

# Addressing DRI\*: The Role of Partnerships

John H. Rex, MD

Chief Medical Officer & Director, F2G Ltd.

Chief Strategy Officer, CARB-X

Non-Executive Director & Consultant, Adenium Biotech ApS

Expert-in-Residence, Wellcome Trust

Operating Partner and Consultant, Advent Life Sciences

Voting Member (2015-18), Presidential Advisory Council on US CARB Initiative (PACCARB)

[john.h.rex@gmail.com](mailto:john.h.rex@gmail.com)

Slides happily shared – just drop me a note

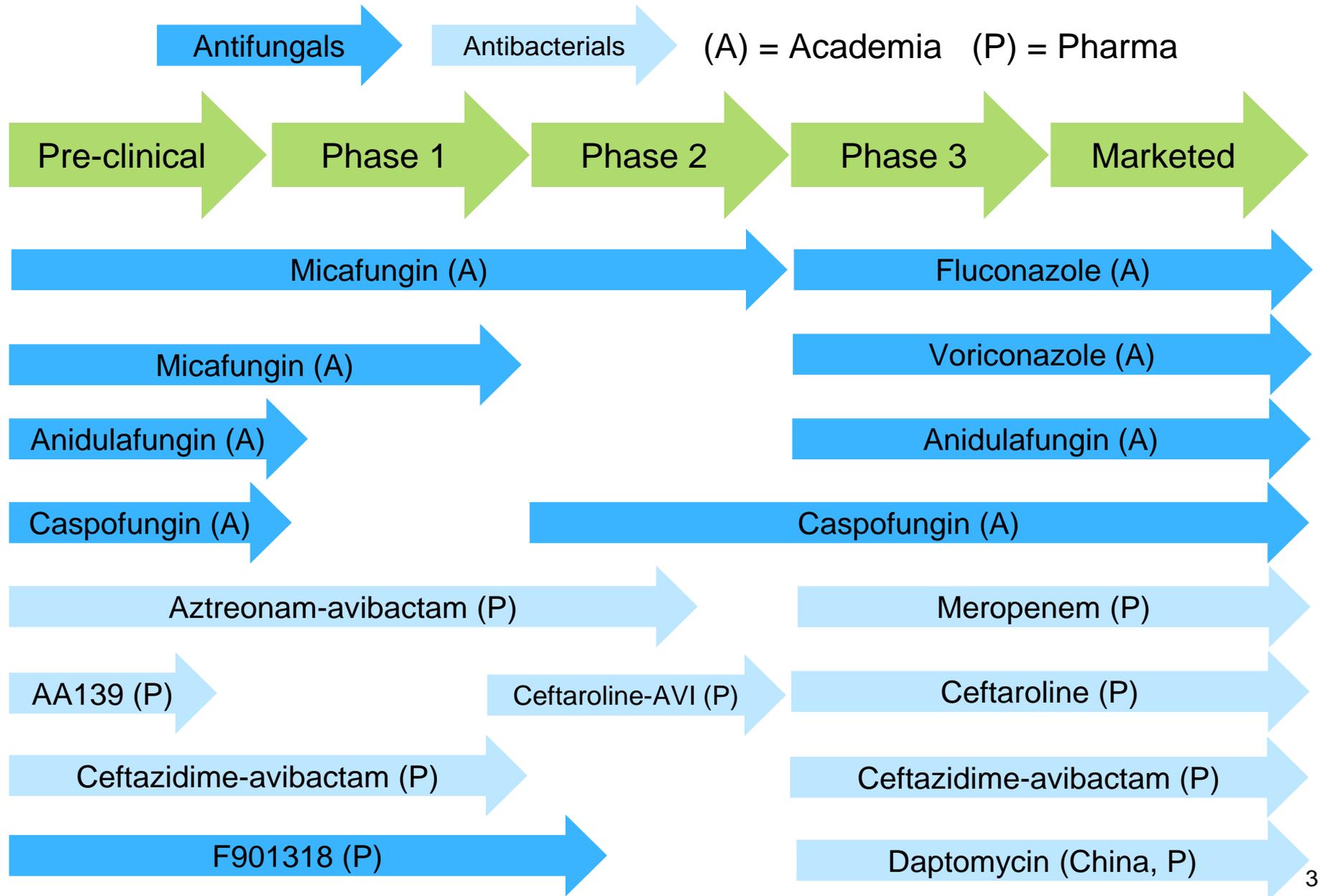
\*DRI = Drug-Resistant Infections. The acronym AMR confuses the lay public as it suggests that somehow the person becomes resistant. DRI more often conveys the right message (Mendelson M et al. Antibiotic resistance has a language problem. Nature 545:23-25, 2017)



# 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



# Partnerships: What is possible?

Goal, scale, & output create a hierarchy

I. Share **I**nformation & methods

– This is the simplest level

J. As in (I) + **J**oint 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 **k** with intent to create public goods with market **k** potential (or **K**nowledge)

– 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)<sup>1</sup>
  - 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

*<sup>1</sup>Lightly edited for flow and reordered to make it easier to give this talk*

# The Global Agenda

- The WHO GAP (Global Action Plan)<sup>1</sup>

- 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

I

J

K

<sup>1</sup>Lightly edited for flow and reordered to make it easier to give this talk

# The Global Agenda

- The WHO GAP (Global Action Plan)<sup>1</sup>

- Improve awareness & understanding of DRI

- Reduce the incidence of infection

- To develop  
sustainable  
diagnostic

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

- Optimize

- Strengthen

(and with apologies in advance for an inability to mention everything!)

- Increase investment in new medicines, diagnostics, vaccines & other interventions

J

K

<sup>1</sup>Lightly edited for flow and reordered to make it easier to give this talk

# Sharing **I**nformation & Methods

- The WHO GAP (Global Action Plan)<sup>1</sup>
  - 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



<sup>1</sup>Lightly edited for flow and reordered to make it easier to give this talk

# Sharing **I**nformation & Methods (1)

- Awareness & understanding of DRI
  - Euro AMR Barometer ([https://ec.europa.eu/health/amr/sites/amr/files/eb445\\_amr\\_generalfactsheet\\_en.pdf](https://ec.europa.eu/health/amr/sites/amr/files/eb445_amr_generalfactsheet_en.pdf))
  - 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 **I**nformation & 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<sup>1</sup> 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



1. IMI: Innovative Medicines Initiative. A multi-year collaboration between the European Commission and the Pharmaceutical Industry

# Sharing **I**nformation & 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**<sup>ed1</sup> and GARDP<sup>2</sup>: Workshops, webinars
  - Pew SPARK<sup>3</sup>: 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 CharitableTrusts: Coming very soon, SPARK (Shared Platform for Antibiotic Research & Knowledge) will be a web-based technical knowledge sharing platform

# **J**oint Priorities & Scale

- The WHO GAP (Global Action Plan)<sup>1</sup>

- 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

I

J

<sup>1</sup>Lightly edited for flow and reordered to make it easier to give this talk

# **J**oint Priorities & Scale

- R&D Networks to study and develop antibiotics & diagnostics
  - GARDP: Networks for neonatal sepsis & sexually transmitted infections
  - JPIAMR: **J**oint **P**rogramming Initiative for AMR: Collaborative EU work
  - Diagnostic prizes: Longitude Prize, EC prize, NIAID prize
  - Wellcome Trust: developing collaborative clinical trial network<sup>1</sup>
- 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...)

<sup>1</sup>McDonnell AM, Rex JH, Goossens H, Bonten M, Fowler VG, Dane A. Efficient Delivery of Investigational Antibacterial Agents via Sustainable Clinical Trial Networks. *Clinical Infectious Diseases*. 2016;63 (Suppl. 2):S57-S9.

Bacteria	WHO (2017)	CDC (2013)	ESKAPE (2008-9)
<i>Acinetobacter baumannii</i> , carbapenem-R	Critical	Serious (MDR)	Yes
<i>Pseudomonas aeruginosa</i> , carbapenem-R	Critical	Serious (MDR)	Yes
<i>Enterobacteriaceae</i> , carbapenem-R, 3 <sup>rd</sup> -gen ceph-R (ESBL+)	Critical	Urgent (carbapenem-R) Serious (ESBL+)	Yes
<i>Enterococcus faecium</i> , vancomycin-R	High	Serious (VRE)	Yes
<i>Staphylococcus aureus</i> , MRSA	High	Serious (MRSA) Concerning (VRSA)	Yes
<i>Helicobacter pylori</i>	High		
<i>Campylobacter</i> spp., macrolide-R	High	Serious (drug-R)	
<i>Salmonellae</i> spp., fluoroquinolone-R	High	Serious (drug-R)	
<i>Neisseria gonorrhoeae</i> , 3 <sup>rd</sup> -gen ceph-R, fluoroquinolone-R	High	Urgent (drug-R)	
<i>Streptococcus pneumoniae</i> , penicillin-NS	Medium	Serious (drug-R)	
<i>Haemophilus influenzae</i> , ampicillin-R	Medium		
<i>Shigella</i> spp., fluoroquinolone-R	Medium	Serious	
<i>Clostridium difficile</i>		Urgent	
<i>Candida</i> spp. fluconazole-R		Serious (Flu-R)	
<i>M. tuberculosis</i>		Serious (drug-R)	
Group A <i>Streptococcus</i>		Concerning (erythro-R)	
Group B <i>Streptococcus</i>		Concerning (clinda-R)	

Priority Pathogen Lists: There are now 3 and they help create global alignment

Bacteria	WHO (2017)	CDC (2013)	ESKAPE (2008-9)
<i>Acinetobacter baumannii</i> , carbapenem-R	Critical	Serious (MDR)	Yes
<i>Pseudomonas aeruginosa</i> , carbapenem-R	Critical	Serious (MDR)	Yes
<i>Enterobacteriaceae</i> , carbapenem-R, 3 <sup>rd</sup> -gen cep-R (ESBL+)	Critical	Urgent (carbapenem-R) Serious (ESBL+)	Yes
<i>Enterococcus faecium</i> , vancomycin-R	High	Serious (VRE)	Yes
<i>Staphylococcus aureus</i> , MRSA	High	Serious (MRSA) Concerning (VRSA)	Yes
<i>Helicobacter pylori</i>	High		
<i>Campylobacter</i>	High	Serious (drug-R)	
<i>Salmonellae</i> spp., fluoroquinolone-R	High	Serious (drug-R)	
<i>Neisseria gonorrhoeae</i> , 3 <sup>rd</sup> -gen cep-R, fluoroquinolone-R	High	Urgent (drug-R)	
<i>Streptococcus pneumoniae</i> , penicillin-NS	Medium	Serious (drug-R)	
<i>Haemophilus influenzae</i> , ampicillin-R	Medium		
<i>Shigella</i> spp., fluoroquinolone-R	Medium	Serious	
<i>Clostridium difficile</i>		Urgent	
<i>Candida</i> spp. fluconazole-R		Serious (Flu-R)	
<i>M. tuberculosis</i>		Serious (drug-R)	
Group A <i>Streptococcus</i>		Concerning (erythro-R)	
Group B <i>Streptococcus</i>		Concerning (clinda-R)	

Looking just at the highest priority pathogens, there is good overall alignment.

# Risk, Knowledge, & Market Goods

- The WHO GAP (Global Action Plan)<sup>1</sup>

- 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

I

J

K

<sup>1</sup>Lightly edited for flow and reordered to make it easier to give this talk

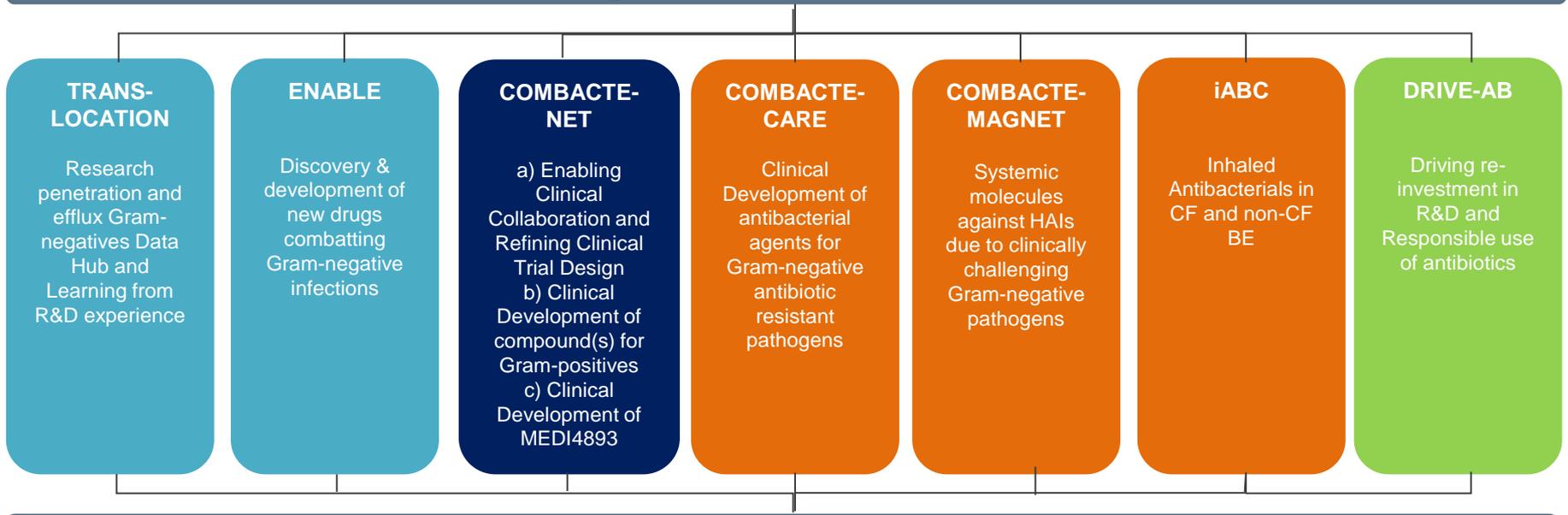
# Risk, Knowledge, & Market Goods

- 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



### ND4BB Information Center

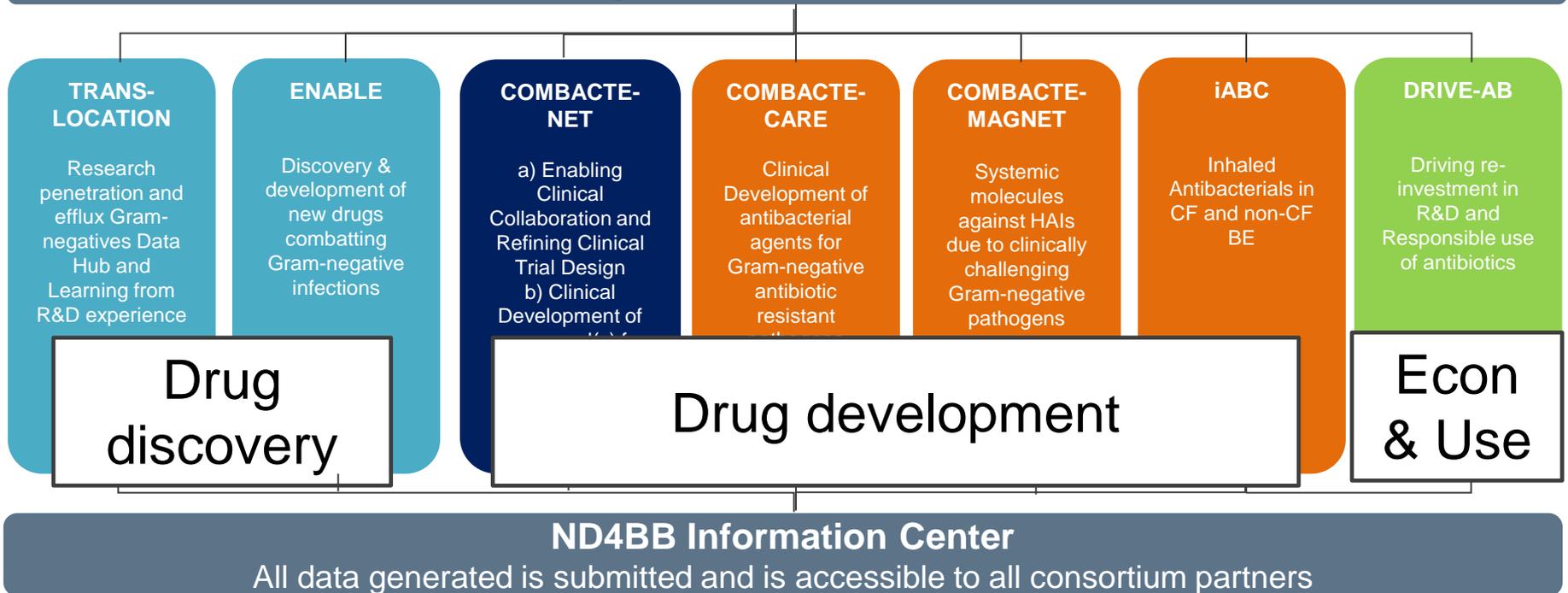
All data generated is submitted and is accessible to all consortium partners

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

# IMI: The ND4BB Programme

## *New Drugs For Bad Bugs*

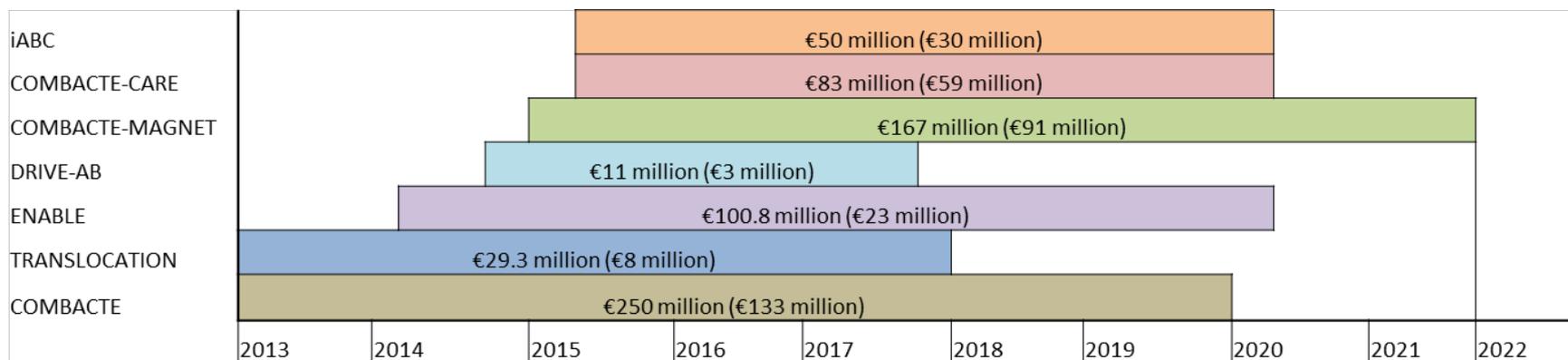
### ND4BB cross topic collaboration and dissemination



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

# Timeline and total budget estimation of the seven topics of the ND4BB programme

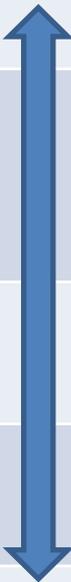
EC contribution (EFPIA contribution)



# CARB-X

- 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)

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

\*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

Sponsor	Product	Novelty			Description	Priority		Development Stage			
		New Abx Class?	New Non-traditional Product?	New Target?		CDC	WHO	Hit to Lead	Lead Optimization	Pre-Clinical	Phase I
Tetraphase Pharmaceuticals	TP-6076				Next-generation tetracycline	✓	✓	<i>Acinetobacter</i> + <i>Enterobacteriaceae</i>			
Cidara Therapeutics	CD201		✓	✓	Bifunctional immunotherapy	✓	✓	<i>Acinetobacter</i> + <i>P. aeruginosa</i> . + <i>Enterobacteriaceae</i>			
Microbiotix	T3SS Inhibitor		✓	✓	Virulence modifier	✓	✓	<i>P. aeruginosa</i>			
Spero Therapeutics	SPR741			✓	Potentiator	✓	✓	Gram-negative activity			
Entasis Therapeutics	ETX000				Oral Gram-negative combination	✓	✓	Gram-negative activity			
Forge Therapeutics	FG-LpxC	✓		✓	Inhibitor of LpxC	✓	✓	Gram-negative activity			
Oppilotech	LPS	✓		✓	Targets synthesis of LPS	✓	✓	Gram-neg activity			
ContraFect	Gram-negative lysins		✓	✓	Recombinant lysin protein	✓	✓	<i>P. aeruginosa</i>			
Redx Pharma	NBTI	✓			Dual-acting topoisomerase inhibitor	✓	✓	<i>Acinetobacter</i> + <i>P. aeruginosa</i> . + <i>Enterobacteriaceae</i>			
Visterra	VIS705		✓	✓	Antibody-drug conjugate	✓	✓	<i>P. aeruginosa</i>			

Sponsor	Type	Technology	Feasibility	Optimization	Develop Product	Integrate & Test
Proteus	Rapid Point-of-Care Diagnostic	Optical bacterial imaging	POC Diagnostic			

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: <http://www.pewtrusts.org/en/multimedia/data-visualizations/2014/antibiotics-currently-in-clinical-development>. Other characterizations by CARB-X experts and external expert opinion. Abx = traditional small molecule antibiotic. Non-traditional Product = not a traditional small molecule antibiotic.

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

Sponsor	Product	Novelty			Description	Priority		Development Stage			
		New Abx Class?	New Non-traditional Product?	New Target?		CDC	WHO	Hit to Lead	Lead Optimization	Pre-Clinical	Phase I
Tetraphase Pharmaceuticals	TP-6076				Next-generation tetracycline	✓	✓	Acinetobacter + Enterobacteriaceae			
Cidara Therapeutics	CD201										
Microbiotix	T3SS Inhibitor										
Spero Therapeutics	SPR741										
Entasis Therapeutics	ETX000										
Forge Therapeutics	FG-LpxC										
Oppilotech	LPS										
ContraFect	Gram-negative lysins										
Redx Pharma	NBTI										
Visterra	VIS705		✓	✓	Antibody-drug conjugate	✓	✓	P. aeruginosa			

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

Sponsor	Type	Technology	Feasibility	Optimization	Develop Product	Integrate & Test
Proteus	Rapid Point-of-Care					

**1 POC diagnostic**

The above projects are Powered by CARB-X. Characterizations of new Abx Class and Novelty are based on the expert opinion of CARB-X experts and external expert opinion. Abx = traditional small molecule antibiotic, non-traditional product = non-traditional small molecule antibiotic. For more information, visit the CARB-X website for updated information. Other characterizations by CARB-X.

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

Sponsor	Product	Novelty		Description	Priority		Development Stage			
		New	New							
Tetrap Pharm										Phase I
Cidara Therap										
Microb										
Spero Therap										
Entasis Therap										
Forge Therap										
Oppilo										
Contra										
Redx P										
Visterr										
Sponso										Integrate Test
Proteu										
The above Character experts and external expert opinion. Not a traditional small molecule antibiotic. Non-traditional Product. Not a traditional small molecule antibiotic.										Information), by CARB-X

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 **I** nformation & methods
- J. **I** + **J** oint setting of priorities + scale
- K. **I** + **J** + shared ris**k** with intent to create public goods with mar**k**et potential (or **K**nowledge)

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

## Thank you!