Development of Non-Traditional Therapies for Bacterial Infections

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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

• The conversations today & tomorrow are 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 problems are deep science questions 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

• The core problem of showing value

• What is a non-traditional (NT) product?
  • Structure vs. Goal

• Potentiators & Enhancers
  • Will diagnostics fix the problem?

• NT Goals

• Why this matters to CARB-X

• Summary
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 create a substantial hurdle
  • Superiority is (usually) out of reach
  • Non-inferiority studies are relatively unsatisfying to payers

• **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.
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 (still) highly effective
  • Must NOT enroll if known to be 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

• NI studies do not capture all of the value to society
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What is a non-traditional (NT)?

• This question has made our heads hurt!
  • Our best answer to date reduces to two categories

• T vs. NT Structure:
  • (T)ypical small molecule \textit{vs.}
  • NT structure: Phage, lysins, monoclonals, charcoal

• T vs. NT Goal:
  • (T)reatment or prevention of a standard infection \textit{vs.}
  • NT goal: Other ideas such as
    • Prevention of development/acquisition of resistance
    • Improving/restoring microbiome status
NT Structure vs. Goal

• **Structure**: Development fundamentals are known
  • If the goal is treat or prevent (say) pneumonia, we have well-defined pathways for this
  • Challenges tend come from the math of small numbers: If the focus is on a rare pathogen, then the hunt for that pathogen is hard (ditto for preventing rare events)

• **Goal**: Under-explored territory
  • Consider a product (or a method of use of a combination of products) that prevents (acquisition of) resistance
  • Such an endpoint lacks an immediate clinical correlate.
  • How then do we show value to society?
    • Is it adequate to show impact just by surveillance?
    • Or, do we need to show fewer resistant infections?
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 usually find them too ambiguous to be helpful in this regulatory context
  • Careful definitions are needed when you do use them
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 we still need to show the core value of the product
  • That is, it still needs to do something useful
  • And, we have to measure that effect
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• Add-ons following this theme are often proposed:
  • Base product + (P)otentiator improves Base product

• A useful framework for such add-ons is this division
  • **Restore:** P restores Base that has lost utility
    • P is a beta-lactamase inhibitor that restores a beta-lactam
  • **Transform:** P enables Base to do something really new
    • P transforms a Gram-positive drug into a Gram-negative drug
  • **Augment:** P augments Base via an effect on the host
    • P activates an immune response system
    • Or, P inhibits a virulence mechanism
Across all these categories...

• ... standard tools generally seem to work
  • BL+BLI is now well studied, for example
  • That said, there are three specific recurring issues

• **MIC:** There can be a dose selection challenge with products that don’t have a measurable MIC
  • But, this seems like something that can be solved

• **Rare pathogen:** This can be a hard numbers game
  • Diagnostics don’t entirely fix this (next slide)
  • The need for adequate empiric therapy may complicate the challenge of showing the effect of the new product

• **Augment:** Must show an improvement on properly dosed Base therapy. This can be hard to achieve
Rare pathogens & diagnostics

• Unfortunately, diagnostics do not have the speed & efficacy of a Star Trek tricorder and hence are an incomplete answer to the diagnostic problem

• 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
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NT Goals

• All of the above presumes a standard goal of treating or preventing a standard infection
  • Most of the examples to be discussed during the workshop seem to fit here ... with a few twists & turns

• But, what if the goal is really different?
  • Perhaps the benefit is not (just) to the patient but also to the community based on reduced selection for resistance
  • You could easily imagine this on the basis of combination therapy designed to avoid selection of R
    • In long-term TB therapy, avoiding selection of R ensures that the therapy works
    • In short-term treatment of (say) an STD, avoiding selection of R may have no measurable benefit to the patient being treated

• One of the case studies explores this theme
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CARB-X mission & scope

• Invest >$500M over 5 years
  • Focused on priority drug-resistant bacteria
  • Agnostic on modality: therapeutics, diagnostics, prevention
• Goal is to reduce the human health impact from drug-resistant bacteria
• Both traditional and non-traditional products
  • Mostly NT products rather than NT goals
  • See next slide...
CARB-X Therapeutics Portfolio: Innovation and Risk Analysis

- **5x:** Known class & mechanism
- **8x:** Non-traditional: mechanism, class, and development risk
- **9x:** Known mechanism, new class compound risk but not target risk
- **11x:** New mechanism & class mechanism & class risk

As of 2Q18

- 1a/1b companies
- 2a companies
- 2b companies

As of 2Q18
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:
  - Population-level clinical benefits (clinically relevant reductions in resistance or carriage)
  - Cf. HPV (reduction in carriage, plus reduction in clinically relevant intermediate stages)
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) could solve most of these problems but do not yet exist
A Tale of Two Compounds

**Patisiran: Alnylam**
- Fast Track, Priority, Breakthrough
- Polyneuropathy caused by hereditary transthyretin-mediated amyloidosis
- 225 patients randomized
- Superior to SOC
- Life enhancing
- Approved Aug. 10, 2018, skipping AdComm
- 10,000 – 15,000 US patients (total)
- Chronic (ongoing)
- Value-based payer agreements
- >$350,000 per patient, per year (net)
- Market cap: $9B

**Plazomicin: Achaogen**
- QIDP, LPAD
- Clinical and microbiological response, to specified Gram-negative bacteria
- 609 patients randomized
- NI to meropenem, Superior to colistin
- Life saving
- Approved June 26, 2018 for cUTI, but not BSI
- ~10,000-50,000 US patients/year
- Acute (cure)
- Medicare Part A DRG bundle
- $10,000 per patient (gross); NTAP cap $2722.50
- Market cap: $263M
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Summary

• Must be clear on the NT nature of the product
• If NT structure, typical demonstrations of utility are likely to be expected
  • Standard development paradigms seem appropriate
  • Several of the cases will explore whether this is correct
• The idea of NT goals is, however, less well-explored
  • The only obvious examples of this to us are centered on preventing creation or acquisition of resistance
  • One of the cases has this theme
• Exploring, refuting, and expanding on these ideas is of value to the R&D community. We hope the debate today & tomorrow achieves these goals
Thank you!

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