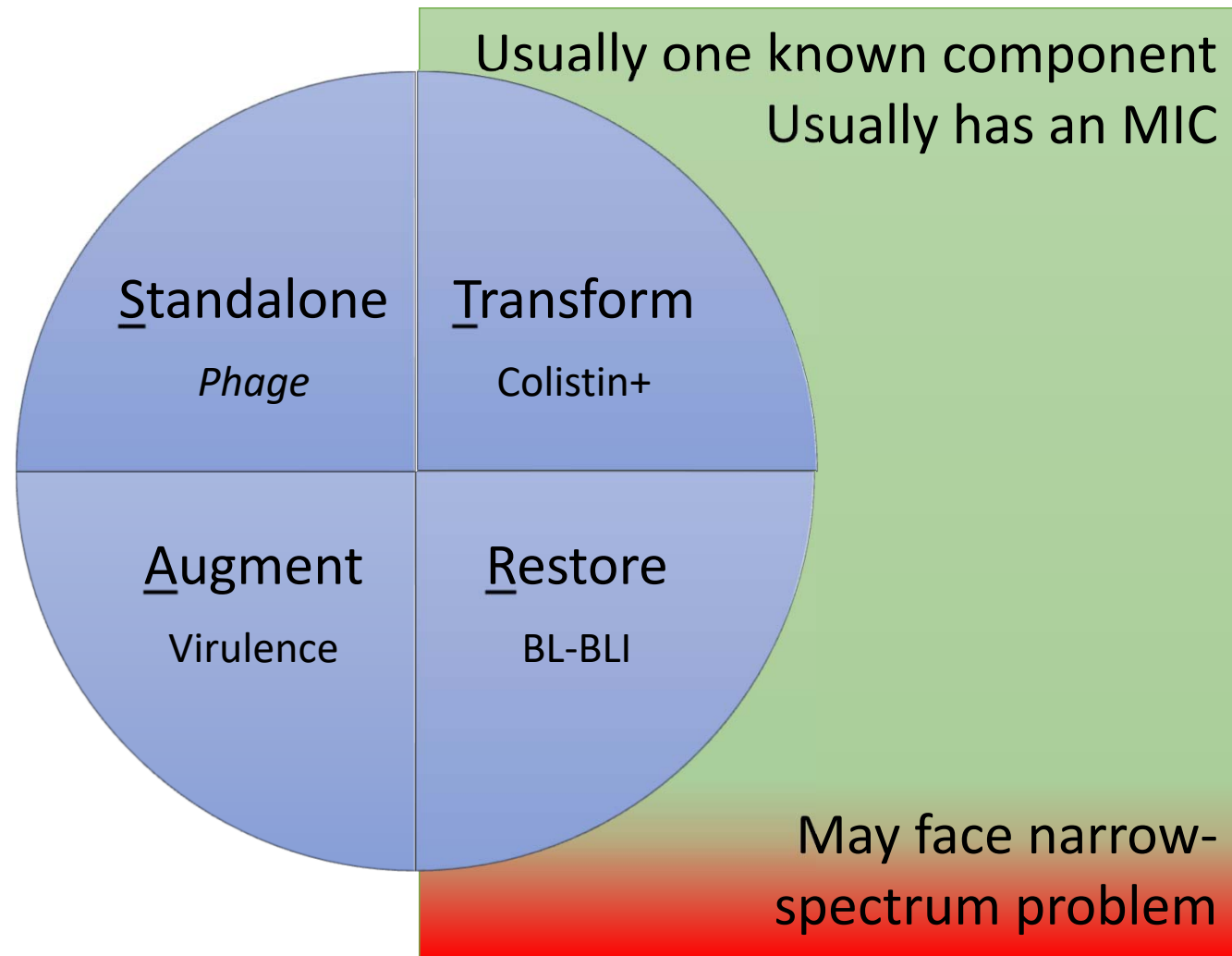
Comparing the four archetypes

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!

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 $\geq 70\%$ 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)

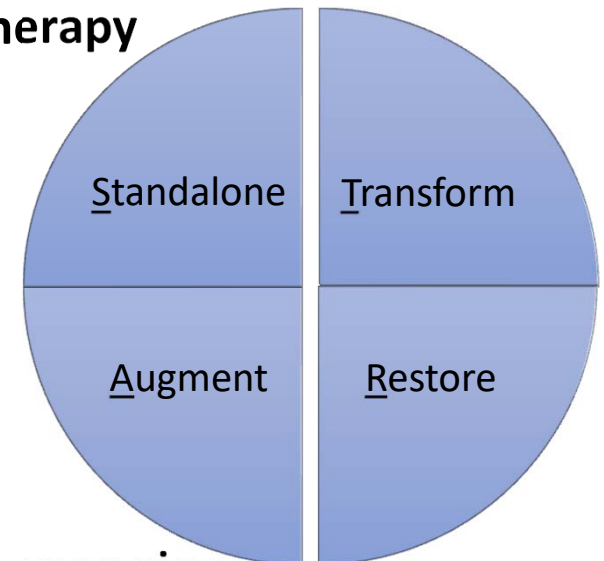
- So ... can we generalize to hips, knees, and so forth?
- FDA briefing book comment
 - As “... rates of invasive *S. aureus* disease across other elective orthopedic surgical populations are ... ~0.25% to ~0.5% within 90 days of surgery ...”
 - “... conducting a randomized, placebo-controlled clinical 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

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Perspective summary

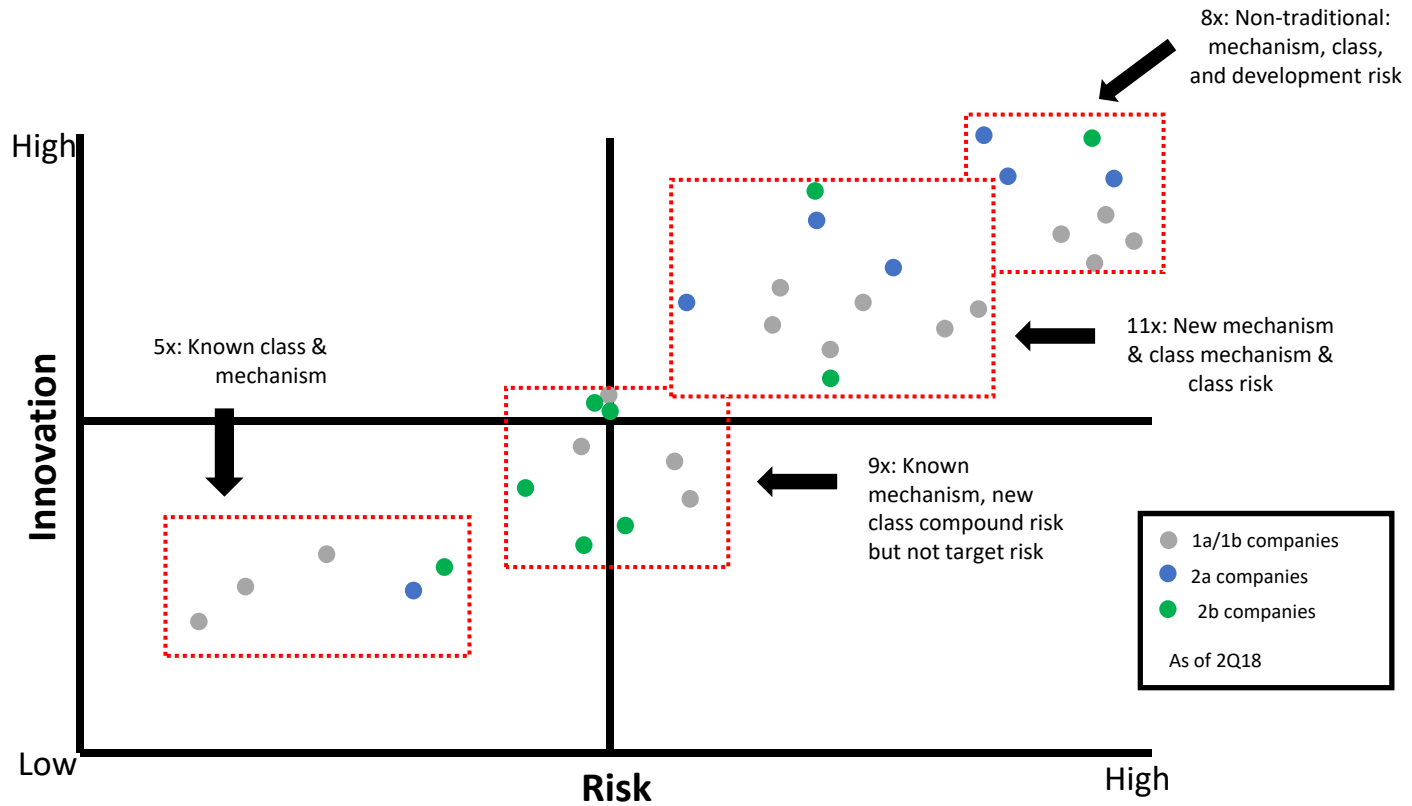
- Fleming: We generally know how to develop these
 - SSSS: Spectrum for a syndrome, speed of sole therapy
- Outside this zone: Non-Fleming
 - Standalone & Augment: Often VERY hard (superiority often needed)
 - Restore & Transform: Easier but not easy. Narrow-spectrum issue can be a challenge
 - Prevent: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

Additional (bad) news...

- FDA approval \neq 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-trationals

- 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.

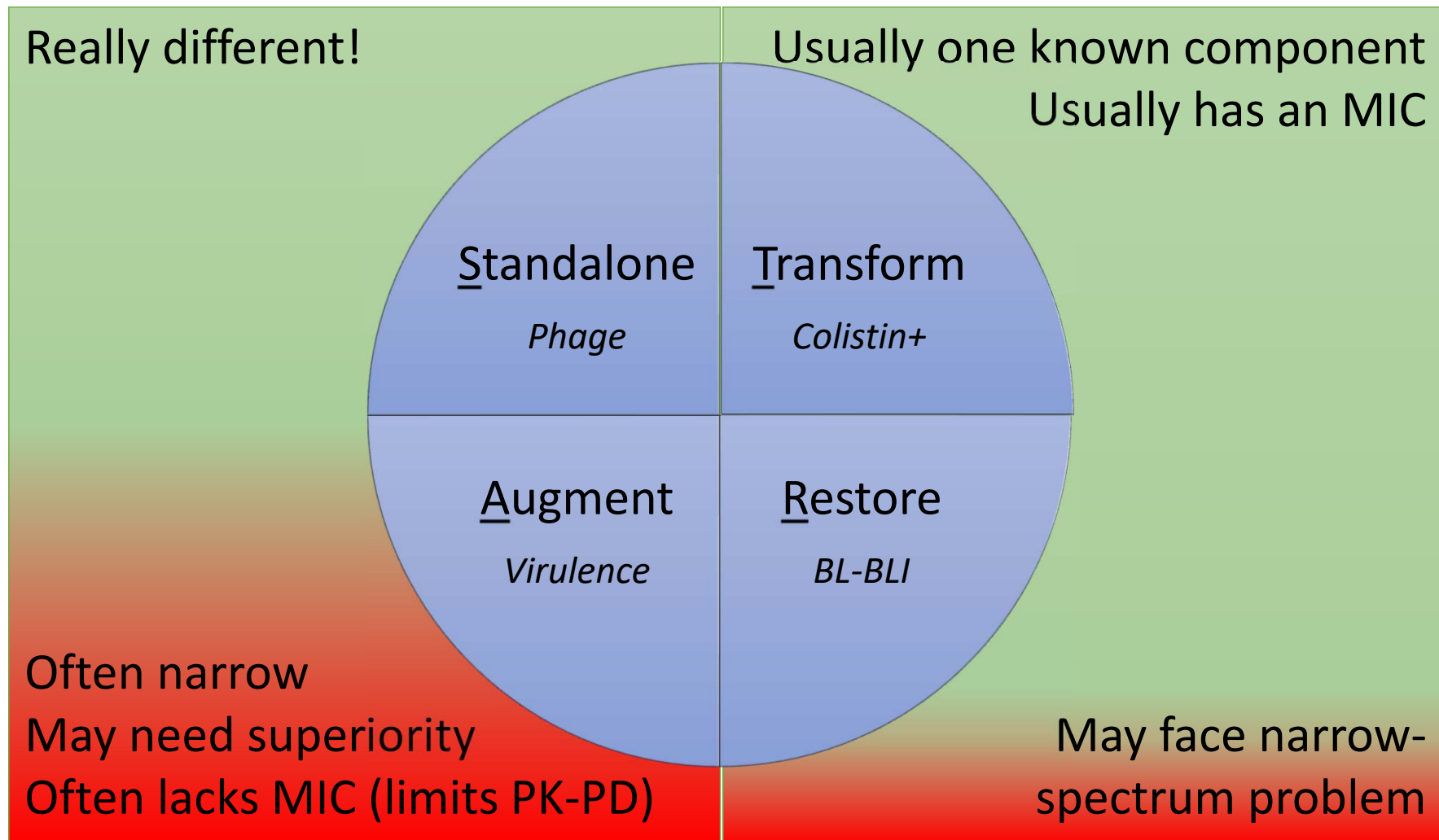
Animal Health Literature

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>

STAR: Four archetypes defining common development challenges

Thank you!
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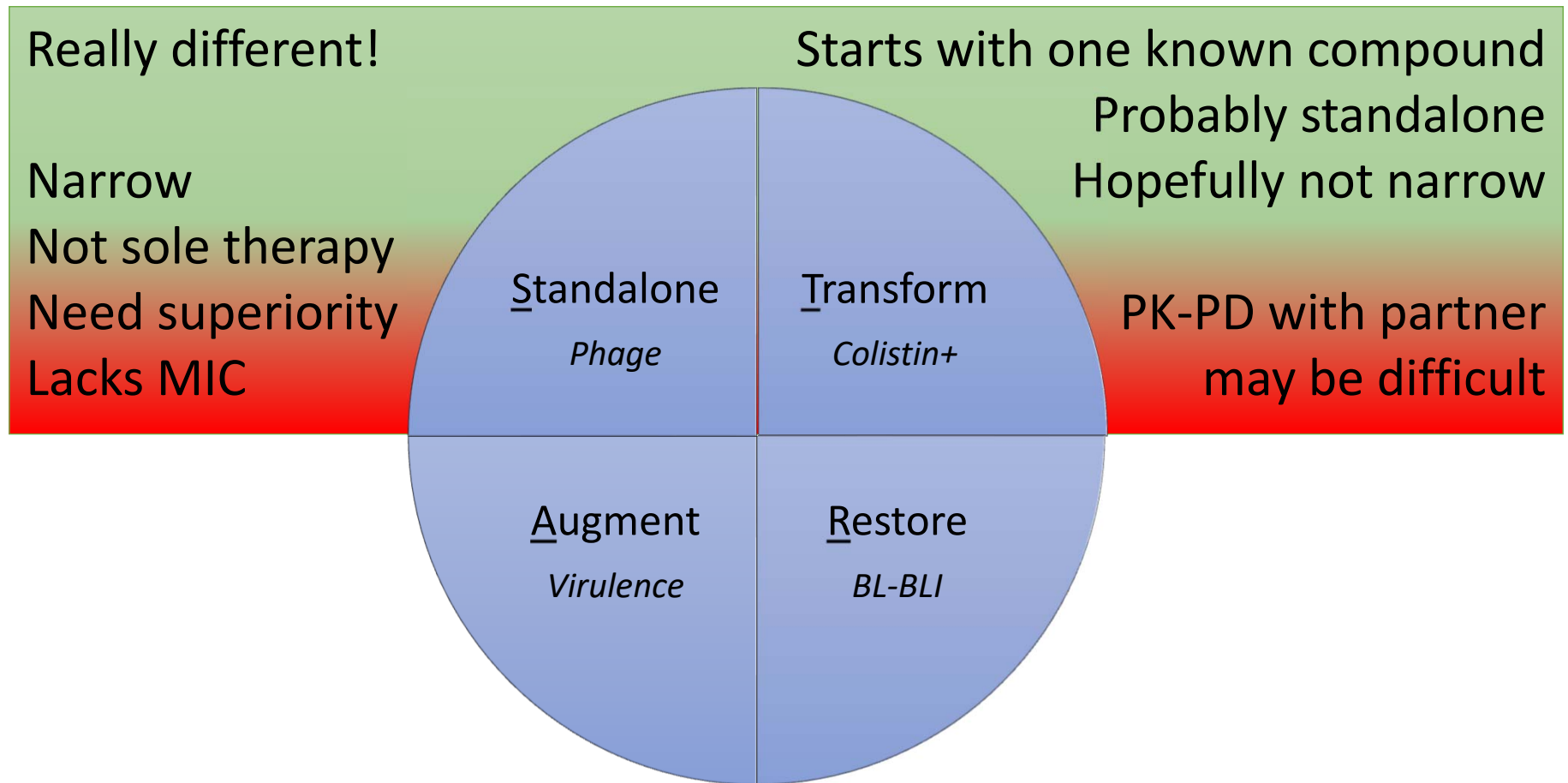


Thank you!

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Treatment: Four archetypes



Treatment: Four archetypes

