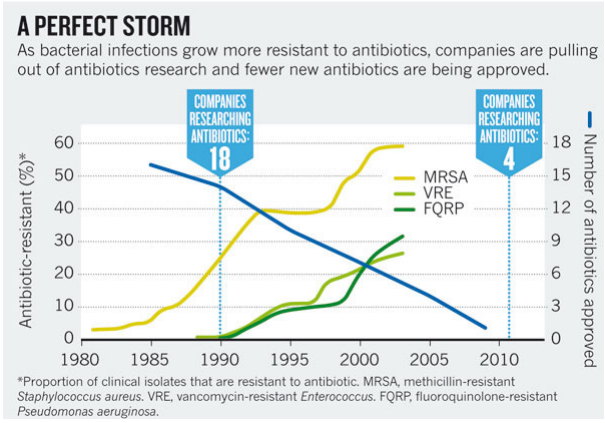
The Perfect Storm



Shlaes & Cooper, Nature (2011) **472;** 32

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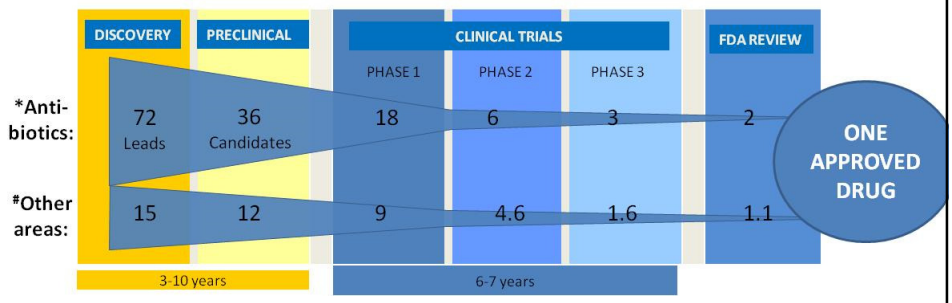
1. The scientific challenge
2. The complexity of clinical investigation
3. The return on investment

Success of antibacterial R&D compared to other 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

**Hit to Phase 2 based on novel mechanism AB discovery (GSK) #Based on Paul, et al (2010), Nature Reviews Drug Discovery 9: 203-214.*

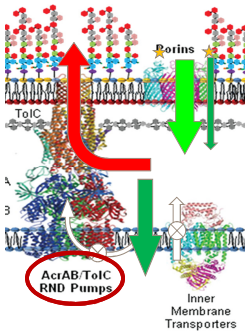
Why is this so difficult ?

Plenty of good AB targets, hard to find good leads

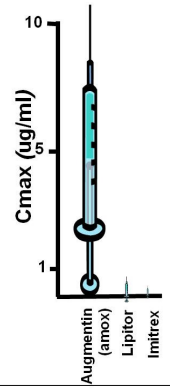
- GlaxoSmithKline#
  - –70 HTS (1995-2001)
  - –Mainly enzyme based
  - –5 Leads
  - –**7% success rate**
- Pfizer*
  - –62 HTS
  - –Mix of whole cell & enzyme
  - –4 Leads
  - –**6.5% success rate**

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

Optimising antibacterial activity is challenging (esp Gram-ves)



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



#published in *Nature Reviews Drug Discovery* 6, 29-40, 2007 **Personal communication from Paul Miller, Pfizer (now AZ)*

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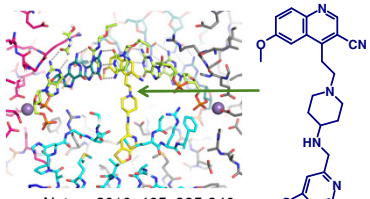
Discovery programs on novel classes can be very long and resource intensive: eg….

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



Nature 2010. 465: 935-940

Nature Struc Mol Biol, 2010, 17, 1152

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

Started 1998. Initial focus to overcome CV liabilities

✓

*GSK203815 X genotox risk

Focus on addressing risk

*GSK966587 X hepatic tox risk

Focus on addressing risk

*GSK945237 X testicular tox & ocular tox risk

Focus on addressing risk

*GSK2140944 ✓ Passed 3 month tox

6 **MICs, efficacy & initial tox all excellent*

1. The scientific challenge
2. The complexity of clinical investigation
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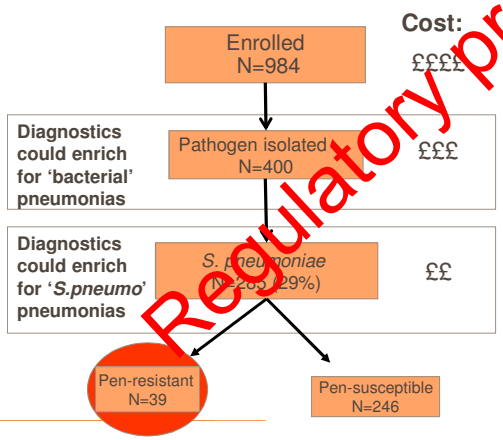
Challenge of antibacterial clinical trials and the role of diagnostics

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



Regulatory process

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

1. The scientific challenge
2. The complexity of clinical investigation
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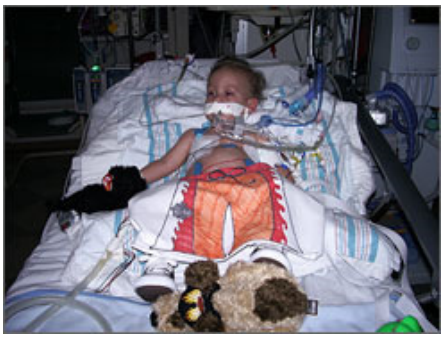
New funding partnerships

- New antibiotics needed to address MDR pathogens in our hospitals



BARDA (Novel portfolio partnership)

- New antibiotics needed to protect against the threat of bioterrorism

DTRA

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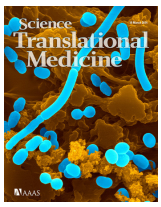
Creation of ND4BB (IMI) as a highly collaborative approach to address challenges



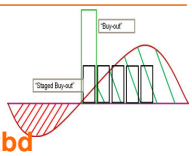
INNOVATIVE MEDICINES INITIATIVE

TRANSLOCATION Project: How to Get Good Drugs into Bad Bugs

THE SCIENTIFIC LITERATURE, LAY PRESS, AND GOVERNMENT BODIES ALL NOW RECognize antimicrobial resistance (AMR) as a major global public health threat (1–3). Although the need for new antimicrobials is overt...Established by the innovative use

www.ScienceTranslationalMedicine.org 19 March 2014 Vol 6 Issue 228 228ed7

TRANSLOCATION
(Drugs into Gram-ves)



Consortia tbd
(Commercial models)

ND4BB

COMBACTE
(Clinical trials)

COMBACTE CLIN-Net: 280 members and Candidate members

ENABLE
(Collaborative hit/lead optimization programs)

COMMENT

ND4BB: addressing the antimicrobial resistance crisis

John H. Rex

The Innovative Medicines Initiative (IMI) recently launched its third public–private partnership, ENABLE (European Gram-negative Antibacterial Engine), to tackle the shortage of effective

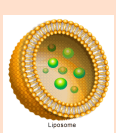
Nature Reviews Microbiology | AOP, published online 10 March 2014; doi:10.1038/nrmicro3245

AstraZeneca Janssen SANOFI basilea PHARMACEUTICA gsk Pfizer CUBIST astellas AiCuris Anti-infective Cures NOVARTIS

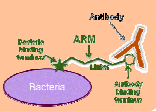
A broader discovery agenda is needed for addressing bacterial infections

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

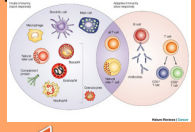
Alternative Approaches to tackling the bacteria
- Zwitterionic Prodrugs
- Pathogenesis
- Virulence
- Inhaled delivery
- Liposome delivery
- Biofilm disrupters



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



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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

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do more feel better live longer

Thank you