Why Target-Based Drug Discovery Has Not Been Very Successful

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CDC Reported In USA ~2 Million Antibiotic Resistant Infections Lead to ~23,000 Deaths Annually and Estimated Costs of $50B+
Our Experience Developing a Novel Mechanism Antibiotic

Gepotidacin
A Novel Triazaacenaphthylene Bacterial Topoisomerase Inhibitor (NBTI)
Gepotidacin: A Triazaacenaphthylene Bacterial Topoisomerase Inhibitor for Gram Positive and Some Gram Negative Infections

- Phase II studies
  - Acute bacterial skin and skin structure infections (complete)
  - Gonorrhea (on-going)
- Developed in partnership with DTRA and BARDA

<table>
<thead>
<tr>
<th>Biothreat</th>
<th>MIC&lt;sub&gt;90&lt;/sub&gt; (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y. pestis (plague) (117)</td>
<td>0.5</td>
</tr>
<tr>
<td>F. tularensis (tularemia) (129)</td>
<td>0.5</td>
</tr>
<tr>
<td>B. anthracis (anthrax) (130)</td>
<td>1</td>
</tr>
<tr>
<td>S. pneumoniae (549)</td>
<td>0.25</td>
</tr>
<tr>
<td>H. influenzae (981)</td>
<td>1</td>
</tr>
<tr>
<td>M. catarrhalis (158)</td>
<td>≤0.06</td>
</tr>
<tr>
<td>S. aureus (1008)</td>
<td>0.5</td>
</tr>
<tr>
<td>S. pyogenes (199)</td>
<td>0.25</td>
</tr>
<tr>
<td>N. gonorrhoeae (145)</td>
<td>0.5</td>
</tr>
<tr>
<td>L. pneumophila (50)</td>
<td>0.25</td>
</tr>
<tr>
<td>M. pneumoniae (5)</td>
<td>≤0.0125</td>
</tr>
<tr>
<td>C. pneumoniae (3)</td>
<td>&gt;64</td>
</tr>
<tr>
<td>E. coli (1012)</td>
<td>2</td>
</tr>
<tr>
<td>E. faecalis (25)</td>
<td>4</td>
</tr>
<tr>
<td>E. faecium (25)</td>
<td>&gt;16</td>
</tr>
</tbody>
</table>

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BTI’s Were Identified From a Phenotypic Screen Dating Back to 1998; Mechanism was Then Identified

Fluoroquinolone binding site

Medicinal Chemistry Made Many Modification over Several Years to Balance Activity and Safety

- Significant commitment
  - Medicinal Chemistry program duration 1998-2007
  - Number of compounds made: ~8,000

GSK'815
1st Candidate
- CV Liabilities
- Genotoxic

GSK'587
2nd Candidate
- Hepatotoxic

GSK'237
3rd Candidate
- Testicular tox
- Ocular Tox

Gepotidacin
4th Candidate
- 3 Month Tox

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GSK is Committed to Developing Gepotidacin, And New Antibacterials, But We Need A Better Technology

• Proud to have discovered gepotidacin
  – Several companies worked on BTI’s
• One of the most advanced novel MoA antibacterials in the industry
• Result of successful PPPs with BARDA & DTRA (US DoD)

• Resources and time required to repeat this effort is prohibitive

• “Necessity is the mother of invention”
  – We need new antibiotics and we need to find an alternative to traditional approaches
In Parallel to Gepotidacin Development, New Technology Promised to Accelerate Drug Discovery

Whole Genome Sequencing

Structure-Based Drug Design

High-Throughput Screening
Unfortunately, High Throughput Screening Did Not Lead to Clinical Candidates

- GSK evaluated > 300 genes, 160 shown to be essential for bacterial survival
- 70 High Throughput Screens were conducted on essential targets, 16 giving viable hits
- Only 5 tractable leads (established mode of action activity) were identified
- None made it to pre-clinical development
- Pfizer: 62 HTS, 4 Leads
- AstraZeneca: 65 HTS, 19 Leads

2. Personal communication from Paul Miller, formerly at Pfizer
2010 Attrition Rate of Antibacterial R&D Programs Compared to Other Therapeutic Areas

• Antibiotic discovery has a higher attrition than other areas
  • Vast majority of historic antibacterial R&D effort focused on ‘small molecule kill the bug’
  • Same science base since Fleming

Poison is in everything and no thing is without poison. The dosage makes it either a poison or a remedy.
Doses of Antibacterial Agents Remain High
We have improved over time, rightly driven by regulatory restrictions.
We Compare Poorly Against Other Therapeutic Areas
Comparison with NCE’s approved in 2013*

Why is this the case? How do we achieve lower doses?

It Takes a Lot of Drug to Kill the Bug
High exposure on outside of bacteria is needed to achieve a therapeutic level on inside

Penetration challenge:
Need to balance physicochemical properties to optimize penetration into cytoplasm

Porin Challenge:
Porins are a good route of entry, but we don’t know enough to build compatible properties

Efflux Challenge:
Bacteria will eject foreign molecules and we still don’t fully understand how to avoid these transporters

Resistance Challenge:
Reduced potency though:
• Resistance mutations at target
• Metabolism of the antibiotic
• Membrane changes
• Porins and efflux mutations/regulation

Biomass Challenge:
• Rapidly reproducing biomass
High Dose Also Driven by Coverage for the Worse Case Scenario ……… Socialist Dosing vs. Precision Medicine?

Distribution of MIC values for an antibiotic varies across a range of clinical isolates

Concentration of antibiotic in plasma varies across a population of patients

Everybody gets a dose for the worse case scenario
- whether they need it or not!
Where do we go from here?
If Traditional Antibiotics are in the Declining Stage of an Industry Cycle, We Need To Identify The Next Technology

- Battery technology
- Optical technology
- Communication technology
- Processor technology
- Material technology
A Broader Discovery Agenda is Needed for Addressing Bacterial Infections

**Enhance Success of Small Molecule Approach**
- Use active transport systems
- Identify potentiation strategies
- Understand how to avoid efflux
- Target outer-membrane proteins
- Concentrate antibiotic at infection site

**Alternative Approaches**
- Antibody therapy
- Phage therapy
- Microbiome
- Enhance host immunity systems

Fundamental research is needed in these areas to boost our understanding. Objective is to have low-dose therapeutic options.
TRANSLOCATION: Getting Drugs Into Bugs

- Microbiologists, structural biologists, biophysicists, and chemists working together to understand penetration:
  - Membrane Proteomics
  - Whole cell penetration assays
  - Cell-free assay systems
  - X-ray structures of porins and efflux pumps
  - Siderophore receptor structure/function
  - Identification of novel uptake systems
  - Computer simulation of transport
  - Electrophysiology channel studies

- With this data we may better understand structure-penetration relationships and design compounds that favor uptake

- We may find new transportation pathways to hijack and deliver drugs into bacteria
Alternative Modalities Offer New Solutions and Different Challenges, Each Will Require Validation

Medimmune multifunctional antibody completed Phase I

Bacteriophage against *P. aeruginosa* delivered by Inhalation

HOST-approaches to:
- Boost innate immunity
- Inhibit excessive inflammation
- Block host factors used by bacteria


Recent Review: Czапlewski et al, Alternatives to Antibiotics – a pipeline portfolio review, THE LANCET, Infectious Disease, 2016, 16, 239-251
What Do We Have and What Do We Need?

**PPPs critical** (BARDA, DTRA, IMI)

- **DISCOVERY**
- **HIT TO LEAD**
- **LEAD OP**
- **PRE-CLINICAL**
- **CLINICAL**

**DEFENSE THREAT REDUCTION AGENCY**

**CARB-X**

**BARDA**

**GAPS**

- Concerted investment to validate alternatives & to increase success of small molecule approach
- Funding for assets to FTIH/IND
- Clinical Trial networks to realize success of other initiatives & PPPs

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Where Do We Go From Here?
Enhance success of small molecule approach & validate alternatives

• Gepotidacin is a novel MoA antibiotic in Phase II
  – Discovery via traditional approach not a viable R&D model
• High doses/exposure main cause of attrition in AB R&D
  – Despite 70 yrs of traditional AB research doses still high
  – We must reduce doses to increase success of AB discovery
• Investment in fundamental early science needed:
  – Enhance success of small molecule approach
  – Validate and progress alternatives (e.g. host approaches)
  – Open innovation/pre-competitive constructs needed
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