The ENABLE project: An antibiotic discovery platform

Anders Karlén
Putting open innovation into practice – case studies from Europe
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The rising threat of antimicrobial resistance

**Public awareness**

Antibiotic-resistant superbug problem will turn devastating.

Antibiotic crisis ‘bigger than Aids’

By Rebecca Booth

Medical Editor

Health warnings, write: rebecca.boo@imf.org

Antibiotics resistance 'as big a risk as terrorism' – UK Medical Chief Officer (2013)

**Political awareness**

This growing "antimicrobial resistance" (AMR) is estimated to cause each year some 25,000 deaths and over €1.5 billion in healthcare expenses and productivity losses in Europe alone.

The IMI-1 portfolio

Nature Medicine 2014, Vol 20, no 1
Overall architecture of ND4BB

**ND4BB cross topic collaboration and dissemination**

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

- **ENABLE**
  - Discovery & development of new drugs combating Gram-negative infections

- **COMBACTE-NET**
  - a) Enabling Clinical Collaboration and Refining Clinical Trial Design
  - b) Clinical Development of compound(s) for S. aureus, C Diff, and A. baumannii

- **COMBACTE-CARE**
  - Clinical Development of antibiotic agents for Gram-negative antibiotic resistant pathogens

- **COMBACTE-MAGNET**
  - Systemic molecules against HAIs due to clinically challenging Gram-negative pathogens

- **iABC**
  - Inhaled Antibacterials in CF and non-CF BE

- **DRIVE-AB**
  - Driving re-investment in R&D and Responsible use of antibiotics

**ND4BB Information Center**

*All data generated is submitted and is accessible to all consortium partners*

- Drug discovery
- Drug development Gram-positives
- Drug development Gram-negatives
- Economics and stewardship

**ND4BB Projects as of 2017**

*Total budget: > € 650 million*
Developing an antibiotic

**Developing an antibiotic requires:**
- Experienced collaborators
- Expertise in drug discovery and development
- Expertise in antibiotic development
- Time
- Money

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### ENABLE has the resources, skills & expertise to perform the work

[Diagram showing various steps in antibiotic development]
ENABLE: European Gram Negative Antibacterial Engine

Consortium with 39 partners:

Public partners

Uppsala University managing entity
20 academic/institute/hospital organizations/non-profits
15 SMEs

Private partners (EFPIA)

GlaxoSmithKline, Pennsylvania, US
Sanofi, AstraZeneca & Basilea

Launched Feb 2014, 6 year run time
Projected budget: €85 million

Goals

• Create a collaborative drug discovery platform
• Kick start Gram-negative antibacterial discovery:
  • increase overall science base in the area
  • identify three Leads
  • identify two Development Candidates
  • progress at least one compound into Phase 1
Managing a Drug Discovery platform across Europe

ENABLE labs
- Medicinal chemistry, microbiology, ADMET, PK, \textit{in vivo} pharmacology all across Europe and working by disciplines
- Representing more than 50 FTEs

Compound handling platform
- Storage of compounds
- ID & Purity control of compounds
- Weigh out of solid material for assays
- Transfer of compounds to microtiter plates/vials
- Distribution of solutions/compounds

Sharing data in ENABLE
- Electronic Lab Notebook (ELN)
- Results database
- File Server

ENABLE management (administrative and scientific)
- Consortium management office (CMO)
- Finance support (UU)
- Legal support (GSK & UU)
ENABLE: collaborative antibacterial drug discovery

ENABLE
- Multiple program teams
- Open sharing of ideas & data—no silos
- Highly supportive of novel approaches
- Novel IP framework

ENABLE Teams
- Leadership & science from multiple partners
- All team members at the table
- Program owner makes final decisions
Heart of ENABLE: PMC (funding) cycle

- **Open Call**
  - Expression of Interest
    - >70 Eols
    - 27 to PMC
    - 16 approved
    - 11 stopped
    - Funding approved
    - Funding continued
    - Funding not approved
    - Funding stopped
  - Portfolio Management Committee
    - Active Programmes
    - Drug Discovery Platform
  - Phase I clinical study
    - 5 active
    - >70 Eols
    - 27 to PMC
    - 16 approved
    - 11 stopped
ENABLE portfolio May 2017

- 16 programmes approved for funding since start of project
- Over 3 years PMC has stopped funding of 11 programmes
Aligning IMI projects

Promising antibiotic programme gets European boost

Innovative Medicines Initiative projects European Lead Factory and ENABLE create pipeline for novel antibiotics from University of Oxford

Utrecht, the Netherlands, 17 November, 2016

Researchers at the University of Oxford have been working with two major EU-funded projects to deliver a novel antibiotic programme for clinical development. The development comes thanks to an alignment between the European Lead Factory (ELF) and the European Gram-Negative Antibacterial Engine (ENABLE) projects, both of which are supported by the Innovative Medicines Initiative (IMI), Europe’s largest public private partnership in life sciences research.

The Oxford team, led by Professor Chris Schotfield, kick started the process through his group’s focus on a potential target within gram negative bacteria that could eliminate resistance against the β-lactam antibiotics, so restoring potency of a group key antibiotics
Hit to Lead development of the new family of antibiotics MDN-0057-0060

- MEDINA compounds (MDN-0057 – 0060) were selected for preclinical Hit-to-Lead (H2L) development within ENABLE
- MEDINA program has involved a multidisciplinary core team from the University of Uppsala (Sweden), SERMAS (Spain), CNB-CSIC (Spain), University of Liège (Belgium), Asclepia (Belgium), MEDINA (Spain) and efpiia advisors
- Hit-to-Lead development program focused primarily on:
  - Generation of improved medicinal chemistry series
  - Mood of Action determination
  - *In vivo* Proof of Concept
## MDN57: Good antimicrobial profile

<table>
<thead>
<tr>
<th>Species</th>
<th>Genotype</th>
<th>MIC ug/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>E. coli</em></td>
<td>WT</td>
<td>8-16</td>
</tr>
<tr>
<td><em>E. coli</em></td>
<td>ΔtolC</td>
<td>8</td>
</tr>
<tr>
<td><em>P. aeruginosa</em></td>
<td>WT</td>
<td>16</td>
</tr>
<tr>
<td><em>P. aeruginosa</em></td>
<td>Efflux-defective</td>
<td>16</td>
</tr>
<tr>
<td><em>K. pneumoniae</em></td>
<td>WT</td>
<td>&gt;64</td>
</tr>
<tr>
<td><em>K. pneumoniae</em></td>
<td>Efflux-defective</td>
<td>8</td>
</tr>
<tr>
<td><em>A. baumannii</em></td>
<td>WT</td>
<td>8</td>
</tr>
<tr>
<td><em>A. baumannii</em></td>
<td>Efflux-defective</td>
<td>8</td>
</tr>
</tbody>
</table>
….. but high resistance frequencies observed

- **Resistance frequencies**: performed on 4 species using susceptible strains: $10^{-4}$ to $10^{-6}$ for all key species at 4-8 x MIC.

- **Whole genome analysis of *E.coli* resistant mutants**:
  - Mutations identified in heme biosynthetic pathway
Good Stability and Permeability …..

ADME assessment of MDN-0057:

- **Chemical stability** of compounds at pHs 2.0, 7.4 and 10.0
- **Good solubility** (over 100 µmol/L)
- **Good in vitro permeability** (Caco-2)
- **Metabolic stability**: Good metabolic stability in both human and mouse liver microsomes and human hepatocytes
- **Acceptable plasma stability** (after 4 h incubation in human plasma)
and preliminary good safety and in vitro toxicity data

Good safety window:

- **NO cytotoxic activity** (on HepG2 and Fa2N4 human cell lines at conc > 512 ug/mL)
- **NO cardiotoxic activity** (20% hERG inhibition at 50 μM)
- **MODERATE CYP3A4 isoform inhibition** ($\text{IC}_{50}$ 2 to 4 μM) and **NO inhibition** of CYP2D6 and CYP2C9 ($\text{IC}_{50}$ > 86 μM)
- **LOW clearance** in human liver microsomes with $t_{1/2}$ > 60 min (predicted intrinsic clearance <11 μl/min/mg microsomal protein)
- **NO haemolysis** (between 0 and 0.5%)
but unexpected in vivo toxicity in mice

Preliminary *in vivo* toxicity of MDN-0057

- **Experimental design:**
  - 3 and 30 mg/kg MDN-0057 given *iv* to fed or fasted mice
  - Sample collection before and 15, 60, 120 min after administration

- **Fast kinetics:** Rapid depletion in MDN-0057 concentration after 15 min to reach undetectable levels in 60 min

- Pronounced toxicity and mice lethality 2-20 h after administration

→ Unexpected acute toxicity and high resistance frequencies recommended the discontinuation of the program (PMC Sept 2014)
Summary

- The ENABLE consortium has brought together the skills and expertise from the public and private sectors to:
  - Create an antibacterial drug discovery platform
  - Recruit the best programmes from across Europe
  - Educate the next generation of antibacterial drug discovery experts
  - Identify two antibacterial development candidates
  - Progress at least one compound into preclinical and Phase 1 clinical studies
- A new model for collaborative drug discovery initiatives in other disease areas
Thank you

Anders Karlén • Professor
Anders.Karlen@orgfarm.uu.se

www.imi.europa.eu
@IMI_JU