Addressing DRI*: The Role of Partnerships

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Non-Executive Director & Consultant, Adenium Biotech ApS
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Operating Partner and Consultant, Advent Life Sciences
Voting Member (2015-18), Presidential Advisory Council on US CARB Initiative (PACCARB)

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Slides happily shared – just drop me a note

*DRI = Drug-Resistant Infections. The acronym AMR confuses the lay public as it suggests that somehow the person becomes resistant. DRI more often conveys the right message (Mendelson M et al. Antibiotic resistance has a language problem. Nature 545:23-25, 2017)
Acknowledgments

• This talk has benefited from experience gained in the CARB-X project and from work with Wellcome Trust

• Particular thanks and credits to
  – Kevin Outterson (CARB-X)
  – Tim Jinks (Wellcome Trust)
  – Joe Larsen (BARDA)

• The conversational nature of reality: The best ideas are produced only in debate with such colleagues!
Point of View: I’m an ID doctor who has spent 30 years (15 in academia, 15 in Industry) developing the tools needed for patient care – mainly new drugs, but also diagnostics

- **Antifungals**
  - Micafungin (A)
  - Caspofungin (A)
  - Anidulafungin (A)

- **Antibacterials (A) = Academia (P) = Pharma**
  - Fluconazole (A)
  - Voriconazole (A)
  - Anidulafungin (A)
  - Micafungin (A)
  - Ceftaroline (A)
  - Ceftaroline-AVI (P)
  - Ceftazidime-avibactam (P)
  - Aztreonam-avibactam (P)
  - AA139 (P)
  - Ceftazidime-avibactam (P)
  - F901318 (P)
  - Meropenem (P)
  - Ceftazidime (P)
  - Ceftazidime-avibactam (P)
  - Daptomycin (China, P)
Partnerships: What is possible?

Goal, scale, & output create a hierarchy

I. Share Information & methods
   – This is the simplest level

J. As in (I) + Joint setting of priorities + scale
   – Moving up to a global view can enable projects to become competitive at the international level

K. As in (J) + shared risk with intent to create public goods with market potential (or Knowledge)
   – Knowledge and public goods can amount to valuable infrastructure and be the equivalent of a road

OK, so the IJK is a little strained … but it helps organize the conversation
Context: The Global Agenda

• The WHO GAP (Global Action Plan)¹
  – Improve awareness & understanding of DRI
  – Reduce the incidence of infection
  – To develop the economic case for sustainable investment in new medicines, diagnostics, vaccines & other interventions
  – Optimize the use of antimicrobial agents
  – Strengthen knowledge through surveillance
  – Increase investment in new medicines, diagnostics, vaccines & other interventions

¹Lightly edited for flow and reordered to make it easier to give this talk.
The Global Agenda

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Things won’t always stay in these simple buckets, but let’s take a tour of the current partnership landscape

(and with apologies in advance for an inability to mention everything!)
Sharing Information & Methods

• The WHO GAP (Global Action Plan)\(^1\)
  
  – Improve awareness & understanding of DRI
  
  – Reduce the incidence of infection
  
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  – Optimize the use of antimicrobial agents
  
  – Strengthen knowledge through surveillance
  
  – Increase investment in new medicines, diagnostics, vaccines & other interventions

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Sharing Information & Methods (1)

• Awareness & understanding of DRI
  – CDC: GET SMART (about antibiotics) (https://www.cdc.gov/getsmart/index.html)
  – General programs like this are easily copied & transferred

• Reducing incidence of both Infection and DRI
  – Good infection control: One hospital at a time
  – Good infrastructure, use of vaccines, etc.
  – Action is local but experience can be shared and transferred
Sharing Information & Methods (2)

- Economic case for sustainable investment in new medicines, diagnostics, vaccines, etc.
  - Antibiotics: the fire extinguishers of medicine
  - Greatest value is in their non-use
  - This creates an economic tension

- Multiple global conversations on new approaches
  - EU: DRIVE-AB (an IMI\(^1\) project): a 3-year multi-stakeholder effort to create novel business models
  - US: Duke-Margolis Antimicrobial Payment Reform Project: An FDA-funded project on delinking use from profit
  - UK: Chatham House; AMR Review: Reports and workshops

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Sharing Information & Methods (3)

• Optimizing use of antibiotics
  – National or regional guidelines for human use
  – Methods to reduce / eliminate agricultural use

• (and one more): Sharing scientific knowledge
  – CARB-X\textsuperscript{ed} and GARDP\textsuperscript{2}: Workshops, webinars
  – Pew SPARK\textsuperscript{3}: A shared-information web platform

1. US Gov’t + Wellcome Trust: CARB-X is a 5-year, $450m public-private partnership that funds preclinical research (http://www.carb-x.org/)
2. DNDi & WHO: GARDP is a project that seeks to deliver data and products addressing specific gaps (https://www.dndi.org/diseases-projects/gardp/)
3. The Pew Charitable Trusts: Coming very soon, SPARK (Shared Platform for Antibiotic Research & Knowledge) will be a web-based technical knowledge sharing platform
Joint Priorities & Scale

• The WHO GAP (Global Action Plan)¹

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Joint Priorities & Scale

• R&D Networks to study and develop antibiotics & diagnostics
  – GARDP: Networks for neonatal sepsis & sexually transmitted infections
  – JPIAMR: Joint Programming Initiative for AMR: Collaborative EU work
  – Diagnostic prizes: Longitude Prize, EC prize, NIAID prize
  – Wellcome Trust: developing collaborative clinical trial network

• Strengthen knowledge through surveillance
  – UK Fleming Fund: a £265 million government investment into improving laboratory capacity for diagnosis and surveillance of AMR
  – GLASS: WHO’s Global Antimicrobial Resistance Surveillance System
  – Plus many more at national scale (e.g., CDC’s NARMS)

• Global priority setting
  – We are steadily aligning on priority pathogens (next slide...)

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<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td><em>Acinetobacter baumannii</em>, carbapenem-R</td>
<td>Critical</td>
<td>Serious (MDR)</td>
<td>Yes</td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em>, carbapenem-R</td>
<td>Critical</td>
<td>Serious (MDR)</td>
<td>Yes</td>
</tr>
<tr>
<td><em>Enterobacteriaceae</em>, carbapenem-R, 3rd-gen ceph-R (ESBL+)</td>
<td>Critical</td>
<td>Urgent (carbapenem-R)</td>
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<tr>
<td><em>Enterococcus faecium</em>, vancomycin-R</td>
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<td>Serious (VRE)</td>
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<tr>
<td><em>Staphylococcus aureus</em>, methicillin-R, vancomycin-I/R</td>
<td>High</td>
<td>Serious (MRSA)</td>
<td>Yes</td>
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<tr>
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Priority Pathogen Lists: There are now 3 and they help create global alignment
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Looking just at the highest priority pathogens, there is good overall alignment.
Ris**k**, **K**nowledge, & Mar**ket** Goods

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Risk, Knowledge, & Market Goods

• These projects create knowledge and goods, both public and private
• Because of the scale, the synergies that flow from any partnership can have very impact
• Examples
  – IMI ND4BB
  – CARB-X
  – Market Entry Reward Partnership
IMI: The ND4BB Programme

New Drugs For Bad Bugs

**ND4BB cross topic collaboration and dissemination**

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

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

**COMBACTE-NET**
- a) Enabling Clinical Collaboration and Refining Clinical Trial Design
- b) Clinical Development of compound(s) for Gram-positives
- c) Clinical Development of MEDI4893

**COMBACTE-CARE**
- Clinical Development of antibacterial 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
- Economics and stewardship
IMI: The ND4BB Programme

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**Drug development Gram-positives**

**Drug development Gram-negatives**

**Economics and stewardship**

2017-06-21 - Partnerships & Philanthropy vs. AMR
Timeline and total budget estimation of the seven topics of the ND4BB programme

EC contribution (EFPIA contribution)
Pooled funding mechanism with $455.5M committed
- US Government (BARDA, NIAID) + Wellcome Trust
- Open architecture for additional funders

Goal: Accelerate preclinical R&D through Phase 1
- Therapeutics, diagnostics, preventatives
- Best science from anywhere in the world

Will fund >50 pre-clinical R&D projects over 5 years

Public-private partnership that leverages capital
- Successful applicants must bring some funds to the table
## CARB-X Portfolio Priorities (Year 1)

<table>
<thead>
<tr>
<th>Area</th>
<th>Sub-Area</th>
<th>Priority*</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct Rx</td>
<td>Gram-negative</td>
<td>Highest</td>
<td>Need to get this area moving</td>
</tr>
<tr>
<td>Diagnostic</td>
<td>Rapid diagnosis</td>
<td></td>
<td>Especially tools that allow therapy to be stopped or not started</td>
</tr>
<tr>
<td>Diagnostic</td>
<td>Predict susceptibility</td>
<td></td>
<td>Especially tools that give strong guidance on initiation (or not) of reserve agents</td>
</tr>
<tr>
<td>Prevention</td>
<td>Any</td>
<td></td>
<td>Scientific and development plausibility must be addressed</td>
</tr>
<tr>
<td>Indirect Rx</td>
<td>Any</td>
<td></td>
<td>Scientific and development plausibility must be addressed</td>
</tr>
<tr>
<td>Direct Rx</td>
<td>Gram-positive</td>
<td>Lowest</td>
<td>Reasonable options, at least for now</td>
</tr>
</tbody>
</table>

*Priorities define the approximate shape of the overall portfolio. Priorities are expected to shift in future years.*
# CARB-X Antibacterial Product Portfolio: Eleven 30 Mar 2017 Awardees

<table>
<thead>
<tr>
<th>Sponsor</th>
<th>Product</th>
<th>Description</th>
<th>Priority</th>
<th>Development Stage</th>
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<tbody>
<tr>
<td><strong>New Abx Class?</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>New Non-traditional Product?</strong></td>
<td></td>
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<tr>
<td><strong>New Target?</strong></td>
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</tr>
<tr>
<td><strong>Description</strong></td>
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<tr>
<td><strong>CDC</strong></td>
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<td><strong>WHO</strong></td>
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<tr>
<td><strong>Hit to Lead</strong></td>
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<tr>
<td><strong>Lead Optimization</strong></td>
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<tr>
<td><strong>Pre-Clinical</strong></td>
<td></td>
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<tr>
<td><strong>Phase I</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Tetraphase Pharmaceuticals</td>
<td>TP-6076</td>
<td>Next-generation tetracycline</td>
<td>✓</td>
<td>Acinetobacter + Enterobacteriaceae</td>
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<td>Cidara Therapeutics</td>
<td>CD201</td>
<td>Bifunctional immunotherapy</td>
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<tr>
<td>Microbiotix</td>
<td>T3SS Inhibitor</td>
<td>Virulence modifier</td>
<td>✓</td>
<td>P. aeruginosa</td>
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<tr>
<td>Spero Therapeutics</td>
<td>SPR741</td>
<td>Potentiator</td>
<td>✓</td>
<td>Gram-negative activity</td>
</tr>
<tr>
<td>Entasis Therapeutics</td>
<td>ETX000</td>
<td>Oral Gram-negative combination</td>
<td>✓</td>
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<tr>
<td>Forge Therapeutics</td>
<td>FG-LpxC</td>
<td>Inhibitor of LpxC</td>
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<tr>
<td>Oppilotech</td>
<td>LPS</td>
<td>Targets synthesis of LPS</td>
<td>✓</td>
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<tr>
<td>ContraFect</td>
<td>Gram-negative lysins</td>
<td>Recombinant lysin protein</td>
<td>✓</td>
<td>P. aeruginosa</td>
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<tr>
<td>Redx Pharma</td>
<td>NBTI</td>
<td>Dual-acting topoisomerase inhibitor</td>
<td>✓</td>
<td>Acinetobacter + P. aeruginosa + Enterobacteriaceae</td>
</tr>
<tr>
<td>Visterra</td>
<td>VIS705</td>
<td>Antibody-drug conjugate</td>
<td>✓</td>
<td>P. aeruginosa</td>
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<table>
<thead>
<tr>
<th>Sponsor</th>
<th>Type</th>
<th>Technology</th>
<th>Feasibility</th>
<th>Optimization</th>
<th>Develop Product</th>
<th>Integrate &amp; Test</th>
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<tbody>
<tr>
<td>Proteus</td>
<td>Rapid Point-of-Care Diagnostic</td>
<td>Optical bacterial imaging</td>
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<td>POC Diagnostic</td>
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<td>Visterra</td>
<td>VIS705</td>
<td>✓ ✓</td>
<td>Antibody-drug conjugate</td>
<td>✓ ✓</td>
<td>P. aeruginosa</td>
</tr>
</tbody>
</table>

### Characteristics
- **New Abx Class?**
- **New Non-traditional Product?**
- **New Target?**

### Priority Development Stage
- **CDC**
- **WHO**
- **Hit to Lead**
- **Lead Optimization**
- **Pre-Clinical**
- **Phase I**

### Additional Information
- The above projects are Powered by CARB-X utilizing non-dilutive funding from BARDA, Wellcome Trust, & NIAID.
- The stage of development is approximate as of March 2017 (please refer to each company's website for updated information).
- Characterizations of new Abx Class and New Target by CARB-X, following Pew pipeline analysis:
- Other characterizations by CARB-X experts and external expert opinion. Abx = traditional small molecule antibiotic. Non-traditional Product = not a traditional small molecule antibiotic.

### Already announced:
- $48m for 10 therapies + 1 diagnostic
- 3 novel class small molecules
- 4 non-traditional products
- 7 new bacterial targets

### 1 POC diagnostic

**CARB-X Antibacterial Product Portfolio: Eleven 30 Mar 2017 Awardees**

<table>
<thead>
<tr>
<th>Sponsor</th>
<th>Product</th>
<th>Novelty</th>
<th>Priority</th>
<th>Development Stage</th>
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<tbody>
<tr>
<td>Tetraphase</td>
<td>TP-6076</td>
<td>✓</td>
<td>✓</td>
<td>Phase I</td>
</tr>
<tr>
<td>Cidara Therapeutics</td>
<td>CD201</td>
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<td>✓</td>
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<tr>
<td>Microbiotix</td>
<td>T3SS Inhibitor</td>
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<td>✓</td>
<td>Phase I</td>
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<td>Spero Therapeutics</td>
<td>SPR741</td>
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<tr>
<td>Entasis Therapeutics</td>
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<td>Phase I</td>
</tr>
<tr>
<td>Forge Therapeutics</td>
<td>FG-LpxC</td>
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<td>✓</td>
<td>Phase I</td>
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<td>Oppilotech</td>
<td>LPS Targets</td>
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<td>Phase I</td>
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<tr>
<td>ContraFect</td>
<td>Gram-negative lysins</td>
<td>✓</td>
<td>✓</td>
<td>Phase I</td>
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<td>Redx Pharma</td>
<td>NBTI</td>
<td>✓</td>
<td>✓</td>
<td>Phase I</td>
</tr>
<tr>
<td>Visterra</td>
<td>VIS705</td>
<td>✓</td>
<td>✓</td>
<td>Phase I</td>
</tr>
</tbody>
</table>

**More to come:** Expect another round of announcements in July

By the end of Year 1, CARB-X will have committed to ~20 projects for up to $115m (if all options are exercised)

Most projects will be therapies. Would expect this level of support to lead to at least one novel mechanism agent.
Market Entry Reward Partnerships

• We need to change the way we buy antibiotics
  – Fire extinguishers again – we buy, but hope not to use
  – In economics terms, antibiotics are a positive externality: You benefit from them even if you don’t (personally) use them

• Market Entry Rewards (MER)
  – An insurance-like approach to addressing the positive externality
  – A reward for registering the agent that balances limited use of agent

• MERs have not yet been implemented but we are trying and this will require at least some global coordination
  – Shared Target Product Profiles for the MERs so drug developers have a relevant and reliable target
  – Allocation of relative financial obligations to avoid free riding (NOT a global fund, but some accountability)
Summary
The power of partnerships

The impact of these partnerships highlights the conversational nature of reality

I. Share Information & methods
J. I + J Joint setting of priorities + scale
K. I + J + shared risk with intent to create public goods with market potential (or Knowledge)

To succeed vs. DRI (AMR), we need to make all 3 work!

Thank you!