Challenges of developing narrow-spectrum and adjunctive therapies

John F. Tomayko, MD
Chief Medical Officer, Spero Therapeutics
jtomayko@sperotherapeutics.com

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Disclosures

- Employed by Spero Therapeutics, Cambridge, MA
- Shareholder GlaxoSmithKline

The opinions expressed in this presentation are my own and are not necessarily shared by Spero Therapeutics or my industry colleagues.
Agenda

• Past, Present, and Future

• Review of the Case Study

• Where we must go

• Conclusions
# History of Antibiotic Discovery and Approval

<table>
<thead>
<tr>
<th>Year Introduced</th>
<th>Class of Drug</th>
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<tbody>
<tr>
<td>1935</td>
<td>Sulfonamides</td>
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<tr>
<td>1941</td>
<td>Penicillins</td>
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<tr>
<td>1944</td>
<td>Aminoglycosides</td>
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<tr>
<td>1945</td>
<td>Cephalosporins</td>
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<tr>
<td>1949</td>
<td>Chloramphenicol</td>
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<tr>
<td>1950</td>
<td>Tetracyclines</td>
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<tr>
<td>1952</td>
<td>Macrolides/ Lincosamides/ Streptogramins</td>
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<tr>
<td>1956</td>
<td>Glycopeptides</td>
</tr>
<tr>
<td>1957</td>
<td>Rifamycins</td>
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<tr>
<td>1959</td>
<td>Nitroimidazoles</td>
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<tr>
<td>1962</td>
<td>Quinolones</td>
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<tr>
<td>1968</td>
<td>Trimethoprim</td>
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<tr>
<td>2000</td>
<td>Oxazolidinones</td>
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<tr>
<td>2003</td>
<td>Lipopeptides</td>
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Last Novel Class of Gram-Negatives: 2003

### Near-term Pipeline*

**Gram-negative infection**
- **Bla-inhibitor combinations**
  - Rempex/MedCo– Carbavance
  - Merck-- Imipenem/ Relebactam
- **Tetracyclines**
  - Tetraphase-- Evarvacycline
- **Aminoglycosides**
  - Achaogen-- Plazomicin
- **Siderophore Cephalosporins**
  - Shionogi-- S-649266

**Gram-positive infection**
- **Ketolides**
  - Cempra– Solithromycin
- **Tetracyclines**
  - Paratek-- Omadacycline
- **Pleuromutilins**
  - Nabriva-- Lefamulin

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*For a complete list see:
“The not so distant Future”

Novel science advances against “threat” organisms/ infections

- **Potentiators of an antibiotic**
  - Facilitating access through the GNR outer membrane, inhibitors of efflux pumps, novel beta-lactamase inhibitors

- **Single pathogen antimicrobials**, e.g. *Pseudomonas aeruginosa* only
  - e.g., Mab, small molecules, peptides, lysins, etc.

- **Therapies that modify pathogen virulence**
  - e.g., transcription regulators, antagonists of type 3 secretion systems, anti-biofilm agents, etc.

- **Novel delivery systems**
  - e.g., Liposomes, nanoparticles, aerosols, etc.

- **Therapies that modify the host response**
  - Up regulate to augment pathogen clearance
  - Down regulate to minimize inflammation and collateral damage
Antibiotic vs. Antibiotic Adjunctive Therapy

- Antibiotics are really amazing therapeutics
  - Treatment effects are huge (Placebo 30%, Treatment ~70-90%)
    - Is it really rational to expect to demonstrate an additional benefit in a clinical trial?
    - ”How much better could you be than than cured?”

- A test therapeutic must make a successful clinical equipoise argument
  - Does it appear that the test therapeutic could be as good or better than the SoC antibiotic treatment?
    - A true state of equipoise exists when one has no good basis for a choice between two or more care options
  - Fortunately there are great translational models in antibacterial research
  - Therefore most “candidate antibacterials” can conduct non-inferiority trials

- Test therapeutics that cannot make this argument, e.g. most Mabs, antivirulence therapies, aerosol abx for VABP, etc.
  - Considered adjunctive to antibiotics, though they may bring great advances to modern medicine, e.g. rescue those who may have died
  - Development is particularly challenging, they must demonstrate an added benefit to abx, i.e. superiority (SoC + novel adjunct vs. SoC alone)
Pipeline agents Facing Development Challenges

- *Pseudomonas aeruginosa* MvfR inhibitor (anti-virulence)
  - Spero Therapeutics/Roche

- Multiple monoclonal antibodies
  - Arsanis (ASN200:*Escherichia coli*, ASN300: *Klebsiella pneumoniae*)
  - Astra Zeneca (Medimmune)– (MEDI3902 *P. aeruginosa*)

- Aerosol Therapies for VABP
  - Cardeas (aerosolized amikacin + fosfomycin)
  - Bayer/Nektar (aerosolized amikacin)

- *P. aeruginosa* macrocycle peptide antibiotic
  - Polyphor
So which way is clinical development heading?

A comprehensive regulatory framework to address the unmet need for new antibacterial treatments

Rex et al. Lancet Infect Dis 2013 13: 269-75
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Case Study: Drug X-1

Injectable narrow spectrum agent (*P. aeruginosa*)

**Strength**
- Novel mechanism of action
- Potent, cidal activity
- Safety margin ≥ 4-fold
- Well distributed
  - 40% ELF/Plasma
  - Unchanged in urine
- Well tolerated in PH1-predictable PK
- + PoC in non-CF bronchiectasis study

**Weakness**
- Resistant subpopulation identified
  - MIC >4-fold higher
- P.a. infections not common in any particular body site
- Unclear development pathway
  - Rapid diagnostic not widely available

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**Frequency of *P. aeruginosa* (% of all enrolled)**

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<tr>
<th></th>
<th>Lit.</th>
<th>Recent drug #1</th>
<th>Recent #2</th>
<th>Recent #3</th>
<th>Kollef</th>
</tr>
</thead>
<tbody>
<tr>
<td>NP</td>
<td>20%</td>
<td>13%</td>
<td>10%</td>
<td>23%</td>
<td>26%</td>
</tr>
<tr>
<td>cIAI</td>
<td>10%</td>
<td>7%</td>
<td>10%</td>
<td>23%</td>
<td>26%</td>
</tr>
<tr>
<td>cUTI</td>
<td>3%</td>
<td>4.30%</td>
<td>2.00%</td>
<td>2.40%</td>
<td></td>
</tr>
<tr>
<td>ABSSI</td>
<td>Rare</td>
<td>Rare</td>
<td></td>
<td></td>
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*But note that non-standard VAP definitions were used*
The painful math—borrowed from John Rex

- **Assume some typical general parameters**
  - An endpoint with about a 20% failure rate
  - A non-inferiority margin of 10%, power of 90%
  - You need ~672 evaluable cases (336/arm)

- **Evaluable = culture-proven → so now we need…**
  - If 22% *P. aeruginosa*, need 3,064 (1,532/arm)
  - If 11% *P. aeruginosa*, need 6,128 (3,064/arm)
  - If 3% *P. aeruginosa*, need 22,466 (11,233/arm)

- **Certainly big enough for the safety database!**
  - But, not feasible for actual development
  - Recent HAP-VAP trial took 5 years to enroll ~1,200 pts

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Practical Issues for Drug X-1

“Tier C” *P. aeruginosa* Specific Trials

**Issues to Consider**

- **Design:**
  - Non-inferiority is possible, but what site of infection, or
  - Pooling across infection sites?
    - VABP has highest incidence of P.a. (but still only 15-20%)
  - Limited choice of comparators/combinations? (Need to fill in spectrum gaps)
  - VABP guidelines recommend double coverage for P.a.
    - Impact of confounding

- **Analysis:**
  - Patients with P.a. infections typically sicker and have higher comorbidity
  - Endpoints are different across body sites
  - What NI margin could you use? Is discounting possible?
  - Or is inferential testing even possible?

- **Enrollability**
  - Is the trial feasible to enroll i.e. costs/time?
  - How much could a rapid diagnostic test help with enrollment?
  - Design acceptable to investigators?
Logistics of clinical research (All comers)

- **Cost**
  - cUTI, cIAI ~$50k/patient
  - HABP/VABP >$100K/patient
  - Costs are amplified when the # of sites increases

- **Time**
  - cUTI/cIAI enroll ~0.25 - 0.5pts/center/month
  - HABP/VABP enroll ~0.08pts/center/month
  - *Now consider that only a small fraction will have P.a.*

- **Investigator fatigue**
  - Site staff works hard screening patients to meet eligibility
  - Their effort is mostly compensated when they enroll a patient
    - Often have other trials that compete for their time and are easier to enroll

- **Investor fatigue**
  - Notoriously impatient
  - They have other choices when it comes to investment
Rapid Diagnostic to the Rescue??

- Have we oversold the value of rapid diagnostics?
  - Diagnostics do not create patients infected with target pathogens, they help identify them before culture results
  - Thus used for enrichment, they *may* save costs

- Logistics
  - Diagnostics often require hardware which must be purchased or leased
    - Other costs which must be factored include reagents and hardware maintenance
  - Site staff must be trained, and diagnostic companies are not working to your study timelines
    - If trained staff not present, patient enrollment can be compromised
  - QC must be maintained
  - Microbiologically evaluable population is based on + culture result
  - All of the above challenges are amplified if the diagnostic is investigational

- Conclusion- One must carefully weigh the value of diagnostics vs. other enrichment criteria

- Aside– Though a rapid diagnostic *may* be valuable in a clinical trial, it will be of great value in a stewardship role.
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Drug X-1 Clinical Development

• Standalone Tier C programs have not yet been submitted for review
  - Small samples may not contain sufficient numbers of target pathogens to allow inferential testing, even with wide NI margins
  - Small samples from a sick population with many comorbidities could generate highly variable results—increasing the risk of failure

  (Tier B works well because it is feasible to enroll clinical studies of acute infection when the agent has a broad enough spectrum)

• What can readily be demonstrated for a narrow-spectrum agent like Drug X-1:
  - MoA, MIC range, potential for resistance—\textit{in vitro} study
  - Target exposures for efficacy, from:
    • \textit{in vivo} preclinical animal models of infection
    • \textit{in vitro} hollow fiber experiments
  - Estimated dose to achieve target exposure in target population
  - Demonstrate PK/PD based on MoA in a small trial population (PoC)
  - Safety in a small population

• With the feasibility challenges highlighted for Drug X-1, can one expect that a clinical trial will meet the requirement for substantial evidence of effectiveness with any predictable certainty?
A comprehensive regulatory framework to address the unmet need for new antibacterial treatments

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A comprehensive regulatory framework to address the unmet need for new antibacterial treatments

Rex et al. Lancet Infect Dis 2013 13: 269-75
A & D Pathways Are Familiar, B & C Are New

A comprehensive regulatory framework to address the unmet need for new antibacterial treatments

Rex et al. Lancet Infect Dis 2013 13: 269-75
Summary

Drug X-1  Clinical Development (Speaker’s View)

- Drug X-1 has a novel MOA and the promising potential to address an important unmet medical need
  - Inappropriate therapy for *P. aeruginosa* is associated with increased mortality\(^1,2\)
  - Increased mortality associated with MDR *P. aeruginosa*\(^1,3\)
  - MDR *P. aeruginosa* more common than KPC and NDM in US

- A strong supportive data package has been generated for Drug X-1

- Given the challenges of recruiting a single-pathogen cohort along with the high degree of heterogeneity in the population, a Tier C approach to meet FDA statutory requirements for effectiveness carries a high degree of unmanageable risk
  - There is no way to argue that results of a Tier C study will favor chance of supporting approval vs. condemning to failure

- We need to consider an alternative approach
  - Could the “Animal Rule” help address this important unmet need …

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Meeting the statutory requirements for a narrow-spectrum therapeutic

- When conduct of an adequate and well controlled clinical study is not ethical or **feasible**, than substantial evidence of efficacy can come from validated animal models
  - First we need to agree that a single pathogen P.a. clinical trial cannot meet the statutory requirement
  - If so, is there a validated animal model of P.a. infection?

- **It is feasible to conduct small studies in the target patients with P.a. infections**
  - Obtain PK to demonstrate that the given dose can generate efficacious target exposures in the population intended for use of the therapeutic
  - Provide descriptive statistics from such clinical trial
  - Collect safety data to support risk benefit analysis

- The Sponsor should present plans to conduct a “Field Study” to further support the benefit risk of the approved therapeutic
Conclusions

• Promising, narrow-spectrum agents are in the pipeline; the development path is currently unclear

• As basic science advances, translational challenges will continue to emerge
  - Establishing effectiveness in a clinical trial for adjunctive therapies may prove especially challenging

• Blending elements proposed under Tier C with the “Animal rule” may allow FDA approval of select narrow-spectrum therapeutics

• Society is approaching a crossroads in addressing antibiotic resistance and we are in danger of slipping backwards, losing a number of the scientific achievements accomplished as part of modern medicine in the 20th century
  - We must continue to advance and replenish the antibiotic pipeline, and find ways to test and approve novel, potentially useful therapeutics
  - We can’t rely on or hope for *only* broadly-active anti-bacterial therapies