New economic models for antibiotic R&D

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Where is innovation coming from?

- **Basic research**: Universities
- **Drug discovery**
  - Universities
  - SMEs
  - Publicly funded research institutes (Institute Pasteur, Frauenhofer, Deutsches Zentrum für Infektionsforschung,...)
  - Public-Private-Partnerships (Bioaster, IMI Lead factory,...)
  - Big Pharma
    - Research groups at GSK, Novartis, Merck, Genentech
    - Discovery partnerships with Roche, Sanofi-Aventis
Where is innovation coming from?

Source and developing companies for antibiotics in Phase 2 or 3 clinical development:

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Source</th>
<th>Developing companies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etromycline</td>
<td>Harvard Univ.</td>
<td>Tetraphase</td>
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<tr>
<td>Plazomicin</td>
<td>Isis</td>
<td>Achaogen</td>
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<tr>
<td>Brilacidin</td>
<td>Univ. of Penn.</td>
<td>Polymedix</td>
</tr>
<tr>
<td>Debio 1450</td>
<td>Univ. of Toronto</td>
<td>Affinium</td>
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<tr>
<td>Solithromycin</td>
<td>Optimer</td>
<td>Campra</td>
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<tr>
<td>Delafloxacin</td>
<td>Wakunaga</td>
<td>Abbott</td>
</tr>
<tr>
<td>Omadaricline</td>
<td>Paratek</td>
<td>Paratek/Bayer</td>
</tr>
<tr>
<td>Nemonoxacin</td>
<td>TaiGen</td>
<td>Procter&amp;Gamble</td>
</tr>
<tr>
<td>Radezolid</td>
<td>Yale University</td>
<td>Rib-X-Melinta</td>
</tr>
<tr>
<td>Lefamulin</td>
<td>Sandoz/Novartis</td>
<td>Nabirva</td>
</tr>
<tr>
<td>Acoraloxacin</td>
<td>J&amp;J (Janssen)</td>
<td>Furiex</td>
</tr>
<tr>
<td>POL7080</td>
<td>Univ. Zürich</td>
<td>Polyphor</td>
</tr>
<tr>
<td>Carvavance (+Triopenem)</td>
<td>Reingep</td>
<td>The Med Comp</td>
</tr>
</tbody>
</table>

* = Merger
University/Small company
Un/Small company +1000 employees
Global pharmaceutical corporation

Antibacterial projects of European SMEs

93 project in 81 companies

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Systemic antibiotics in clinical development

Clinical development pipelines for Gram-negatives:

- **Ph3**
  - BLI-comb, cephalosporin
  - Tetracycline
  - Aminoglycoside
  - Quinolone
  - Monobactam/BLI

- **Ph2**
  - Small molecules

- **Ph1**
  - New class

What to expect?

- **Adjunctive therapies**
  - Require an active antibiotic
  - Virulence factors, biofilm formation, persisters
  - Immune system stimulation, microbiome modifying
  - Phages

- **Potentiators**
  - Resistance determinants (e.g. beta-lactamase-inhibitors, efflux pump inhibitors)
  - Facilitating penetration
  - Changing the sensitivity of the bacterial cell

- **Targeted therapies**
  - Traditional antibiotics, antibodies
  - Single pathogen, especially S. aureus or P. aeruginosa

- **Prevention**
Pipelines are inappropriate

Discrepancy between antibiotic R&D pipelines and public health needs

Scientific challenges

- **Expertise**
  - Diminished pool of experience

- **Basic research**
  - Less attractive to funders and academic institutions

- **Science**
  - Penetration and efflux
  - High protein binding
  - Poor solubility, compounds not amendable to medicinal chemistry
  - Toxicity
  - High mutation frequency
WHO - Global Action Plan AMR

- Improve awareness and understanding
- Strengthen knowledge through surveillance and research
- Reduce incidence of infection
- Optimize the use of antimicrobial medicines
- Ensure sustainable investment in R&D

Convergence of principles

- Need for both push and pull mechanisms
- De-linkage (i.e., revenues delinked from volumes sold)
- Clear priority setting
- Access and sustainable use are integral considerations for all mechanisms
- Global collaboration and financing necessary
R&D financing and incentive mechanisms

- Discovery
- Preclinical
- Phase I
- Phase II
- Phase III
- Licensure

Delinkage / Push mechanisms

Pull mechanisms

- Open knowledge innovation
- Milestone and end prizes
- PDP financing
- Grants
- Subsidies
- Tax breaks

- Advance Market Commitment (AMC)
- Debt / loans
- Equity / bonds
- Government-backed volume guarantees

New economic models

- Industry proposal
  - De-linkage
  - Value based pricing in developed countries
Cross-project communication & collaboration

- **COMBACTE (Topic 1)**: Enabling clinical collaboration and refining clinical trial design. Clinical dev. of MEDI4893.
- **TRANSLOCATION (Topic 2)**: Research on penetration and efflux in Gram-negative bacteria. Data hub and learning from R&D experience.
- **ENABLE (Topic 3)**: Discovery and development of new drugs combating Gram-negative infections.
- **DRIVE-AB (Topic 4)**: Driving re-investment in R&D and the responsible use of antibiotics.
- **COMBACTE CARE (Topic 5)**: Clinical development of antibacterial agents for Gram-negative, antibiotic-resistant pathogens.
- **COMBACTE-MAGNET (Topic 6)**: Systemic molecules against healthcare-associated infections due to clinically challenging Gram-negative pathogens.
- **ABC (Topic 7)**: Inhaled anti-bacterials (inhaled monobactam, tobramycin) in cystic fibrosis and non-cystic fibrosis bronchiectasis.

ND4BB Information Centre
All data generated is submitted and made accessible to all partners

New economic models

www.drive-ab.eu

@DRIVE_AB

- Conservation
- Sustainable use
- Innovation
- Prioritisation
- Access
- Small markets LMIC

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• Prioritising models
• Providing research data
  – Defining challenges and bottlenecks, medical need
  – What does sustainable use mean, how to deal with equitable access?
  – Value of antibiotics
• Testing models
  – Fit high-level parameters? Mitigate a bottleneck?
  – How to pair with sustainable use and access?
  – Will it stimulate action? By whom? Cost/benefit?
  – How can it be implemented?
• Stakeholder involvement, implementation plan

New economic models

• Stimulate innovation + sustainable use + equitable access
• Models researched
  o Grants
    ➢ Determines research at universities, non-dilutive capital for companies
  o Product Development Partnerships
    ➢ Non-profit entity (the PDP) and private sector industry to develop drugs on a not-for-profit basis. Innovation?
  o Post-approval payments (aka lump sum payments)
    ➢ Structure of payments, source of funding, how much?
  o Payer licenses
    ➢ Annual license fee and still charge unit costs, how much?
All incentives to stimulate innovation will be paired with
- Sustainable use policies, conservation measures
- Equitable access provisions

THE WAY FORWARD
From discussion to testing and implementation

Conference on
Stimulating innovation, sustainable use and global access to antibiotics

Amsterdam, 2nd June 2016