

# **CARB-X** and support for new tools for management of drug-resistant bacterial infections

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Slides happily shared – just drop me a note

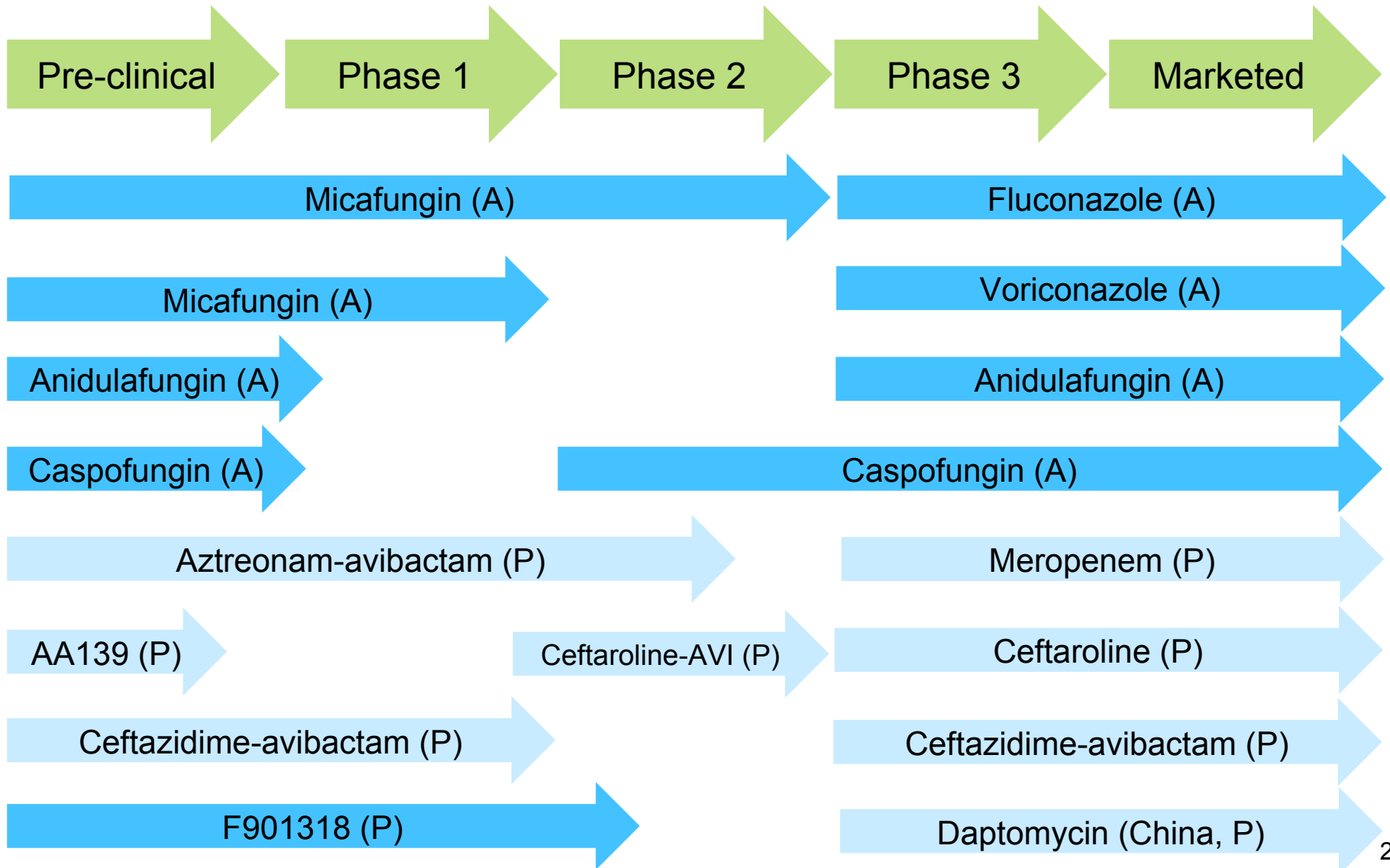
# John H. Rex, MD

# Drug development history

Antifungals

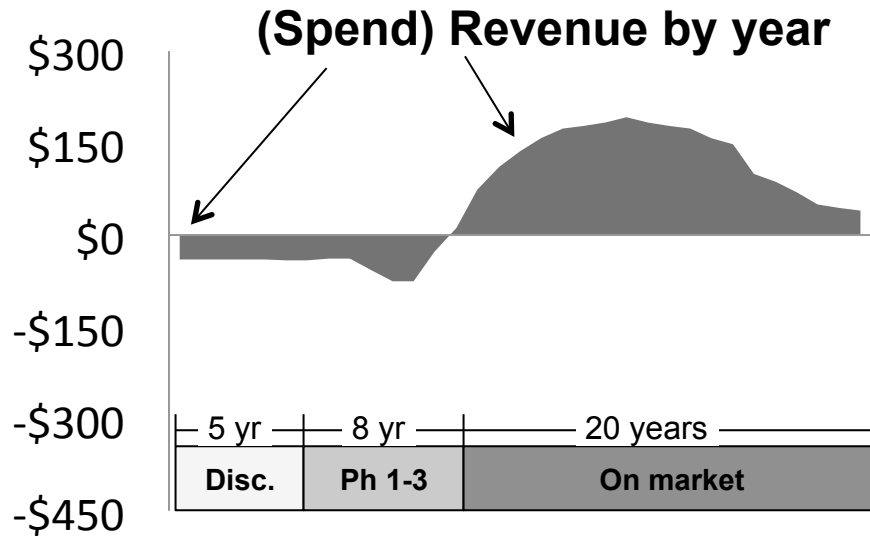
Antibacterials

(A) = Academia (P) = Pharma



To finish first,  
first you must finish

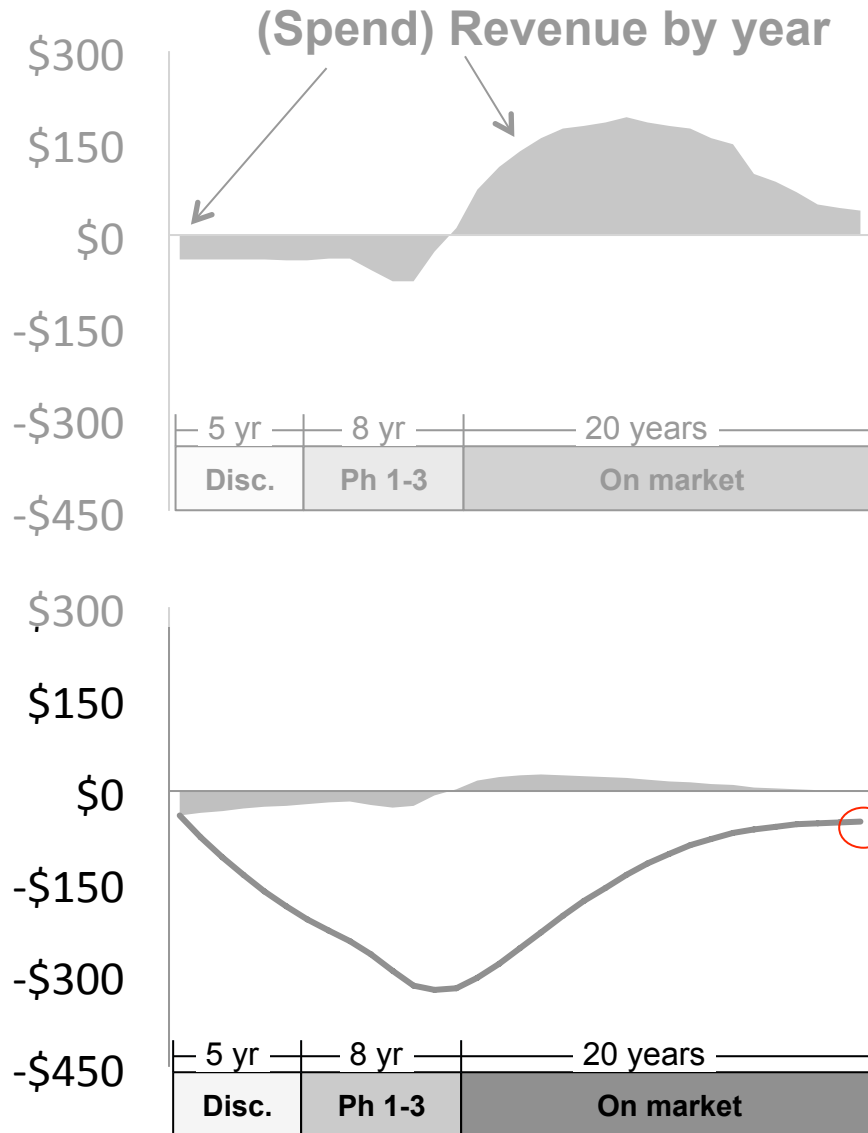
# One way to see the problem is that...



- The typical antibiotic lifecycle can be modeled from start to finish<sup>1,2</sup>
- The model at left is typical
- It allows for failed drugs
- Spend and revenue are based on industry average data

<sup>1</sup>Sharma, P. & Towse, A. New drugs to tackle antimicrobial resistance: analysis of EU policy options. OHE website, 2011; Spellberg et al. Nat Rev Drug Discov 11: 168, 2012.

# ... antibiotic R&D is financially irrational

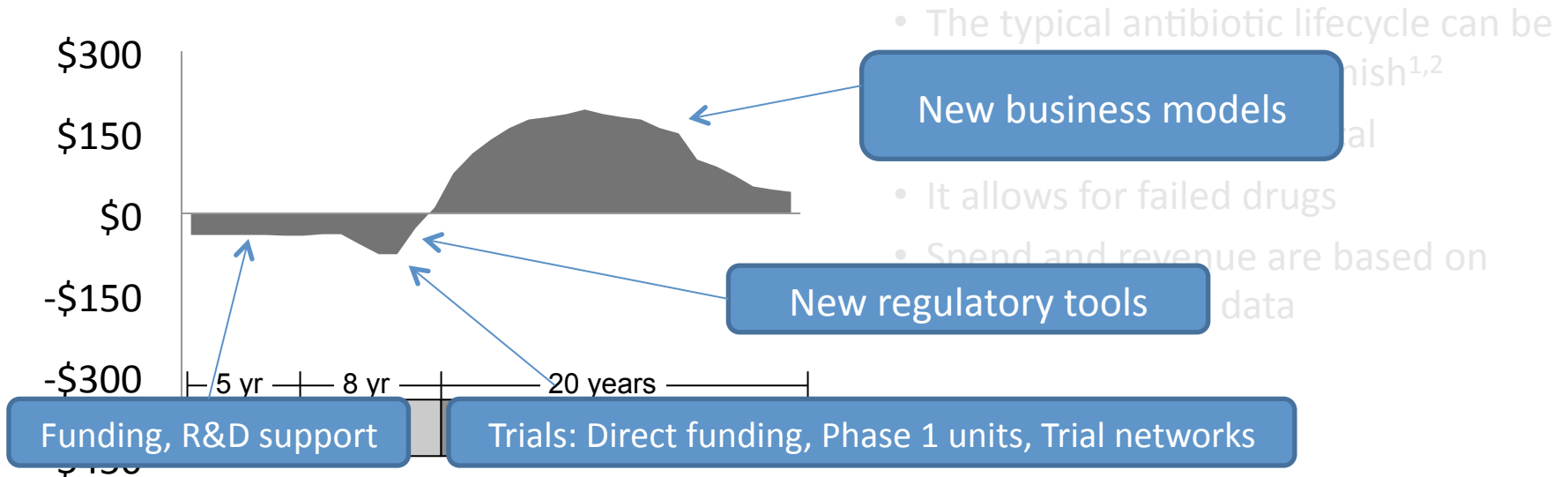


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- Converted into NPV terms and considered from Year 0 looking to Year 33...
- It yields an average loss of **-\$50m**
- Other analyses (e.g., Sertkaya 2014) give the same result

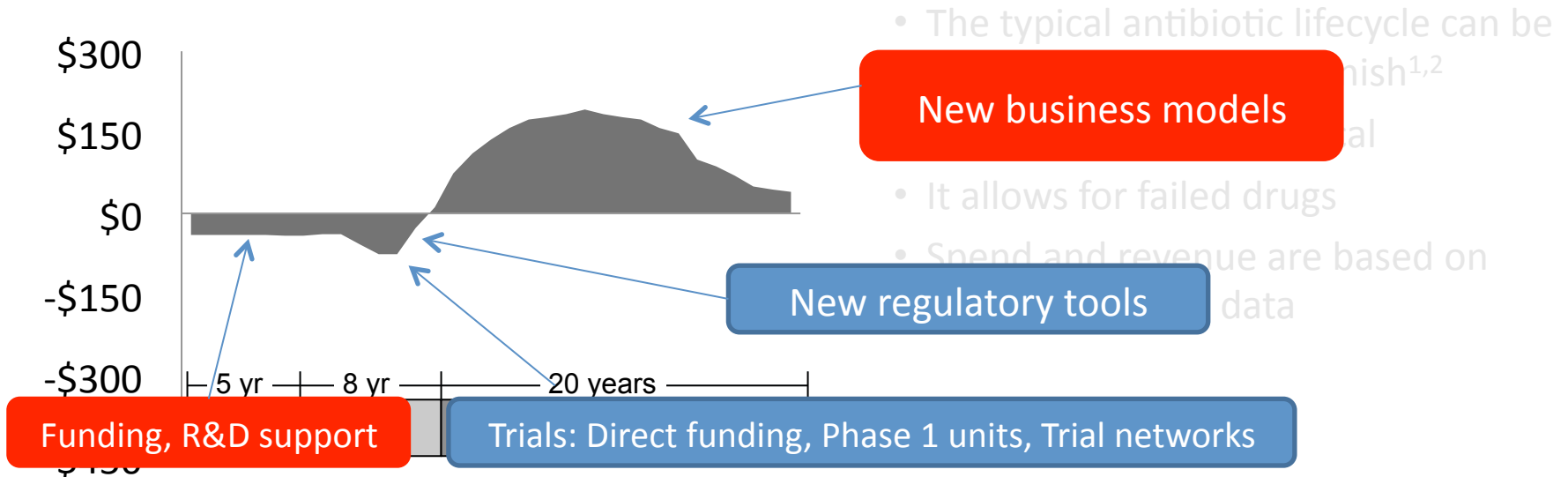
<sup>1</sup>Sharma, P. & Towse, A. New drugs to tackle antimicrobial resistance: analysis of EU policy options. OHE website, 2011; Spellberg et al. Nat Rev Drug Discov 11: 168, 2012.

# To fix, must address whole ecosystem



- A variety of tools are needed
- Relevant tools vary by phase
  - In particular, tools encouraging to a small company may differ from those that encourage a multinational

# To fix, must address whole ecosystem



- A variety of tools are needed
- Relevant tools vary by phase
  - In particular, tools encouraging to a small company may differ from those that encourage a multinational
- Today, I'm going to talk about these two elements

# Agenda

*To finish first, first you must finish*

- Introducing **CARB-X**
  - Areas of focus for **CARB-X**
- The future of the economics of antibiotics
  - What kind of product(s) will best succeed?
- Common drug R&D mistakes
- Conclusions



# CARB-X is...

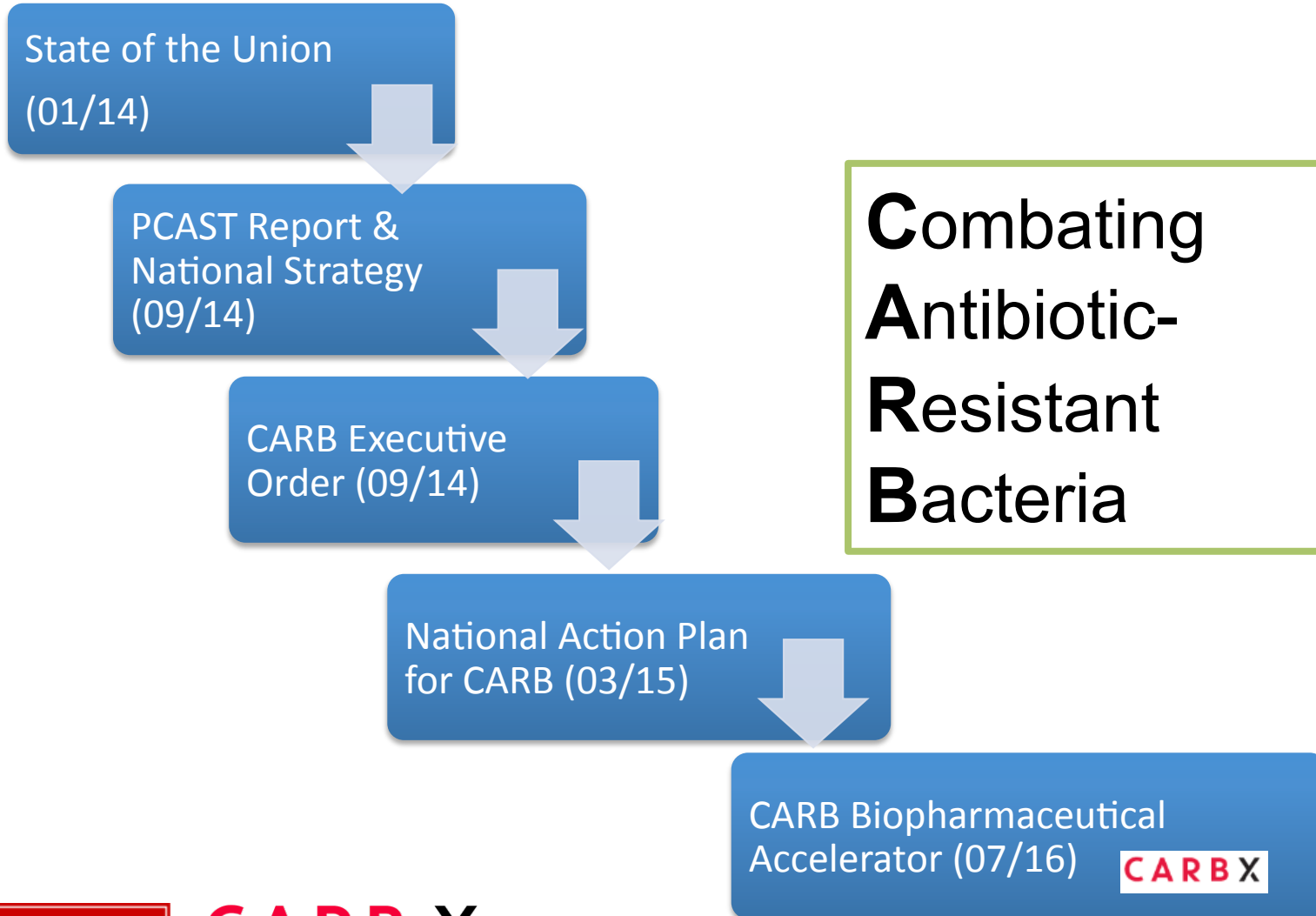
- A public-private partnership
- Based at Boston University
- A collaboration of many partners

*How did it come about?*



**CARB-X**

# Presidential Initiatives



# US National Action Plan (2015)

- GOAL 1: Slow the Emergence of Resistant Bacteria and Prevent the Spread of Resistant Infections.
- GOAL 2: Strengthen National One-Health Surveillance Efforts.
- GOAL 3: Advance Development and Use of Rapid and Innovative Diagnostic Tests
- GOAL 4: Accelerate Basic and Applied Research and Development for New Antibiotics, Other Therapeutics, and Vaccines.
- GOAL 5: Improve International Collaboration and Capacities

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CARB-X supports goals 3, 4, & 5

# CARB-X

- **Accelerate**
- **Global**
- **Antibacterial**
- **Innovation**
- More than \$350 m for pre-clinical antibiotic R&D over 5 years
- Progress more than 20 products towards IND/IDE



**CARB-X**

Outterson K, Rex JH, et al. Nat Rev Drug Disc  
2016 Sep;15(9):589-90.

# CARB-X

- Accelerate
- **Global**
- Antibacterial
- Innovation
- US-UK partnership
- Open architecture for additional partners
- No geographic restrictions on funding

# CARB-X

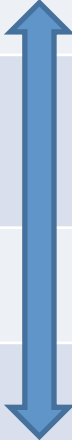
- Accelerate
- Global
- **Antibacterial**
- Innovation
- CDC Urgent & Serious Threat List (2013)
- Bacteria only
- Year 1 emphasis on therapeutics for Gram-negative bacteria

# CARB-X

- Accelerate
- Global
- Antibacterial
- **Innovation**
- No restrictions on modalities
- Therapeutics, diagnostics, and preventatives
- Bias towards game-changing innovation



# Portfolio priorities: An overall perspective

Area	Sub-Area	Priority*	Comment	
Direct Acting	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 Acting	Any		Scientific and development plausibility must be addressed	
Direct Acting	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.

# Requirements

- Applicant must be a viable developer
  - For Year 1, must be a corporate entity with money in the bank sufficient for a year
- Applicant must provide a portion of the funds
- Project must be TRL\* 3-6
  - Slightly beyond screening (a hit) to First-in-Man
- The team & plan must be plausible

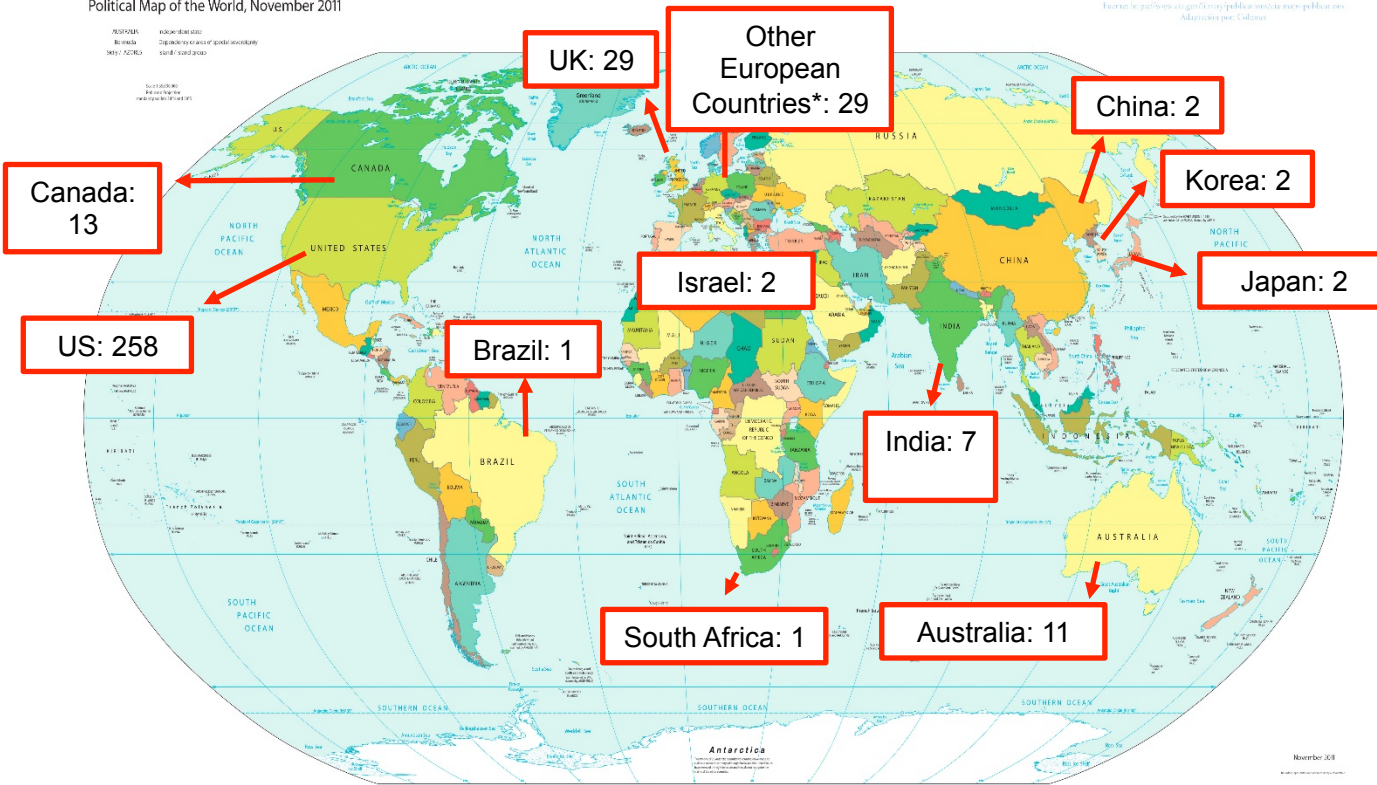
# Services provided

- To awardees
  - Funding
  - In-kind support
  - *Awardees retain all IP & ownership rights*
- To the community
  - Business support via the regional business accelerators (CLSI, MassBio)
  - Sharing insight on “how, what, and why” when making R&D choices

# CARB-X Cycles 1 & 2: EOI by Geography

Number of applications by region

Political Map of the World, November 2011



## \*Other European Countries

- Belgium: 2
- Denmark: 1
- France: 7
- Germany: 3
- Ireland: 1
- Italy: 1
- Netherlands: 2
- Norway: 1
- Portugal: 1
- Spain: 2
- Sweden: 2
- Switzerland: 6



**CARB-X**

EOI: Expression of Interest

# CARB-X: What's next?

- Year 1:
  - Aug 2016 to Jul 2017
  - No further application period is envisioned
  - Now digesting the applications on the prior slide
- Years 2+:
  - Funding cycles will be announced
  - Next cycle will be during 2H17
- Sign up for our newsletter: [www.carb-x.org](http://www.carb-x.org)

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# Current economic model is broken

- Current approach
  - Everyone is delighted to have a new drug
  - But, use is delayed and deferred in effort to preserve new antibiotic
- Stewardship perspective: Entirely rational
- Economic perspective: A financial loss
  - Many analyses show same thing: Not financially rational to do antibiotic R&D
- Problem: Current pay-per-use model reimburses for only a piece of the value

# What's a fire extinguisher worth?

- Fire extinguisher: 2 roles
  - Put out fires
  - **Be on hand to put out** fires
  - Keeps everybody safe!
- Antibiotics: 2 uses
  - Treat infections
  - Know that you **could** treat!
  - Keeps everybody safe!



*Antibiotics are the fire extinguishers of medicine!*



# Buzzword: Delinkage

- Must find economic models that separate reward from usage
- DRIVE-AB (ND4BB): Options actively being developed & piloted
- Ideas such as
  - Lump sum access fees
  - Insurance-like models
  - Market entry rewards

- Jan 2016 Davos Declaration
- 100 companies, 13 trade groups
- Ready to work in partnership with leading countries to deliver sustainable solutions to meet this global challenge.
- We seek proposals that (a) support reduction in the link between financial revenues for new antibiotics and the amount they get used while (b) mitigating the financial risk for both developers and health systems.
- <http://amr-review.org/industry-declaration>

# Implication: Novelty above all

- Fire extinguishers come in different categories
  - You need one of each!
- Incremental extensions
  - Some of this is OK
  - But, it will only go so far
- Scientific value + Unmet Need is best path to economic value
  - Novel mechanisms
  - Novel molecular basis of resistance
  - Addressing *strong* Unmet Need

KNOW YOUR FIRE EXTINGUISHER				
CHOOSING THE RIGHT EXTINGUISHER CAN PREVENT PROPERTY DAMAGE AND SAVE LIVES				
Extinguisher Type →	Water	Foam	CO <sub>2</sub>	Dry Chemical
Type of Fire ↓				
<b>A</b> Paper, Wood & Plastic	✓	✓	X	✓
<b>B</b> Flammable & Combustible Liquids	X	✓	✓	✓
<b>C</b> Electrical Equipment	X	X	✓	✓

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# (Lack of) Dose justification

- PK-PD! You can't do too much!
- One animal model + one isolate = inadequate
- You need clear data on the PD driver, clear data on a target PD index magnitude
- Such preclinical data allow you to conclusively prove you have a dose that gives the right exposure
  - And then prove to yourself **before Phase 3** that you can get that exposure **in the target population**

# (Mis)Reading Regulatory Feedback

- For Phase 1 and Phase 2 studies...
  - Agencies only say “NO!” if you are likely to injure someone
  - Designs that use exploratory endpoints for dose-finding are acceptable BUT acceptance of same does not endorse those endpoints for pivotal trials
- Following regulatory advice is an under-used strategy
  - Go talk to the Agencies. They really will make time to help
  - Listen closely!
    - It is so tempting to hear what you want to hear
    - Pay close attention when you hear the words “... sponsor risk ...”

# (Unrealistic) Expectations #1 & #2

- Expecting superiority over a fully dosed comparator
  - This really should be rare
  - Must avoid designs that deliberately enroll subjects whose infection is likely due a comparator-resistant isolate
    - Unless, of course, there are actually no other options because we've failed as a community to stay ahead of this problem...
- Chasing the really hard indications first
  - Endocarditis? Bacteremia? Osteomyelitis?
  - There may be a path here, but you must first understand general safety and pharmacology
  - Do one of the basic indications to get started!

# (Unrealistic) Expectation #3

- “We want to be labeled for treatment of *CRE*”
  - This does not happen!
- Instead, your drug will be indicated for
  - Treatment of Infection X
    - caused by strains of Y
      - that are susceptible to *your drug*
- Especially across compound classes, resistance to one drug does not have a 1:1 linkage to susceptibility to another drug

# The seduction of potentiators

- Potentiators of other drugs have long intrigued
- Two categories (with a continuum between)
  - Lights on/lights off: Beta-lactamase inhibitors protect the partner Beta-lactam (the BL itself can look completely R)
  - Shift the MIC : polymyxin derivatives seem to improve activity of a partner, but only if the partner is still active
- This is a very subtle and easily misunderstood area
  - The combination needs to have the clarity of single drug
  - The PK (and site penetration) of the partners must match
- DO NOT IMPLICITLY PLAN ON SUPERIORITY
  - In the “Shift MIC” paradigm, final clinical test boils down to showing Partner + Potentiator > Partner **in terms of clinical effect**
  - I think this is *extremely* high risk
  - This is NOT a regulatory problem: Why would you pay otherwise?



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# Key points

- CARB-X has now come to life
  - Initial focus on Gram-negative therapeutics
  - Ultimately open to all modalities
- Seek novelty that addresses Unmet Need!
- Keep it simple!
  - Avoid the common drug R&D mistakes, especially those that implicitly rely on superiority
  - Required # of miracles should be less than one

**Thank you!**