CARB-X

Combating Antibiotic Resistant Bacteria

BOSTON UNIVERSITY

CARB-X 2019 Funding Rounds

Supporting innovation to fight drug-resistant bacteria

April 30, 2019

CARB-X

Combating Antibiotic Resistant Bacteria

Today's agenda

- CARB-X in brief
- How CARB-X funding works
- CARB-X 2019 Funding Rounds in detail
  - Non-traditional approaches
  - Vaccines and Biotherapeutics
  - Diagnostics
  - Direct-acting small molecule
- Questions and discussion

CARB-X

Combating Antibiotic Resistant Bacteria

A global public-private partnership supporting great science to fight drug-resistant bacteria

FUNDERS

ASPR ASSISTANT SECRETARY FOR PREPAREDNESS AND RESPONSE

BARDA BIOMEDICAL ADVANCED RESEARCH AND DEVELOPMENT AUTHORITY

wellcome

NIH National Institute of Allergy and Infectious Diseases

UKaid from the British people

Federal Ministry of Education and Research

ALLIANCE PARTNER

BILL & MELINDA GATES foundation

ACCELERATORS

BASEL AREA. SWISS

BioInnovation Institute

CLSI CALIFORNIA LIFE SCIENCES INSTITUTE

C-CAMP Centre for Cellular and Molecular Platforms

DZIF German Center for Infection Research

FIND Because diagnosis matters

ILSE INSTITUTE FOR LIFE SCIENCE ENTREPRENEURSHIP

MassBio MASSACHUSETTS BIOTECHNOLOGY COUNCIL

RTI INTERNATIONAL

wellcome

CARB-X is investing > $550 million in 2016-2021

- Non-profit partnership supporting R&D from around the world to address the most serious drug-resistant bacteria
  - Non-dilutive funding and accelerator support for the early development of antibiotics, diagnostics, vaccines and other life-saving products
  - Since it was established in 2016, CARB-X has announced $110.8 million in awards, plus an additional $106.6 million if project milestones are met
  - Since it was established, CARB-X has supported 42 projects in 7 countries

CARB-X Portfolio currently has 29 Projects in 5 Countries

North America

Forge Therapeutics**
San Diego, CA

Inhibrx
La Jolla CA

Amicrobe Inc.
Calsbad, CA

Recida Therpeutics
Menlo Park, CA

Talis Biomedical
Menlo Park, CA

MicuRx Pharmaceuticals
Hayward, CA

SciBac
San Francisco, CA

Specific Diagnostics
Mountain View, CA

Curza
Salt Lake City, UT

VenatoRx Pharmaceuticals
Malvern, PA

Integrated Biotherapeutics
Rockville, MD

Contrafect Corporation**
Yonkers, NY

Seres Therapeutics
Cambridge, MA

T2 Biosystems
Lexington, MA

Helixbind Inc.
Marlborough, MA

Tetraphase Pharmaceuticals
Watertown, MA

Macrolide Pharmaceuticals
Watertown, MA

Entasis Therapeutics **
Waltham, MA

Microbiotix Inc.
Worcester, MA

Europe and Asia

Proteus IRC
Edinburgh, Scotland

Summit Therapeutics
Oxford, UK

Antabio
Labège, France

Idorsia
Allschwil, Switzerland

Polyphor
Allschwil, Switzerland

Debiopharm International S.A.
Lausanne, Switzerland

Bugworks Research India Pvt Ltd.
Bangalore, India

* As of April 18, 2019
** More than 1 project funded

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Powered by CARB-X

Diversified portfolio, continually growing and evolving

- **3** in Ph 1 clinical trials; plus 3 graduates in the clinic
- **12** focused on new classes of antibiotics
- **8** non-traditional projects including 2 microbiome
- **11** new molecular targets
- **5** rapid diagnostics
- **1** vaccine

More awards from 2018 Funding Rounds to be announced soon

CARB-X Antibacterial Treatment and Prevention Product Portfolio 2019.04.18

Sponsor	Product	Novelty: New Abx Class	Novelty: New Non-traditional Product	Novelty: New Target	Description	Priority: CDC	Priority: WHO	Development Stage: Hit to Lead	Development Stage: Lead Optimization	Development Stage: Pre-Clinical	Development Stage: Phase I
Amicrobe	Amicidin-β		✓		Next-generation lead antimicrobial	✓	✓			Broad spectrum	
Antabio	PDI		✓	✓	Pseudomonas virulence inhibitor	✓	✓		P. aeruginosa		
Bugworks Research	GYRI/II	✓			Gyrase-topoisomerase inhibitor	✓	✓		Gram-negative activity		
CorinPact	Gram-negative phage/lysin	✓			Phage-encoded lytic therapeutic	✓	✓	Gram-negative activity			
CorinPact	Gram-negative lysin		✓	✓	Recombinant lysin protein	✓	✓	P. aeruginosa			
Curza	C2-02	✓		✓	Novel class Gram-negative	✓	✓		Broad Spectrum		
Debiopharm International SA	Debio1453	✓		✓	Narrow-spectrum inhibitors of FtsA	✓	✓	Neisseria Gonorrhoeae			
Entasis Therapeutics	ETX0282/CPD P				Oral Gram-negative combination	✓	✓			Gram-negative activity	
Entasis Therapeutics	Non-BL PBPi	✓			Non-beta-lactam PBPi	✓	✓		Gram-negative activity		
Forge Therapeutics	FG-LpxC-LUNG	✓		✓	LpxC inhibitor	✓	✓		Gram-negative activity		
Forge Therapeutics	FG-LpxC-UTI	✓		✓	LpxC inhibitor	✓	✓		Gram-negative activity		
Iderxia	TopESKAPE	✓			Oral acting topoisomerase inhibitor	✓	✓		Acinetobacter, Pseudomonas, & Enterobacteriaceae		
Inhibrx	INBRX-111		✓	✓	Multi-specific antibody	✓	✓			P. aeruginosa	
Integrated BioTherapeutics	iBT-vi02		✓		Multi-valent toxoid vaccine	✓	✓			E. aureus	
Macrolide	Novel Macrolides				Novel macrolide antibiotics with Gram-negative activity	✓	✓		Gram-negative activity		
Microbiotix	T3SS inhibitor		✓	✓	Virulence modifier	✓	✓	P. aeruginosa			
Micuffa	MRX-8				Soft drug polymyxin	✓	✓			Gram-negative activity	
Polyphor	DMPTA POL7306	✓		✓	Novel class, MDR/XDR CRAB/PE	✓	✓			Gram-negative activity	
Recida Therapeutics	RC-01	✓		✓	LpxC inhibitor	✓	✓				Enterobacteriaceae + P. aeruginosa
Scibac	SCB-102		✓		Microbiome	✓	✓		C.difficile		
Seres Therapeutics	SER-155		✓		Microbiome - transplant patients	✓	✓	Broad spectrum activity vs CRO/VRE			
Summit Therapeutics	SMT-571 Series	✓		✓	Novel class, orally active antibiotic	✓	✓		Neisseria Gonorrhoeae		
Tetraphase Pharmaceuticals	TP-6076				Next-generation tetracycline	✓	✓				Acinetobacter & Enterobacteriaceae
Venatorx	VNRX-PBP	✓			β-lactamase-resistant PBP inhibitor	✓	✓	Enterobacteriaceae			

CARB-X Antibacterial Devices and Diagnostic Product Portfolio

Sponsor	Type	Technology	Description: Feasibility Demonstration	Description: Optimization and Preparation for Development	Description: Product Development	Description: System Integration and Testing
Hatabind	Hospital Dx	Automated culture-free pathogen ID			Bloodstream infections	
Proteus	Rapid POC Dx	Optical bacterial imaging			POC Diagnostic	
Specific Diagnostics	Hospital Dx	Colorimetric Sensor Array to detect VOCs			Bloodstream infections	
Talis	Point-of-care Dx	Pathogen ID, Phenotypic AST	AST Neisseria gonorrhoeae, MDR-TB and Chlamydia trachomatis			
T2 Biosystems	Hospital Dx	Expanded bacteria and resistance panels for T2Dx			Bloodstream infections	

As of April 18, 2019

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Global Accelerator Network

Business and Scientific Expertise and Support

CARB-X

Global Accelerator Network

10 world class accelerators in 6 countries supporting the development of antibiotics and other life-saving products to fight drug-resistant superbugs

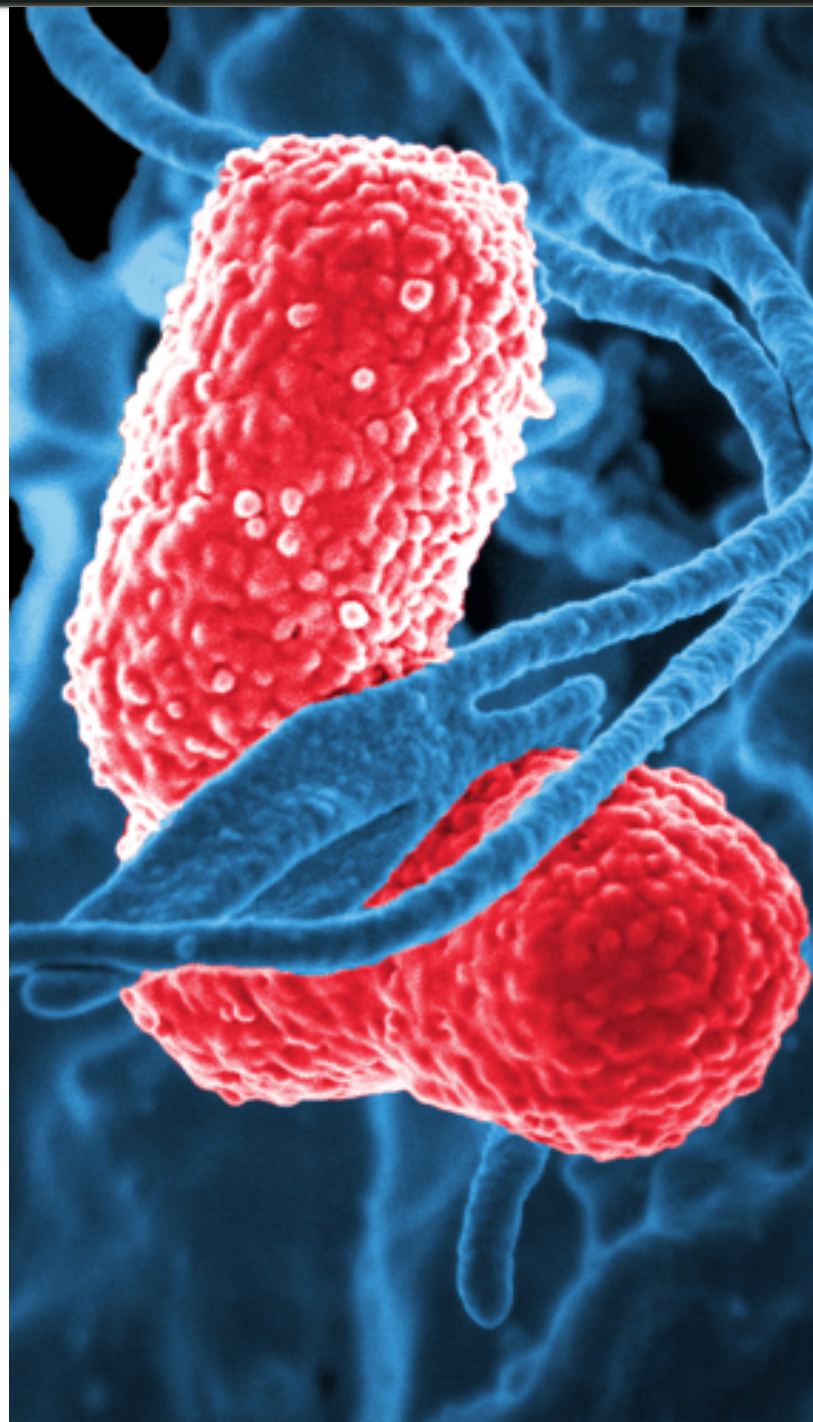
The CARB-X Advantage

- A global approach, with the world's largest early development antibacterial portfolio
- Entrepreneurial culture, accelerating the most urgently needed innovative products with both funding and expert business, technical and regulatory support
- Focused on the most dangerous bacterial pathogens. Making a difference in the fight against drug resistance
- Investment community and policy makers gain valuable insight into potential new products, science and technology
- Bias towards more innovative, ground-breaking projects

What CARB-X Funds

- Early development projects that address serious bacterial threats
  - antibiotics and therapeutics
  - prevention such as vaccines, microbiome, antibodies
  - rapid diagnostics (pathogen ID/AST)

- Projects must target specific bacteria on the Antibiotic Resistance Threats List issued by the Centers for Disease Control and Prevention (CDC) in 2013 or on the Priority Bacterial Pathogens list published by the World Health Organization (WHO) in 2017



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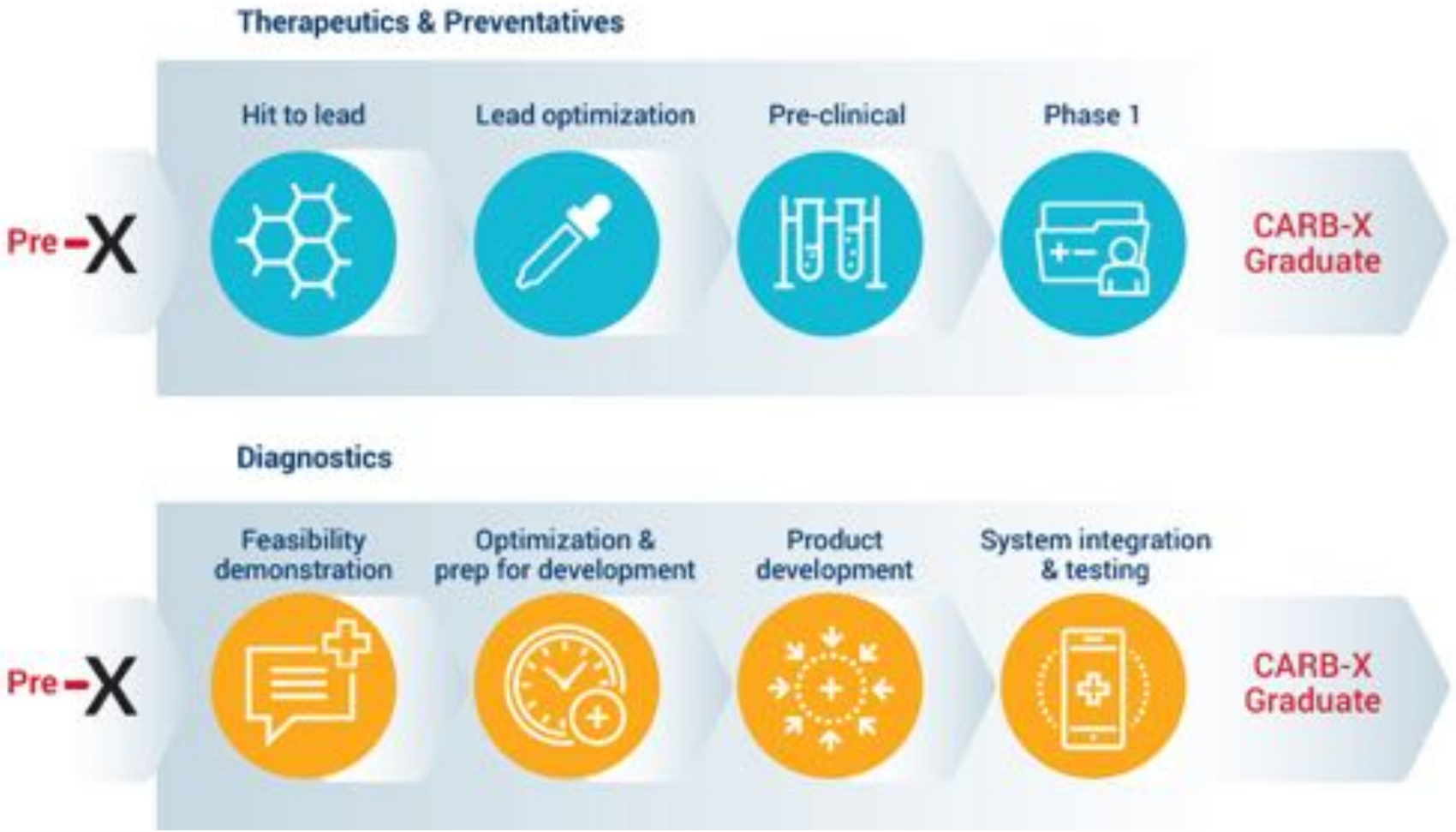
CARB-X supports projects in Early Development



NB - scope definitions will be refined prior to the opening of that specific funding round

How Funding Decisions are Made

- Projects are selected through a global competitive process
- Science Advisory Board reviews applications and makes recommendations
- Joint Oversight Committee makes funding decisions

Who Can Apply for CARB-X Funding?

CARB-X welcomes applications from around the world

- Projects must be in scope – CARB-X and specific round
- Applicants must have a legal entity
- Applicants must be able to contribute at least 20% of the cost of the project/program ('cost-share') – base and option stages. At the time of execution of the sub-award (contract), applicants must
  - Have secured cost-share funds for the base stage of the project
  - Be a going concern or have a viable strategy to achieve/maintain financial sustainability
- At the time of execution of a sub-award (contract), applicants must own or have rights to the intellectual property and reasonable expectation of freedom to operate required to carry out the project
- Applicants must have operations or capabilities in place to support product development, particularly through development stages in scope for CARB-X
- Applicants must be able to comply with UK NC3R requirements and US regulatory requirements for animal and human subjects research
- Applicants from noncommercial centers or academic institutions must meet additional requirements (next slide)

CARB-X Welcomes Applications from Academic and Non-commercial Developers

Organization must be able to demonstrate R&D/business capabilities

- Capabilities similar to those expected of a drug development industry partner, particularly through the development stages in scope for CARB-X.
- Access to and use of relevant experts (internal and/or external) to advance projects toward clinical investigation within the framework of a major regulatory agency, e.g. FDA, EMA, PMDA
- Active management of IP supporting the project
- Well-developed strategy for advancement to early clinical development
- Capabilities in commercial (business) development and technology transfer with options for 'exit strategy' (e.g. spin out, licensure to biotech)
- Financial commitment and stability to cover cost share of at least 20% of the base stage (and any subsequent option stages as these are contracted)

Please note: CARB-X does not fund basic research/drug discovery including screening for novel targets

Research Compliance Requirements

- CARB-X is committed to the highest ethical standards in all research and business operations.
- CARB-X funded companies must comply with US Government regulatory requirements for animal research and human subjects research, even if the research is conducted outside the United States
  - **Office of Laboratory Animal Welfare (OLAW)** requirements for studies involving any vertebrate species
  - **USDA Registration** requirements for US-based research facilities performing studies involving warm-blooded animals not specifically excluded from the definition of "animal" in the US Animal Welfare Act and Animal Welfare Regulations
  - **Office of Human Research Protections (OHRP)** requirements for human subjects research
- CARB-X funded companies must make every reasonable effort to comply with NC3R guidance for studies involving large animals (primates, cats, dogs, equines)
- These requirements may impact both time and budget; they are critical to consider when building your project plan

UK Government Funding to CARB-X

- The UK Government's contribution to CARB-X is designated as 'official development assistance' or ODA
- The CARB-X application process uses the term ‘ODA’ to categorize this specific funding stream
- These funds are for R&D which can demonstrate specific benefits to people living in low- and middle-income countries (LMICs)
- Companies with projects that are applicable or can be adapted to suit the needs of people in LMICs are welcome to apply for these funds
- Applicability can be demonstrated in a number of ways including (but not limited to)
  - The method of intervention designed for use in resource-poor healthcare settings
  - The choice of target pathogen which has a demonstrably high burden in LMICs
  - The ability to reduce costs of the product to increase affordability for LMICs
  - As well as other solutions

UK Government Funding to CARB-X cont'd

- Scope includes programs which can be designated as 'alternatives to traditional antibiotics', e.g.
  - Bacteriophage
  - Microbiome
  - Vaccines
  - Antibodies
  - potentiators (including beta-lactamase inhibitors)
  - anti-biofilm approaches
  - anti-virulence approaches
  - and other approaches exemplified in the Lancet publication by Czaplewski et al entitled *'Alternatives to antibiotics—a pipeline portfolio review'* (if within the general CARB-X funding scope)
- Direct-acting small molecule and diagnostic programs are not included in the GAMRIF funding scope

- ODA-eligible research and development
  - Must target problems directly and primarily relevant to LMICs
  - Should investigate a specific problem or seek a specific outcome which will impact LMICs in the immediate or longer-term
  - Demonstrate appropriate pathways to ensure LMIC benefits from the research
  - While LMICs should be the primary beneficiaries, the research can also be relevant and have secondary benefits for higher-income countries

Details https://carb-x.org/apply

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What to Expect When You Apply

About 8 months from EOI to decision

1	2	3	4	5	6	7	8
Cycle begins	**Expression of Interest**	**Review by CARB-X**	**Short Form**	**Review by CARB-X**	**Long form**	**Final Review**	**Funding**
CARB-X sets the scope and timing of funding cycle, and opens the application period.	Product developers submit a non-confidential Expression of Interest (EOI) summarizing the product proposed as a candidate for support.	CARB-X evaluates the application and selects qualifying projects. CARB-X invites selected applicants via email to provide more detail in a confidential Short Form.	Selected companies submit a confidential Short Form.	CARB-X evaluates the Short Form and invites selected applicants via email to provide more detail in a confidential Long Form.	Selected applicants submit a Long Form and detailed budget.	Long Form applicants are invited to present their project proposals in person to an Advisory Board panel. Applicants undergo due diligence.	Final funding decisions made by CARB-X's JOC. Sub-award negotiations begin on project plan, milestones and budgets. Applicants must agree contractually to certain standards and conditions. Project support begins.

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2019: Four Funding Rounds

- Funding Round 1 – Non-traditional approaches
  - Open for applications: June 3 – June 10, 2019, 5 PM ET
- Funding Round 2 – Vaccines and biotherapeutics
  - Open for applications: July 8 – July 15, 2019, 5 PM ET
- Funding Round 3 – Diagnostics
  - Open for applications: August 12 – August 19, 2019, 5 PM ET
- Funding Round 4 – Direct-acting small molecule
  - Open for applications: November 12 – November 19, 2019, 5 PM ET

The only way to apply

Applicants must complete and submit the online Expression of interest form at https://carb-x.org/apply during the periods specified for each round. The online application tool will be functional only during these periods.

CARB-X 2019 Funding Round 1

- Scope: Non-traditional approaches
  - Indirect acting small molecules (virulence, potentiators, BLI combinations etc.)
  - Direct- and indirect-acting large molecules (peptides, etc.)
  - Phage
  - Microbiome
  - Nucleic acid/anti-sense
  - Drug conjugates (ADC, other dual acting drug conjugates)
  - See next slide for scope in detail
- Expressions of Interest (EOI) accepted online only https://carb-x.org/apply
- EOI must be submitted June 3 - June 10, 2019, 5 PM ET

Applying for Round 1?
Mark your calendar
June 3 – 10, 2019, 5 PM ET

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CARB-X 2019 Funding Round 1 – Non-traditional approaches

Examples: indirect-acting small molecules (anti-virulence approaches, potentiators, BLI combinations etc.), direct acting or indirect-acting large molecules (peptides etc.), microbiome, phage, nucleic acid/antisense, drug conjugates (ADC, other dual acting drug conjugates) etc. as per the pathogens below. Host-directed therapies are not in scope. Biocides/antiseptics/disinfectants are not in scope. EOI must be submitted online June 3 - June 10, 2019, 5 PM ET. https://carb-x.org/apply

Pathogen Scope	Area Scope		
	Prevention	Indirect Tx	Direct Tx*
Acinetobacter baumannii, carbapenem-R	YES	YES	YES
Pseudomonas aeruginosa, carbapenem-R	YES	YES	YES
Enterobacteriaceae, *carbapenem-R, 3rd-gen ceph-R (ESBL+)*	YES	YES	YES
Enterococcus faecium, vancomycin-R	YES	YES	NO
Staphylococcus aureus, methicillin-R, vancomycin-I/R	YES	YES	NO
Campylobacter spp., fluoroquinolone-R	YES	YES	NO
Salmonellae spp., fluoroquinolone-R	YES	YES	YES
Neisseria gonorrhoeae, 3rd-gen ceph-R, fluoroquinolone-R	YES	YES	YES
Streptococcus pneumoniae, penicillin-NS	YES	YES	NO
Shigella spp., fluoroquinolone-R	YES	YES	YES
Group A *Streptococcus*	YES	YES	NO
Group B *Streptococcus*	YES	YES	NO

Tx = therapeutic

NB: For BLI products – scope is restricted to products that are both 1) broad spectrum (product needs to address both serine and metallo-betalactamases) and 2) have oral delivery

*the spectrum of direct acting products can include Gram-positive pathogens however the program must prioritize the Gram-negative pathogens included in the product's spectrum, as evidenced by the data developed at time of application and the workplan/TPP presented to CARB-X

Mode of administration preference guidance:
For Enterobacteriaceae offerings: If Tx is only for ESBL (e.g. lacks CRE), PO options are higher priority than IV only
For *Salmonellae spp*., *Shigella spp*. and *Neisseria gonorrhoeae* offerings – if Tx (direct or indirect), oral delivery is strongly preferred
The only topical delivery in scope is inhalation (e.g. dermal, nasal, intra-wound/surgical site, ocular etc. are not in scope)

CARB-X 2019 Funding Round 2

- Scope: Vaccines & Biotherapeutics
  - Vaccines
  - Therapeutic and preventative antibodies and fragments
  - Other large molecule biotherapeutics (not direct- or indirect-acting peptides)
  - See next slide for scope in detail
- Expressions of Interest (EOI) accepted online only https://carb-x.org/apply
- EOI must be submitted July 8 – July 15, 2019, 5 PM ET

Applying for Round 2?
Mark your calendar
July 8 – 15, 2019, 5 PM ET

CARB-X 2019 Funding Round 2 – Vaccines & Biotherapeutics

Vaccines, therapeutic and preventative antibodies and fragments, other large molecule biotherapeutic approaches (not including direct- or indirect-acting peptides) as per the pathogens below. Host-directed approaches are not in scope.

EOI must be submitted online July 8 – July 15, 2019, 5 PM ET. https://carb-x.org/apply

Pathogen Scope	Area Scope		
	Prevention	Indirect Tx	Direct Tx*
Acinetobacter baumannii, carbapenem-R	YES	YES	YES
Pseudomonas aeruginosa, carbapenem-R	YES	YES	YES
Enterobacteriaceae, *carbapenem-R, 3rd-gen ceph-R (ESBL+)*	YES	YES	YES
Enterococcus faecium, vancomycin-R	YES	YES	NO
Staphylococcus aureus, methicillin-R, vancomycin-I/R	YES	YES	NO
Campylobacter spp., fluoroquinolone-R[1]	YES	YES	NO
Salmonellae spp., fluoroquinolone-R[1]	YES	YES	YES
Neisseria gonorrhoeae, 3rd-gen ceph-R, fluoroquinolone-R	YES	YES	YES
Streptococcus pneumoniae, penicillin-NS	YES	YES	NO
Shigella spp., fluoroquinolone-R[1]	YES	YES	YES
Group A *Streptococcus*	YES	YES	NO
Group B *Streptococcus*	YES	YES	NO

Tx = therapeutic

*the spectrum of direct acting products can include Gram-positive pathogens however the program must prioritize the Gram-negative pathogens included in the product's spectrum, as evidenced by the data developed at time of application and the workplan/TPP presented to CARB-X

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CARB-X 2019 Funding Round 3

- Scope: Diagnostics
  - Pathogen ID/AST
  - See next slide for detailed pathogen list
- Expressions of Interest (EOI) accepted online only https://carb-x.org/apply
- EOI must be submitted August 12 – August 19, 2019, 5 PM ET

CARB-X 2019 Funding Round 3 – Diagnostics

Only pathogen ID/AST approaches are in scope, as per the pathogens below. Host-biomarker approaches are not in scope.

EOI must be submitted online August 12 – August 19, 2019, 5 PM ET. https://carb-x.org/apply

Pathogen Scope
Acinetobacter baumannii, carbapenem-R
Pseudomonas aeruginosa, carbapenem-R
Enterobacteriaceae, *carbapenem-R, 3rd-gen ceph-R (ESBL+)*
Enterococcus faecium, vancomycin-R
Staphylococcus aureus, methicillin-R, vancomycin-I/R
Campylobacter spp., fluoroquinolone-R
Salmonellae spp., fluoroquinolone-R
Neisseria gonorrhoeae, 3rd-gen ceph-R, fluoroquinolone-R
Streptococcus pneumoniae, penicillin-NS
Shigella spp., fluoroquinolone-R
Clostridium difficile
Group A *Streptococcus*
Group B *Streptococcus*

CARB-X 2019 Funding Round 4

- Scope: Direct-acting small molecule
  - Restricted to new class and/or new target
  - See next slide for scope in detail
- Expressions of Interest (EOI) accepted online only https://carb-x.org/apply
- EOI must be submitted November 12 – November 19, 2019, 5 PM ET

CARB-X 2019 Funding Round 4 – Direct-acting small molecule

Restricted to new classes and/or new targets only

EOI must be submitted online November 12 – November 19, 2019, 5 PM ET. https://carb-x.org/apply

Pathogen Scope*
Acinetobacter baumannii, carbapenem-R
Pseudomonas aeruginosa, carbapenem-R
Enterobacteriaceae, *carbapenem-R, 3rd-gen ceph-R (ESBL+)*
Salmonellae spp., fluoroquinolone-R
Neisseria gonorrhoeae, 3rd-gen ceph-R, fluoroquinolone-R
Shigella spp., fluoroquinolone-R

*the spectrum of direct acting products can include Gram-positive pathogens however the program must prioritize the Gram-negative pathogens included in the product's spectrum, as evidenced by the data developed at time of application and the workplan/TPP presented to CARB-X

New class is defined as: a core chemical structure (or scaffold) that does not have an antibiotic approved for human use by the FDA, EMA as of May 1, 2019

If program is an LpxC inhibitor program, applicants should access information available on the PEW Spark database, particularly, if the program is hydroxymate based to ensure proposals have considered the learnings appropriately and have these addressed upfront in these application submitted to CARB-X

Mode of administration preference guidance:
For Enterobacteriaceae *offerings:* If only for ESBL (e.g. lacks CRE), PO options are higher priority than IV only
For *Salmonellae spp., Shigella spp*. and *Neisseria gonorrhoeae* offerings – oral delivery is strongly preferred
The only topical delivery in scope is inhalation (e.g. dermal, nasal, intra-wound/surgical site, ocular etc. are all not in scope)

Biocides /antiseptics/disinfectants are not in scope

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Applying for CARB-X funding, in brief

- Funding Round 1 – Non-traditional approaches
  - June 3 – June 10, 2019, 5 PM ET
- Funding Round 2 – Vaccines and biotherapeutics
  - July 8 – July 15, 2019, 5 PM ET
- Funding Round 3 Diagnostics
  - August 12 – August 19, 2019, 5 PM ET
- Funding Round 4 – Direct-acting small molecule
  - November 12 – November 19, 2019, 5 PM ET

- CARB-X welcomes applications from around the world
- Expressions of Interest applications must be submitted online, only during the periods indicated https://carb-x.org/apply/
- To qualify for funding and support, projects must be in scope and organizations must meet certain criteria

For full details, please visit https://carb-x.org/apply/

For specific questions, please contact carbxapp@bu.edu

NB: Webinar on Funding Rounds May 16, 2019 – details to come

NB: Watch for webinars on Research Compliance and ODA in the coming weeks

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Combating Antibiotic Resistant Bacteria

Thank you!

Questions and discussion

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Combating Antibiotic Resistant Bacteria

Research Compliance

Research Compliance Requirements

- CARB-X is committed to the highest ethical standards in all research and business operations. CARB-X funded companies must comply with United States Government regulatory requirements for animal research and human subjects research, even if this research is conducted outside the United States. Requirements include
  - **Office of Laboratory Animal Welfare (OLAW)** requirements for studies involving any vertebrate species
    - Every performance site for CARB-X funded studies must have either domestic or foreign OLAW Assurance.
    - An Inter-Institutional Assurance (IIA) is required for product developers that do not/cannot have their own Assurance and must rely on a CRO or other third party performance site that has an Assurance
    - Boston University must prompt OLAW on behalf of the CARB-X subawardees. OLAW does not accept or process unsolicited applications
  - **USDA Registration** requirements for US-based research facilities performing studies involving warm-blooded animals not specifically excluded from the definition of "animal" in the US Animal Welfare Act and Animal Welfare Regulations
  - **Office of Human Research Protections (OHRP)** requirements for human subjects research
    - Study start prerequisites including, but not limited to, the approved study protocol, investigator brochure, IRB or IEC approved informed consent document, OHRP FWA number, and IRB or IEC approval letter. Note that BARDA and BU must review and approve all documents before a study may begin
    - Monitoring including bi-weekly clinical teleconferences and independent monitoring.
    - Monthly, annual, and ad hoc reporting, including certain reports that must be filed within either 24 hours or 3 days of occurrence.
- CARB-X funded companies must make every reasonable effort to comply with NC3R guidance for studies involving large animals (primates, cats, dogs, equines)
- These requirements will impact both time and budget; they are critical to consider when building your project plan

Research Compliance Requirements

- Consider requirements and the approximate timelines when building your project plan
- Submit the Attachment A and A-1 form detailing all planned animal studies and human subjects research when your application reaches the Long Form stage
- CARB-X will review and determine whether further action is required. This may be in advance of a positive funding decision
- Here is what you can be doing now in case you receiving a positive funding decision and successfully negotiate a sub-award with CARB-X
  - For animal studies
    - Select a CRO that has OLAW assurance if possible. If this is not possible, confirm the CRO meets OLAW requirements for assurance and begin compiling the required documentation (VAS describing studies per OLAW guidelines and IACUC approval letters for the protocols under which the studies will be conducted)
    - If your studies involve large animals, confirm the CRO is familiar with NC3R guidelines. Reach out to CARB-X for further guidance
    - Prepare the required documentation: the VAS describing studies per OLAW guidelines and IACUC (or IACUC equivalent) approval letters for the protocols under which the studies will be conducted
  - For human subjects research
    - Review Human Subjects Research Checklist; begin compiling the required documentation

Human Subjects Research Checklist: Prerequisites to Study Start

- ❑ Study Protocol
- ❑ Investigator Brochure
- ❑ Institutional Review Board (IRB) or Institutional Ethics Committee (IEC) approved informed consent document
- ❑ Office for Human Research Protection (OHRP) federal wide assurance (FWA) number, or the IRB or IEC name and registration number, for each of the following:
  - Each Study Site (e.g. university, hospital, etc.)
  - IRB or IEC that will review the study
  - Any other body directly involved in the research
- ❑ Name and contact information for the primary physician at the center and/or CRO that will be primarily accountable for managing a subject/AE/SAE/etc.
- ❑ Approval letter from an IRB or IEC
- ❑ Documentation that the sub-recipient and all study staff responsible for the design or conduct of the research have received training in the protection of human subjects.
- ❑ Approval letter (or equivalent) from the relevant regulatory agency in the US or any other country involved, e.g. FDA approval letter for an IND application for a US trial. Written documentation from FDA regarding comments, etc.
- ❑ Statement acknowledging satisfaction of all regulatory requirements of any country involved in the clinical trial, and responsibility for ongoing regulatory compliance.
- ❑ Description of the process used for scientific review of the Clinical Trial Protocol, e.g. who reviewed it, when it was reviewed, sign-off, etc.
- ❑ Written summary of PD's plans and procedures for: (1) Management of side effects; (2) Assessing and reporting adverse events; and (3) Data and safety monitoring, and monitoring of the clinical study site, pharmacy, and laboratory.
- ❑ Existing FDA or other regulatory agency submission documentation and correspondence
- ❑ Documentation of registration on ClinicalTrials.gov

NB: BARDA and BU must review and approve all documents before a study may begin

Human Subjects Research: Monitoring Requirements

Form	Expectations
Bi-Weekly Clinical Teleconferences	• PDs will be expected to participate in calls every two weeks (in addition to CST calls) at least one month prior to study start and through final study report.
	• PDs will be expected to provide status updates about the trial and report findings.
	• PDs will be expected to circulate an agenda in advance and email minutes in follow up to the call.
	• At least one PD expert associated with the trial will be expected to provide this update; BARDA clinical experts and a CARB-X representative will participate.
Non-HSR Specific Monitoring	• Monthly Company Support Team Meetings, to provide support and guidance with respect to the position of HSR work in the overall PD program.
	• Establishment or demonstration of an SAB with adequate oversight over HSR work.
Independent Monitoring	• *This is strongly recommended* for any clinical research involving more than minimal risk to volunteers.
	• The type of monitoring appropriate for the research should be determined jointly by the PD and BU prior to enrollment, and may take the form of an Independent Safety Monitor, Committee, or DSMB.
	• If independent monitoring is used, 1) PD should inform BU of any upcoming site visits or audits; 2) BU and BARDA may attend such site visits or audits; and 3) The PD should provide a written summary to BARDA of all monitoring reviews within 3 days of the review.

Human Subjects Research: Reporting Requirements

Timing	Reporting Requirement
Reports Required Immediately or Within 24 Hours	• All FDA submissions, reports, or correspondence
	• **Required Time Sensitive Notifications** are FDA safety reports of serious adverse events under IND or IDE
	• Notification to BU of an FDA or EMA audits is required within 5 days of a scheduled audit or site visit OR within 12 hours of an ad hoc audit or site visit
Reports Required Within 3 Business Days of Occurrence	• Major changes to the status of IRB approvals and ongoing protocols
	• Any reviews by an institutional biosafety committee or the NIH Recombinant DNA Advisory Committee
Monthly Reporting	• Monthly technical/progress reporting as outlined in Attachment 4 & 6, including a comprehensive status update of clinical studies actively enrolling patients for each study site
Annual Reporting	• Continuing IRB review by each institution involved in the research or the central IRB, if review is ceded to a single IRB
	• Adverse events documented during the trial and which are reportable in the annual IND or IDE report
Other Ad Hoc Reporting	• Ongoing safety reporting for research not performed under an IND/IDE
	• Ad hoc reporting as requested under Attachment 4a regarding clinical study information
	• A written report when the PD completes a Milestone
	• A final technical/progress report is required to be submitted within 30 days after the end of the period of performance

Animal Research: Key Terms & Resources

Term	Acronym	Definition
Office for Laboratory Animal Welfare	OLAW	OLAW is a United States Government agency responsible for ensuring the humane care and use of animals in Public Health Service-supported research, testing, and training. OLAW is responsible for granting assurance and Interinstitutional Assurance. More detail is available on the OLAW website https://olaw.nih.gov/

Domestic Assurance		Domestic Assurance is required for any US-based performance site performing animal studies as part of a CARB-X subaward. OLAW negotiates domestic assurance with US-based performance sites that
		• control their own animal facilities
		• conduct animal research on-site
		• have an animal care and use program with:
		  • an Institutional Official (IO)
		  • an Institutional Animal Care and Use Committee (IACUC)
		  • a veterinarian with program authority
		The OLAW website includes a list of performance sites with domestic assurance https://grants.nih.gov/grants/olaw/assurance/300index.htm

Foreign Assurance		Foreign Assurance is required for any performance site outside the United States performing animal studies as part of a CARB-X subaward. OLAW negotiates foreign assurance with non-US based performance sites that • control their own animal facilities • conduct animal research on-site • have an animal care and use program with an authorized institutional signing official The OLAW website includes a list of performance sites with foreign assurance https://grants.nih.gov/grants/olaw/assurance/500index.htm
Interinstitutional Assurance	IIA	OLAW negotiates IIAs with PDs who do not have their own domestic or foreign assurance and are contracting with an external performance site that does
National Centre for the Replacement, Refinement and Reduction of Animals in Research	NC3R	NC3R is a UK-based scientific organization dedicated to replacing, refining and reducing the use of animals in research and testing. CARB-X funded companies must make every reasonable effort to comply with NC3R guidance on treatment of large animals (primates, cats, dogs, equines). More detail is available on the NC3R website https://www.nc3rs.org.uk/

Animal Research: Key Terms & Resources (cont'd)

Term	Acronym	Definition
Contract Research Organization	CRO	An organization that provides research services to a PD on a contract basis.
Institutional Animal Care and Use Committee	IACUC	An IACUC is a federally mandated committee that oversees its institution's (PD, CRO, academic site) animal care and use program, facilities, and procedures
Joint Oversight Committee	JOC	CARB-X's governing board
Memorandum of Understanding	MOU	An agreement required between Boston University, the PD, and, if applicable, the performance site. The MOU must be fully executed before a PD can invoice CARB-X for its studies
Office of Sponsored Programs	SP	SP is the group within Boston University Research Administration which requests assurance on behalf of PDs
Performance Site		The physical location where animal research is conducted. OLAW assurance is specific to a performance site. If a PD or CRO has more than one site, each site must have the proper assurance
Product Developer	PD	A CARB-X funded entity
Vertebrate Animal Section	VAS	A document describing the planned animal studies required by OLAW prior to issuing an assurance or IIA. PDs working with their CROs (if applicable) must include a sufficient level of detail on 1. Description of Procedures 2. Justifications of Animal Use 3. Minimization of Pain and Distress 4. Method of Euthanasia For a full description of the VAS, visit the OLAW website https://olaw.nih.gov/guidance/vertebrate-animal-section.htm

CARB-X

Combating Antibiotic Resistant Bacteria

ODA Eligibility

ASPR ASSISTANT SECRETARY FOR PREPAREDNESS AND RESPONSE

BARDA BIOMEDICAL ADVANCED RESEARCH AND DEVELOPMENT AUTHORITY

wellcome

NIH National Institute of Allergy and Infectious Diseases

UKaid from the British people

Federal Ministry of Education and Research

BILL & MELINDA GATES foundation

BASEL AREA. SWISS

BIO Innovation Institute

CLSI CALIFORNIA LIFE SCIENCES INSTITUTE

C-CAMP Centre for Cellular and Molecular Platforms

FIND Because diagnosis matters

DZIF German Center for Infection Research

ILSE INSTITUTE FOR LIFE SCIENCE ENTREPRENEURSHIP

MassBio MASSACHUSETTS BIOTECHNOLOGY COUNCIL

RTI INTERNATIONAL

CARB-X

BOSTON UNIVERSITY

ODA Eligibility - Checklist

- ☑ Applying for ODA support is optional but encouraged
- ☑ The target country/countries is featured on the OECD DAC list*
- ☑ The primary objective of the project, or portion of the project, is the promotion of economic development and welfare of an LMIC
- ☑ The project, or portion of project, seeks a specific outcome which will have an impact on a developing country or countries
- ☑ The applicant can articulate with credible evidence what the specific need is and why this is a problem for the LMIC(s)
- ☑ The applicant has identified and articulated appropriate pathways to impact to ensure that the LMIC(s) benefits from the research
- ☑ The project team has the appropriate knowledge and expertise to deliver

* http://www.oecd.org/dac/financing-sustainable-development/development-finance-standards/DAC_List_ODA_Recipients2018to2020_flows_En.pdf

UK GAMRIF investment funds will be focused on those projects which 1) comply with ODA eligibility requirements and 2) meet the GAMRIF scope which includes programs which can be designated as 'alternatives to traditional antibiotics', for example: bacteriophage, microbiome, vaccines, antibodies, potentiators (including beta-lactamase inhibitors), anti-biofilm approaches, anti-virulence approaches and other approaches exemplified in the Lancet publication by Czaplewski et al entitled 'Alternatives to antibiotics—a pipeline portfolio review' (if within the general CARB-X funding scope). Direct-acting small molecule and diagnostic programs are not included in the GAMRIF funding scope.

ODA Eligibility

Key Criteria	Applicability to CARB-X Applicants
Promote the welfare and economic development of LMICs	This might be accomplished through ▪ New development- e.g., a new vaccine or therapeutic ▪ Meeting unmet challenges of LMICs ▪ Building research capacity - e.g., a program that increases the skills and knowledge base and supports the development of the research capability within LMIC(s)
Directly and primarily relevant to the problems of LMICs	▪ Research does not need to be solely relevant to LMICs, but LMICs must be the primary beneficiaries ▪ Commercialization of research cannot solely take place in developed countries ▪ Issues which are global in nature (e.g. global good) are not necessarily ODA compliant unless the research (or a particular work package of the research) can articulate the primary intention of benefitting people in LMIC (i.e. LMICs as the primary beneficiaries)
Investigate a specific problem or seek a specific outcome which will impact LMICs in the immediate or longer-term	▪ The problem or need must be clearly articulated, credible and backed up (where possible) with evidence/statistics; applications should articulate a development impact even if outside the timeframe of CARB-X funding ▪ The pathways to impact must be realistic and appropriate to the particular LMIC's context ▪ Applications should describe the nature and scale of the problem or challenge they are seeking to address through this research (e.g., how many people would be affected by progress in this area?) ▪ The LMIC must be able to access or make use of the data, technology or model beyond the grant period ▪ Where the research could lead to commercialization, the LMIC(s) must have an existing or potential ability to grow the industry
Demonstrate appropriate pathways to impact that ensure the LMIC benefits from the research.	The likelihood and scale of beneficial impact are increased by the following factors ▪ If the research is orientated towards a problem or challenge where there is potential to benefit a large number of people to a significant degree ▪ If the research team can demonstrate experience or understanding of successful impacts within the specific context ▪ If stakeholders that are close to the problem private sector and/or public sector and government, are actively involved in the research ▪ If there are specific commitments from institutions/enterprises from LMICs to adopt/apply outcomes of the research ▪ If stakeholder collaboration and knowledge exchange activities enhance local innovation and research capacity at an individual, institutional or whole system level

ODA Eligibility - FAQs

1. **Which countries are considered low and middle income countries (LMICs)?**
   Countries on the Development Assistance Committee (DAC) list are considered LMICs. The DAC list designation is based on gross national income (GNI) per capita as published by the World Bank. The link to the list can be found here at http://www.oecd.org/dac/financing-sustainable-development/development-finance-standards/DAC_List_ODA_Recipients2018to2020_flows_En.pdf

2. **Can ODA eligible research also be relevant to developed countries?**
   Yes. Research does not need to be solely relevant to LMICs, but LMICs should be the primary beneficiaries. Any benefit to developed countries has to be a secondary consideration. Also, commercialization of research cannot solely take place in developed countries.

3. **AMR is a global issue. Does this mean that every AMR project is ODA eligible?**
   It depends on how the primary intention of the project is articulated. The primary objective of the research must have a specific impact in the developing country. The applicant must identify the challenge in the context of the impact upon the welfare of developing country populations and back it up with figures if available.

4. **My project is in an early stage of development; do I need to articulate a development impact?**
   Applications must articulate a development impact even if outside the timeframe of the CARB-X funding. The focus should be on the impact upon LMIC populations, and how their lives will be improved.

5. **Can research carried out in a developed (non LMIC) country be ODA eligible?**
   Yes, as long as the intention of the research directly and primarily benefits LMICs.

6. **How does an applicant balance the uncertainty of research in assessing impact?**
   It is recognized that the impact of research is uncertain, often unexpected and cannot be guaranteed; however, it is important that the pathways to impact are realistic and appropriate to the particular LMIC's context.

7. **Is it possible to have just a part of a project be considered as ODA eligible?**
   Yes, it is possible that a discrete package of work within a project complies with ODA.

CARB-X

Combating Antibiotic Resistant Bacteria

Thank you!