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 *vs.*
  - NT structure: Phage, lysins, monoclonals, charcoal
- T vs. NT Goal:
  - (T)reatment or prevention of a standard infection *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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(NT) Potentiators & Enhancers

- 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
  - **R**estore: P restores Base that has lost utility
    - P is a beta-lactamase inhibitor that restores a beta-lactam
  - **T**ransform: P enables Base to do something really new
    - P transforms a Gram-positive drug into a Gram-negative drug
  - **A**ugment: 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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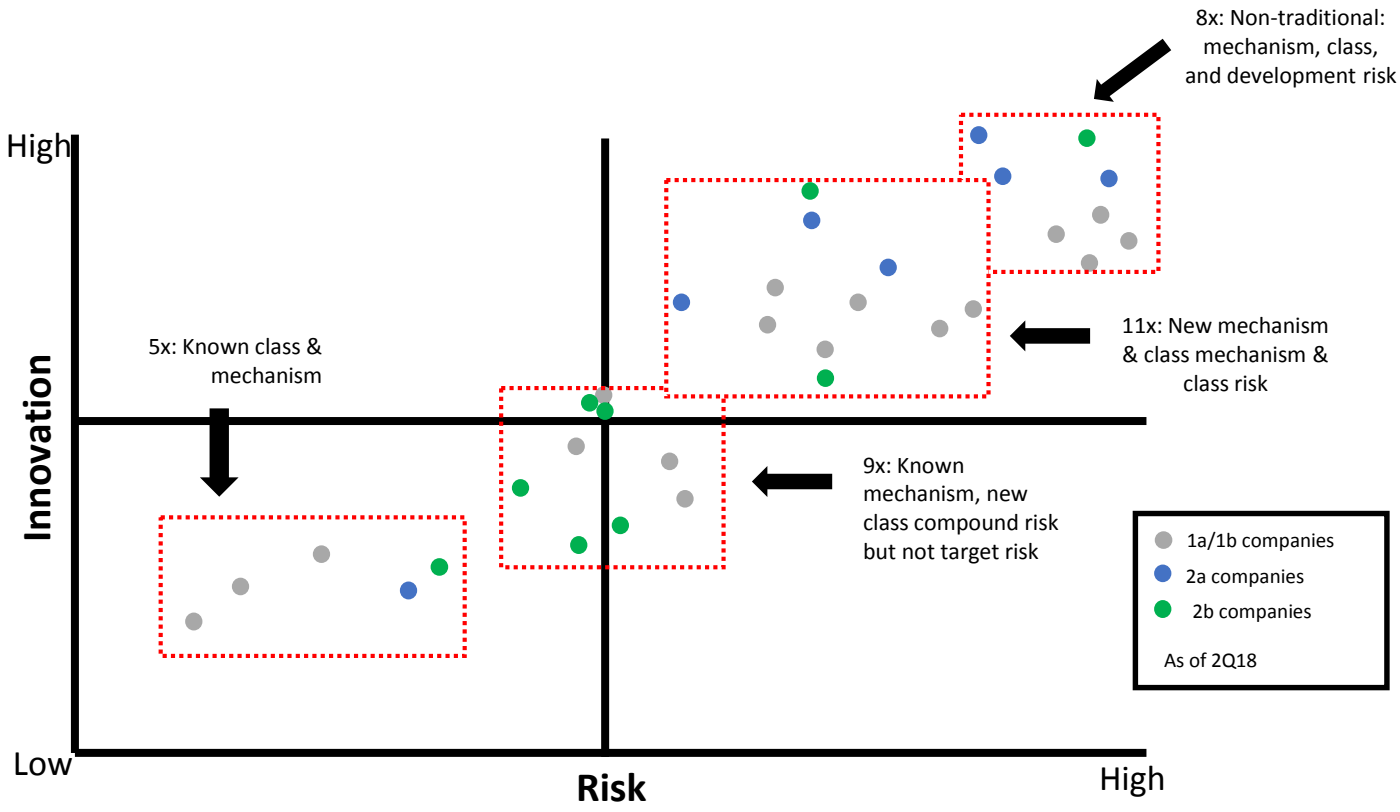
CARB-X mission & scope

- 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



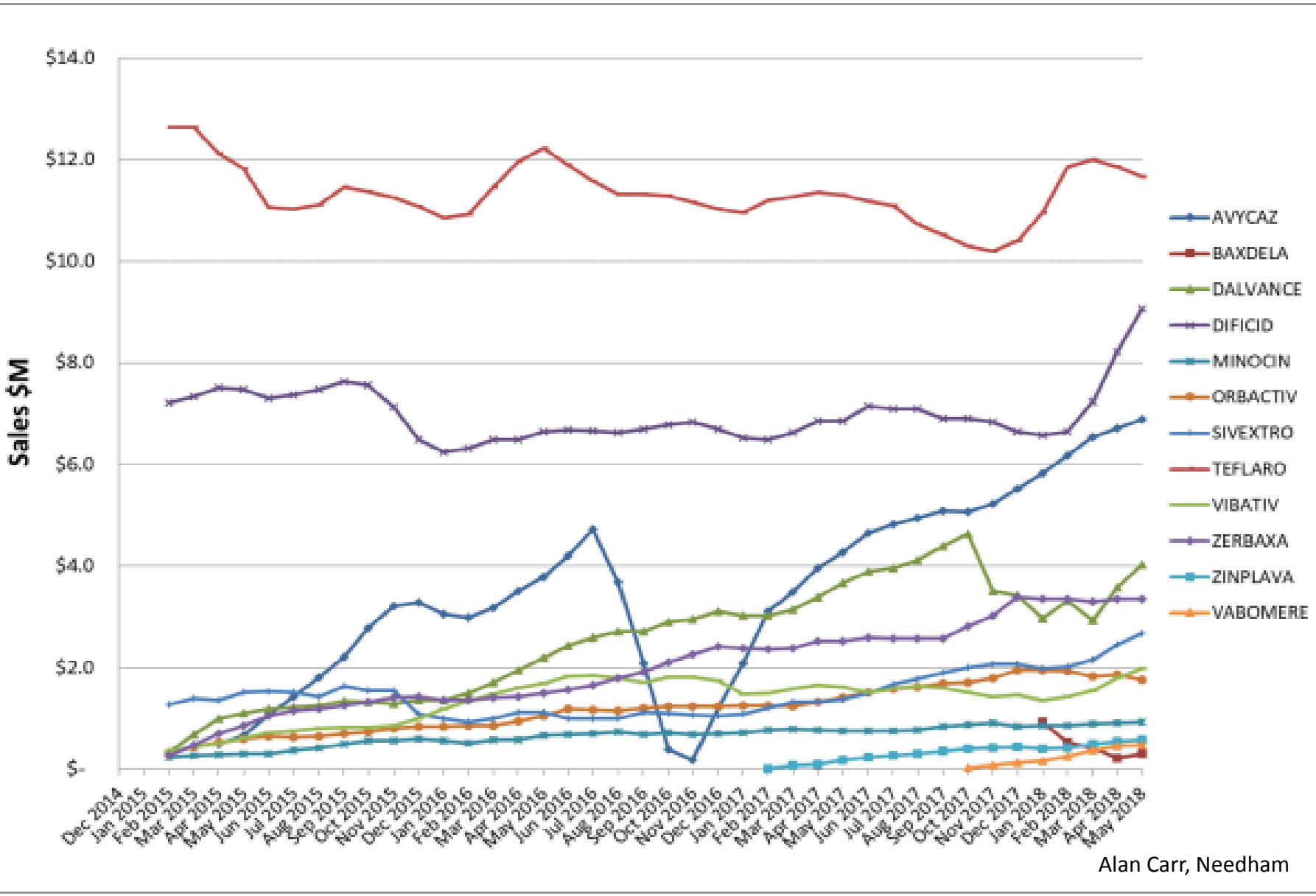
CARB-X role in today's workshop

- 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

IMS Monthly Sales Data: Antibiotics (3-Month Moving Average; FDA approvals since 2009)



Alan Carr, Needham

A Tale of Two Compounds

Patisiran: Alnylam	***Plazomicin: Achaogen***
• Fast Track, Priority, Breakthrough	• QIDP, LPAD
• Polyneuropathy caused by hereditary transthyretin-mediated amyloidosis	• Clinical and microbiological response, to specified Gram-negative bacteria
• 225 patients randomized	• 609 patients randomized
• Superior to SOC	• NI to meropenem, Superior to colistin
• Life enhancing	• Life saving
• Approved Aug. 10, 2018, skipping AdComm	• Approved June 26, 2018 for cUTI, but not BSI
• 10,000 – 15,000 US patients (total)	• ~10,000-50,000 US patients/year
• Chronic (ongoing)	• Acute (cure)
• Value-based payer agreements	• Medicare Part A DRG bundle
• >$350,000 per patient, per year (net)	• $10,000 per patient (gross); NTAP cap $2722.50
• Market cap: $9B	• 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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