A PPP Approach to boost antimicrobial resistance R&D: the ND4BB IMI platform

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Antibiotic-resistant infections spread through Europe

Antibiotics resistance 'as big a risk as terrorism' – UK medical chief -

Antibiotic resistance: we must act now, says WHO

Three million Europeans catch infections in hospital annually

17 Janvier 2008: La résistance des bactéries aux antibiotiques a atteint une dimension planétaire
A solution? : The New Drugs 4 Bad Bugs initiative

13:56 17Nov11 RTRS-UPDATE 1-Europe kickstarts R&D fightback against superbugs
* Need to combat antibiotic resistance now "critical"
* EU to accelerate new drug approvals, ensure adequate pricing
* Plan to boost R&D collaboration via IMI initiative
* Drugmakers welcome fresh incentives for antibiotic research
ND4BB: Need for public-private collaboration

The overall vision of ND4BB is to create an innovative collaborative Public-Private Partnership (PPP)-based approach that will encompass all aspects from the discovery of new antibiotics to Phase 2 and 3 clinical trials with the aim of reinvigorating antibiotic R&D.

Three key challenges in antibiotic R&D:

1. **Discovery**: Unique scientific bottlenecks
2. **Development**: Challenging regulatory environment
3. **Economics**: Low return on investment
Antibacterials: The science is tricky
- Validated Targets with Access Problems

- Many tractable targets exist in bacteria, but getting drugs to them is difficult

Staph (MRSA)
Enterococcus
Strep
C. difficile

K. pneumoniae
E. coli
Salmonella
Pseudomonas
Acinetobacter
Many others
Antibiotic resistance is increasing: Europe

Multi-drug resistant *Klebsiella pneumoniae*

- Numerous examples of rapid global spread of clones & resistances
- **Spread is unpredictable, heterogeneous and can be sporadic**
- Takes 10+ years to make an AB
- Long term strategy needed for threats of today and the future
The economic model?

One product can take 10-15 years...

... and an investment of $600-$1 billion!

And once approved, novel antibiotics are used initially as “last resort” treatment for small patient groups

How do we reward value and innovation and ensure responsible use
ND4BB Structure

ND4BB cross-topic collaboration and dissemination

**Topic 1:** COMBACTE
- Enabling Clinical Collaboration and refining clinical trial design
- Clinical Development of GSK1322322

**Subtopic 1C:** Clinical development of MEDI4893

**Topic 2:** TRANSLOCATION
- Research penetration and efflux Gram-negatives
- Data Hub & Learning from R&D experience

**Topic 3:** Development of new drugs combatting Gram-negative infections

**Subtopic 3A:** Management and Resource Hub

**Subtopic 3B:** Hit-to-Lead and Lead-to-Candidate Portfolio

**Topic 4:** Driving re-investment in R&D and Responsible use of Antibiotics

**Topic 5:** Clinical development of antibacterial agents for Gram-negative antibiotic resistant pathogens

ND4BB Information Centre

Projects from Call 6 initiated 1/01/2013
Topics launched under Call 8 (Dec 2012)
Topics launched under Call 9 (July 2013)
**Topic 1: COMBACTE**

- Create a self-sustaining premier antibacterial development network
  - Expanding research and laboratory networks
  - Optimal alignment of clinical trials with investigator sites
  - Clinical and epidemiologic data also supports stewardship

- Increase efficiency of antibiotic development
  - Align clinical trials with cutting edge molecular methodologies and trial design
  - Conduct clinical trials with GSK1322322, MEDI 4893

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**COMBACTE Clinical Trial & Lab Network**

- GSK 1322322 phase II/III Trials CABP/ABSSI
- Phase 1b/2 study with MEDI 4893
- Future Trials IMI/non-IMI

**Future Trials**

- Biomarker/Diagnostic Development
- Statistical Centre of excellence
Current status of COMBACTE CLIN-Net: 280 members and Candidate members
Topic 2: Translocation

Discovery: improve understanding of penetration into Gram-negatives
Efficiency: creation of a data centre to compile and analyze AB and ND4BB information

Discovery

- **WP1**: create assays to measure components of penetration and/or efflux
- **WP2**: better understanding of how porins work
- **WP3**: transport systems we can hijack to achieve active uptake of new antibacterials
- **WP4**: a novel approach for permeabilizers or altering penetration / efflux
- **WP5**: integrate learnings from WP1-4

Efficiency

- **Legacy R&D data (EFPIA) / public**
- **ND4BB Data (Topic 1, 2...)**
- **INFORMATION CENTRE**
  - Best Practices in Antibacterial R&D
  - Dissemination Of Information & Best Practices
**ND4BB TRANSLOCATION: Discovery**

- **Challenge:** Making inhibitors of Gram negative targets is not a substantial challenge – **getting them into Gram negative bacteria is the bottleneck**

- **Goal:** Merging the best science of microbiology, structural biology and biophysics to bring **unprecedented understanding of penetration into Gram negatives, including novel assays and design concepts** increasing overall probability of success to deliver novel antibacterials across the industry

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- electrophysiology
- mass spec
- X-ray crystallography
- all atom kinetic modeling
Goal: create a drug discovery platform to optimize hits from public partners and GSK/Sanofi into Candidates and progress into Phase 1
New Topics : Deliverables - Topic 4

**Topic 4 : Driving re-investment in R&D and Responsible use of antibiotics**

- Generate an analysis of the societal impact and cost of anti-infectives resistance
- Create a multi-disciplinary, multi-stakeholder community with an in-depth comprehension of the complexities of antibacterial R&D and the challenges of the current commercial model
- Develop implementable options for new commercial models that address the needs of multiple stakeholders,
- Validate options through modelling on selected case studies

Launched in IMIJJU 9th Call – 09/07/2013
Deadline for expressions of interest - 09/10/2013

EACPT 2013 Congress - 29 August – CICG Geneva
**New Topics : Deliverables - Topic 5**

<table>
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<tr>
<th>Topic 5 : Clinical development of anti-bacterial agents for Gram-negative antibiotic resistant pathogens</th>
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<tr>
<td>Observational clinical and microbiological data sets to make recommendations for the development of novel antibiotic agents for MDR Gram-negative pathogens</td>
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<tr>
<td>Understanding of the clinical management and outcomes of patients with serious hospitalised infections to validate our understanding of the clinical outcomes for patients in areas of emerging and endemic antibiotic resistance.</td>
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<tr>
<td>Successful therapeutic clinical trials demonstrating the pharmacology, safety and efficacy of novel agents/combinations, in particular aztreonam-avibactam (ATM-AVI), directed towards treatment of infections due to priority pathogens.</td>
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ND4BB – Summary

• Antibiotic resistance is a societal problem needing a societal response
• IMI ND4BB platform is a visible and growing European response
• Addressing the key barriers to new antibacterial agents
• Collaboration and sharing of success and failures is core to the approach.