Combating Antibiotic Resistance: New Drugs 4 Bad Bugs (ND4BB)

David Payne/Seamus O’Bien for Astra Zeneca, Basilea, GlaxoSmithKline, J&J & Sanofi
Need for public-private collaboration

Challenges of AB R&D:
1. Unique scientific bottlenecks
2. Challenging regulatory environment
3. Low return on investment

Challenges too great for any single entity to solve, collaboration is essential
Antimicrobial resistance is unpredictable

- NDM spread to ICUs across Europe in <18 months
- Numerous examples of rapid global spread of clones & resistances
- Takes 10+ years to make an AB
- Long term strategy needed for threats of today and the future

Nordmann et al (2011); Emerging InfectDis 17; 1791-8.
Klugman (2002); J. Antimicrob Chemother, 50; S2, 1-5.
Walsh et al (2011); Lancet, 11,(5) , 355- 362
Objectives of the full project

• Response to the European Strategy to combat antibiotic resistance
  – AB R&D PPPs have been the subject of years discussion; ND4BB establishes Europe as a leader in addressing AMR

• Information sharing amongst collaborators in a way we have never done before
  – Need to increase the overall success of AB R&D, as an industry we cannot afford to make the same mistakes twice

• Projects focused on the treatment/prevention/management of resistant infections caused by:
  – Drug-resistant Gram-negative pathogens
  – Clostridium difficile, MRSA
Expected impact on the R&D process

• Sharing of successes and failures amongst the industry will increase the efficiency of AB R&D
• Potential to create smaller & more efficient clinical trials
  – Biomarker research and rapid diagnostics could enable targeted patient enrolment
• Creation of a clinical trial consortium for antibacterials
  – Creation of more sites in areas of high resistance
  – Communication of best practice and learnings
• Ability to rationally design compounds that penetrate Gram negatives will facilitate the delivery of a pipeline of AB for Gram negatives
Suggested architecture of the project

ND4BB cross topic collaboration and dissemination (Topic 1 WP1, Topic 2 WP8, Topic 3 WP1, Topic n WPn)

Subtopic 1 A: Enabling Clinical Collaboration and refining clinical trial design
- Subtopic 1 B: Clinical Development of GSK1322322
- Subtopic 1 C: Clinical Development of MEDI4893 and AZD9773

Topic 2: Learning from success and failure & Getting Drugs into Bad Bugs

Topic 3: Discovery/development of new drugs combating Gram-negative infections

ND4BB Data Hub (all data generated is submitted and is accessible to all consortium partners)

Topics launched under Call 6
Future Topics to be launched
Key deliverables of the full project: Topic 1

- **Challenge being addressed:** funding for AB clinical trials is a major cost of AB development (in some cases prohibitive)
- **Goal & Deliverables:** Provide clinical data on new agents for tackling priority pathogens and improve the efficiency of AB clinical trials
  - Generation of clinical data that demonstrate the efficacy, safety and pharmacology of new agents for priority pathogens
  - Create the first clinical trial consortium for ABs
  - Create opportunities to test diagnostics/biomarkers etc
  - Create new clinical trial sites in regions/institutions of high resistance
  - Innovative Phase 2 and Phase 3 designs
Subtopic 1A: Enabling clinical collaboration & refining clinical trial design

• Key Objectives
  – Facilitate and enable a highly functional, compliant and trained clinical trial investigator network.
  – Ensure cross collaboration between ND4BB projects

• Work Package Outline
  – WP1: Overall communication amongst Topic 1 investigators and ND4BB
  – WP2: Training AB clinical trial investigators for consortium network
  – WP3: Surveillance with new AB agents to assess pre-existing resistance and pinpoint regions/institutions of high resistance
  – WP4: Innovative Phase 2 and 3 design
Subtopic 1B: Innovative trial design & Clinical drug development

• Key Objectives
  – Conduct prospective clinical trials to evaluate safety, pharmacology and efficacy data for GSK1322322.
  – Validate novel bacterial diagnostics or novel biomarkers with the aim of reducing the size and cost of clinical trials.

• Work Package Outline
  – WP5A: 1st Phase 3 GSK1322322 in ABSSSI with oral switch
  – WP5B: 2nd Phase 3 GSK1322322 in ABSSSI with oral switch
  – WP5C: Phase 2Ilb: GSK1322322 for hospitalised CABP with oral switch
  – WP5D: GSK1322322: Pivotal Phase 3 trials for hospitalised CABP

ABSSSI: acute bacterial skin and skin structure infections
CABP: Community acquired bacterial pneumonia
GSK322 Inhibits the PDF Enzyme
An Unprecedented Antibacterial Target

Compound Overview

• Entirely novel antibacterial target
• No cross-resistance with currently available antibiotics
• Targeted in vitro spectrum against typical and atypical community acquired pneumonia pathogens including MRSA
• IV & oral formulations
• Phase I and IIa completed
• Provisional safety and efficacy data from completed Phase IIa study in ABSSSI (MRSA skin infections)

Peptide Deformylase (PDF)

PDF: Removes N-formyl group from newly-synthesized peptides

Structure-based design efforts led to the discovery of ‘322

Novel hydrazinopyrimidine PDF inhibitor series
**In vitro activity of GSK1322322**

<table>
<thead>
<tr>
<th>Organism (N)</th>
<th>MIC&lt;sub&gt;90&lt;/sub&gt; (µg/mL)</th>
<th>GSK1322322</th>
<th>Azithromycin</th>
<th>Clindamycin</th>
<th>Levofloxacine</th>
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<tbody>
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<td><em>S. pneumoniae</em> (961)</td>
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<td>2</td>
<td>&gt;8</td>
<td>&gt;4</td>
<td>1</td>
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<td>&gt;8</td>
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<td>2</td>
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<tr>
<td>MSSA (556)</td>
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<td>Atypical organisms*</td>
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<td>NT</td>
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<td><em>C. pneumoniae</em></td>
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<td><em>L. pneumophila</em> #</td>
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<td>NT</td>
<td>0.03</td>
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</tbody>
</table>

* MICs reported as a range
# MIEC (Minimum Extracellular Concentration Inhibiting Intracellular Growth)

Study conducted by IHMA
Subtopic 1C: Innovative trial design & Clinical drug development

Subject to Future Call

### Objectives
- Create new insights into the epidemiology of surgical site infections in the EU
- Clinical trials with MED14893 to prevent MRSA infections and AZD 9773 for treating sepsis which is caused by uncontrolled infection

### WP6: Clinical Trials supporting the development of MEDI4893, a monoclonal antibody (mAb) targeting *S. aureus* alpha toxin:
- WP6A: Epidemiologic surveillance of surgical site Infections (SSI) in the EU
- WP6B: Evaluate the role of *S. aureus* (inc. MRSA) virulence factors in SSIs
- WP6C & D: Ph 1b/2 trials for prevention of *S. aureus* (MRSA) VAP and SSIs

### WP7: Phase 3 AZD9773: Ab targeting tumor necrosis factor alpha for the treatment of the severe sepsis, including septic shock

SSI: surgical site Infections; VAP: ventilator associated pneumonia
Expected contributions of the applicants: Topic 1

• Experts in serious hospitalised bacterial infections to participate in pan-European consortium
• Project Leadership and co-ordination infrastructure
• Hospital and healthcare institutions to join a clinical trial network with capability to run Phase 1, 2 & 3 clinical trials
• SMEs to provide training to ensure a compliant network of clinical trial sites and micro labs
• SMEs with diagnostics suitable for use in clinical trials, experts in novel biomarker research
• Clinical research organisation with global experience
• Expertise in statistics and pre-clinical PK/PD modeling
• Coordination & conducting microbiology surveillance programs
Expected (in kind) contributions of EFPIA members: Topic 1

- Clinical trial expertise
- Knowledge & expertise on GSK1322322, MEDI4893 & AZD9773
  - Provision of study drug, regulatory support, project management, pharmacovigilance, clinical expertise etc.
- Non-Europe component of the clinical trial
- Project/Alliance Management personnel
- Statistics (eg Bayesian), PK/PD modeling & simulation expertise
- Expertise in designing surveillance programmes
- Clinical micro procedures/protocols required in clinical trials
Key deliverables of the full project: Topic 2

- **Challenge**: Making selective inhibitors of novel Gram negative targets is not a substantial challenge – getting them into Gram negatives to reach their lethal target is the bottleneck
  - Industry concludes this is the biggest scientific barrier to the success of Gram negative drug discovery programmes

- **Goal & Deliverables**: Create a partnership with EU academics (inc those new to AB R&D) to enable more rational approaches to design Gram negative AB by enhancing our understanding of how to:
  - Avoid efflux
  - Optimally penetrate porins & Gram negative membranes
  - Hijack active uptake pathways (‘Trojan horse’ approach)
How will Topic 2 address the penetration challenge?

WP5: will integrate learnings from WP1-4

WP1: create assays to measure components of penetration and/or efflux

WP2: How do porins work? How do we design compounds to optimally enter?

WP3: Which transport systems can we hijack to achieve active uptake of new antibacterials?

WP4: novel approaches for permeabilizers or altering penetration / efflux

very different characteristics
Expected contributions of the applicants: Topic 2

WP1-5

• Expertise in measuring cellular penetration and/or efflux (including novel techniques and knowledge transfer from mammalian systems)
• Expertise in studying porin function / SAR
• Expertise in bacterial uptake pathways
• Medicinal chemistry expertise to build in recognition features for uptake pathways into antibacterials
• Techniques to find new targets which alter permeability / efflux

WP6-8

• IT expertise for database infrastructure, web design, etc.
• Scientific communications expertise
Expected (in kind) contributions of EFPIA members: Topic 2

- SAR on novel series of investigational ABs for data mining
- Supply of lead molecules for building in ‘recognition’ features for novel uptake pathways
- Medicinal chemistry expertise specific to the antibacterial therapeutic area
- Supply of lead molecules for ‘mechanism of penetration’ experiments
- Assay development expertise
- Potential to run HTSs for novel potentiator targets
- Bacterial strains, tool strains, engineered strains
- Data visualization and mining expertise, computational and statistical analysis expertise
- Data on our successes and failures
What’s in it for you?

• Patients
  – AB resistance threatens our ability to treat common and life threatening infections
  – ND4BB will increase our preparedness to tackle multi-resistant pathogens today and unexpected resistances in the future

• Academic researchers
  – Research opportunities and participation in the 1\textsuperscript{st} AB clinical trial consortium
  – Translation of fundamental science into AB discovery programs
  – Integration & learnings into all aspects of AB R&D

• SMEs
  – Evaluation of promising diagnostics in well controlled trials
  – Training opportunities across Europe to create new clinical trial investigators and compliant sites for AB clinical trials
  – Contract research organisations to work with pharma
Questions?

• Contact the **IMI Executive Office**
  – E-mail: infodesk@imi.europa.eu
  • Website: www.imi.europa.eu

• Links to pages of interest on IMI website
  – Link to call: www.imi.europa.eu/content/6th-call-2012
  – Participating in IMI projects: http://www.imi.europa.eu/content/call-proposals

• Remember: Final date for submission of expression of interest: 9 July 2012
Backups
AZD9773 : Topic 1C

• **Compound overview**
  
  – AZD9773 is a potential treatment of severe sepsis and septic shock.
  
  – Sepsis arises through the body’s response to infection.
  
  – There are currently no specific treatments for severe sepsis.
  
  – Sepsis is the most common cause of death in the ICU.
  
  – Patients with any difficult bacterial infection, both resistant and susceptible, will benefit from access to a treatment for sepsis.
  
  – A sepsis treatment would support antibiotic stewardship goals.
  
  – AZD9773 is an ovine-derived polyclonal antibody fragment of IgG against human TNF-α.

• **Project Status**
  
  – AZD9773 is currently completing a placebo-controlled Phase 2b study.
  
  – If this study is positive, confirms prior work and suggests that Phase 3 development is appropriate, IMI will release a Call for investigators for this Phase 3 project later during 2012.
MEDI4893 : Topic 1C

• Compound overview
  – *S. aureus* produces tissue and organ damage in part via toxins
  – Targeting these toxins preemptively may prevent serious *S. aureus* (including MRSA) disease in high-risk patients, independent of the antimicrobial resistance status.
  – MEDI4893 is not expected to contribute to resistance to antibiotics
  – MEDI4893 is a potent human IgG1 that binds to *S. aureus* alpha toxin

• Current Status
  – MEDI4893 is current completing preclinical studies.
  – If these studies are successful, MEDI4893 will enter clinical development later this year
  – If this occurs, IMI will release a Call for investigators both epidemiologic and clinical studies in support of MEDI4893’s initial development
Scientific challenge: Gram negative penetration adds to already daunting set of requirements

- Selective inhibition of target
- Penetration into Gram-negatives
- Therapeutic window (safety, genetox, QT, etc)
- Suitable PK/PD
- Developable/ Stable Crystalline form
- Scaleable process /viable CoGs

Antibiotics require higher serum levels than many other types of medicines

- Augmentin (amox)
- Avandia
- Imitrex

Cmax (μg/ml)