Addressing the challenges of antibacterial discovery and development

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The Perfect Storm

As bacterial infections grow more resistant to antibiotics, companies are pulling out of antibiotics research and fewer new antibiotics are being approved.

Slaes & Cooper, Nature (2011) 472; 32
1. The scientific challenge

2. The complexity of clinical investigation

3. The return on investment

Success of antibacterial R&D compared to other areas

*Antibiotics:
- 72 Leads
- 36 Candidates

*Other areas:
- 15
- 12

- 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

Why is this so difficult?

Plenty of good AB targets, hard to find good leads
- GlaxoSmithKline*
  - 70 HTS (1995-2001)
  - Mainly enzyme based
  - 5 Leads
  - 7% success rate
- Pfizer*
  - 62 HTS
  - Mix of whole cell & enzyme
  - 4 Leads
  - 6.5% success rate

AB have to achieve v. high exposures with a viable therapeutic index

Optimising antibacterial activity is challenging (esp Gram-ves)

Industry average success (all TAs) for leads = 80%

Discovery programs on novel classes can be very long and resource intensive: eg....

Novel Bacterial type II Topoisomerase Inhibitors (NBTI) class of AB, different mechanism to quinolones

Started 1998. Initial focus to overcome CV liabilities
- *GSK203815 X genotox risk
- *GSK966587 X hepatic tox risk
- *GSK945237 X testicular tox & ocular tox risk
- *GSK2140944 Passed 3 month tox

Program focused on Gram –ve and Gram +ve, but only Gram +ve delivered


*Published in Nature Reviews Drug Discovery 6, 29-40, 2007 *Personal communication from Paul Miller, Pfizer (now AZ)
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**Challenge of antibacterial clinical trials and the role of diagnostics**

e.g.: Challenge of seeking penR *S. pneumoniae* infections in a CAP trial

- Enrolled N=984
- Pathogen isolated N=400
- S. pneumoniae N=285 (29%)
- Pen-resistant N=39
- Pen-susceptible N=246

Impact of diagnostics in antibiotic trials
- Enable patients with resistant pathogens to be targeted
- Decreases size & cost of trials
- Enriched populations will improve end points

Cost:
- ££££
- £££
1. The scientific challenge

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New funding partnerships

- New antibiotics needed to address MDR pathogens in our hospitals
- New antibiotics needed to protect against the threat of bioterrorism
Creation of ND4BB (IMI) as a highly collaborative approach to address challenges

**TRANSLOCATION** (Drugs into Gram-ves)

**CONSORTIA tbd** (Commercial models)

**COMBACTE** (Clinical trials)

**ENABLE** (Collaborative hit/lead optimization programs)

**COMMENT**

**ND4BB: addressing the antimicrobial resistance crisis**

A broader discovery agenda is needed for addressing bacterial infections

- Most of the antibacterial effort focused on the traditional antibiotic model of ‘small molecule kill the bug’
- A broader research agenda is needed eg:

  - Alternative Approaches to tackling the bacteria
    - Zwitterionic Prodrugs
    - Pathogenesis
    - Virulence
    - Inhaled delivery
    - Liposome delivery
    - Biofilm disrupters

  - New Modalities (not small molecule)
    - Bacteriophage
    - Antibody-drug conjugates
    - Antibody Recruiting Molecules (ARMs)
    - Bacterial delivery systems
    - Monoclonal Antibodies

  - Host Targets
    - Adhesion/invasion
    - Modulate Inflammation
    - Targeting innate immunity and immunomodulators
    - Repurposing opportunities
1. The scientific challenge

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New regulatory paths globally harmonised to expedite development of antibacterials

- Regulatory pathways evolving to expedite dev’t of AB
  - EMA: Pilot project on adaptive licensing
  - FDA: ‘Antibacterial therapies for patients with unmet medical need for treatment of serious bacterial diseases’ (‘streamlined’ development)’

- Limited Population Antibacterial Drug (LPAD), IDSA
  - Expedite approval for drugs that target resistant infections with few options
  - Safety/effectiveness in smaller trials, higher dependence PK/PD
  - Label informs about uncertainties to ensure appropriate use (special logo)
  - New data can subsequently broaden the intended use

- Global harmonisation for these new routes is key
- Pursuing these paths for current & future unmet needs

LPAD: Limited population Antibacterial Drug; IDSA: Infectious Diseases Society of America