Innovation in Solutions for AMR: the CARB-X Portfolio

Erin Duffy, PhD
Boston University & CARB-X

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What is CARB-X?

A global non-profit partnership created in 2016 to support the early development of new therapeutics, preventatives and diagnostics to fight drug-resistant bacteria.
Where Does CARB-X Funding Come From?

- ASPR
- BARDA
- Wellcome
- UKaid
- Federal Ministry of Education and Research
- Bill & Melinda Gates Foundation
- NIH

in-kind services
Key Facts about the CARB-X Portfolio

- 71 innovative PROJECTS funded since inception
- 45 active PROJECTS
- 10 different COUNTRIES Represented
- 7 project GRADUATES
Treatment and Prevention Portfolio Targeting Priority Pathogens for US and Worldwide

**CDC**
- Serious: 55%
- Urgent: 44%
- Concerning: 1%

**WHO**
- Critical: 83%
- High: 16%
- Other: 1%
Portfolio Addresses Many Syndromes for which New Therapies are Needed

Critical for clinical-trial conduct and market uptake
Optimization of Performance Characteristics is Key for New Entrants to Treat a Syndrome

-- although several new antibiotics that addressed the 2000s call for new drugs to treat *S. aureus* and MRSA, dosing regimen and side-effect profiles mean there is still room for new therapies with optimized performance characteristics--

- Ceftaroline (2010) IV only
  - Anaphylaxis, drug-induced hemolytic anemia, CDAD
- Dalbavancin (2014) IV only
  - ALT elevations, infusion-related reactions, CDAD
- Tedizolid (2014) IV/PO
  - Neutropenia, CDAD
- Oritavancin (2014) IV only
  - DDI (warfarin), coagulation interference, CDAD, infusion-related reactions
- Delafloxacin (2017) IV/PO
  - Tendinitis/tendon rupture, peripheral neuropathy, CNS effects, CDAD
- Omadacycline (2018) IV/PO
  - Tooth discoloration/enamel hypoplasia, inhibition of bone growth, CDAD
Therapeutics Portfolio Emphasizes Many Validated MOAs with New Chemistries and (Sometimes) New Mechanisms of Inhibition

- FabI (enoyl-ACP reductase) inhibitors
- aa tRNA synthetases
- trans translation
- non-FQ
- fatty-acid biosynthesis
- protein synthesis
- RNA synthesis
- DNA synthesis
- Novel 5%
- Cell-wall, non-peptide 20%
- Cell-wall, peptide 40%
- oral BL/BLI
  - novel PBPIs
  - lpxC
- polymyxin softdrug
  - lytic peptides
  - AMPs
  - StAMPs
  - OMPTAs (BamA and LptA)
  - octapeptins
Validated Mechanism Projects Cover All Stages of Program Maturation

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<th>Stage</th>
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Direct-acting Tx Portfolio: Risks/Challenges

- Translation of some animal models to humans
- Toxicity and understanding of underlying mechanisms
- Existing pools of resistance (cross-project initiative to address this commenced)
- Inconsistent employment of good tools to address permeability and efflux
- Access to good bioanalytical methods development
- COVID impacts on R&D supply chain
Therapeutics Portfolio Includes Several Trailblazing Non-traditional Programs

Biofilm-targeting

PPNAs

FimH

lasB

AgrA

T3SS

amidins

klebicins

Polymyxin-linker-alpha-immune-recruiting

nansponge

Novel 8%

Anti-virulence 34%

Potentiators 8%

Immune-directing 8%

Antisense 8%

Protein 17%

Antibody 17%
Non-traditional Programs Cover All Stages of Program Maturation

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Non-traditional Tx Portfolio: Risks/Challenges

- Translation of *in vitro* activity to animal models
- Translation of animal models to humans
- Regulatory guidance/paths
- PK/PD matching
- Proof that can act as monotherapy
- Proof of additional benefit over SOC antibiotics
- For antibody-based programs
  - Humanization
  - Permeation/access to site
Prevention Portfolio

- **S. aureus**
- **K. pneumoniae**
- **GAS**
- **Kp/Ab/Pa**
- **CRE**
- **VRE**
- **ESBL**
- **Phage** 12%
- **Microbiome** 25%
- **Small-molecule** 13%
- **Vaccine** 50%
- **C. difficile**
Prevention Portfolio Earlier in Development

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Vx Portfolio: Risks/Challenges

- Access to adjuvants that work in humans but that are proprietary and thus not accessible for screening
- Access to human serum samples for baseline titers
- Access to genome sequence data from recent clinical isolates, particularly from LMICs, and thus to antigenic conservation data (cross-project initiative to address this has kicked-off)
- Translation of animal models to humans
Other Pv Portfolio: Risks/Challenges

- Translation of animal models to humans
- Regulatory guidance/paths
- Production of drug substance
- For microbiome-based programs specifically
  - Rationale for selecting membership in defined consortia
  - Defining dose for clinical trials
  - Impact of diet (eg HIC vs LMIC)
  - Slower onset
Summary

• CARB-X is supporting financially and scientifically many product developers, building a robust pipeline that physicians and patients need
• Push incentives in the CARB-X window are critical to ensuring a rich and robust flow of opportunities for late-stage clinical development and commercialization
• All programs begin with a laser focus on priority and emerging pathogens
• Building an important target-product profile must include a focus on the right syndromes, the right molecular characteristics
• Investing in a diagnostics portfolio matched to the treatment and prevention portfolio is key to successful conduct of clinical trials and in market uptake
• A diversity of modalities and spectrum of novelty is important for “shots-on-goal” success
• The right screening strategy, asking the key questions, is critical to delivering a product with the legs to make it through development. Cross-project initiatives can help the portfolio and broader ecosystem to tackle some of the big challenges
Thank you!

emduffy@bu.edu
www.carb-x.org