CARB-X

Combating Antibiotic-Resistant Bacteria

ACCELERATING THE GLOBAL RESPONSE TO ANTIMICROBIAL RESISTANCE

ANNUAL REPORT 2023

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At a time when more than one million people die every year from drug-resistant bacterial infections, CARB-X drives innovation to save lives.

This year marks significant milestones in our journey with the addition of two new funders, the completion of three funding rounds, and a refresh of our R&D strategy.

We are thankful that the German and UK governments have renewed their multi-year grants to CARB-X, and we are proud that the Canadian government and the Novo Nordisk Foundation have decided to join our initiative as its newest funders. Together with the US government, Wellcome and the Gates Foundation, these partners offer crucial resources to accelerate products aimed at preventing, diagnosing, and treating drug-resistant infections.

We are grateful to the G7 and G20 members for highlighting the importance of our work. In June, the G7 Health Ministers reinforced their commitment to contribute to our pooled efforts. In August, the G20 Health Ministers welcomed R&D on novel antimicrobials through our international initiative. We are encouraged by this widespread support and look forward to engaging with more government partners to strengthen our collective response to antimicrobial resistance (AMR).

During the 2022-2023 funding rounds, CARB-X received 237 expressions of interest from around the world. They are developing oral therapeutics, vaccines for neonatal sepsis, and gonorrhea products. 91% come from micro to medium companies and academic institutions. This shows that small teams continue to lead antibacterial R&D, and this vulnerable ecosystem needs our assistance.

In the second half of the year, we embarked on a strategic review of our R&D priorities to align with the most burdensome infections worldwide. The review is a commitment to action, so our investments can make the most significant impact.

With gratitude to our partners for their support and shared vision of success, we move forward with determination and hope. Together, we are making a difference.

Kevin Outterson, Esq.
Executive Director,
CARB-X

Erin Duffy, Ph.D.
Chief of Research and
Development, CARB-X

Celebration of New Funding

CARB-X strengthens existing partnerships and welcomes new donors

IN 2023, FOUR FUNDERS ANNOUNCED SUPPORT FOR CARB-X.

Germany's Federal Ministry of Education and Research (BMBF) committed an additional

€41 MILLION

to CARB-X and its Global Acceleration Network over the next 4 years.

"There are more and more antibiotic-resistant bacteria worldwide, some of which are resistant to a number of antibiotics. This is why we urgently need new approaches for the prevention, diagnosis and treatment of these superbugs, which are becoming increasingly dangerous to humans. Therefore, the Federal Research Ministry has been supporting the international CARB-X partnership since 2019."

Bettina Stark-Watzinger, BMBF Federal Research Minster

Professor Dame Sally Davies, UK Special Envoy on AMR

"AMR threatens modern medical systems for current and future generations. I am proud that CARB-X's global partnership and commitment to cutting-edge innovation, equitable global access, and sustainable stewardship will bring exciting new treatments, preventatives and diagnostics to those across the world who most need them."

Through its Global AMR Innovation Fund (GAMRIF), the UK government committed up to

£24 MILLION

to CARB-X over the next four years.

The Public Health Agency of Canada announced an investment of CAD

$6.3 MILLION

to CARB-X over the next two years.

"The Government of Canada is proud to support CARB-X in its innovative efforts to combat antimicrobial resistance (AMR). This investment will help strengthen the research and development space in Canada and contribute to global AMR innovation by strengthening the discovery and development for new antimicrobial drugs. Continued collaborative efforts such as this are crucial and Canada is committed to working with its global partners to make tangible progress on AMR."

The Honourable **Mark Holland**, Minister of Health, Government of Canada

Peter Lawætz Andersen, Senior Vice President, Infectious Diseases at Novo Nordisk Foundation

"Like CARB-X, the Novo Nordisk Foundation is committed to driving innovation in the fight against drug-resistant infections. By partnering, we can help ensure that the best research gets translated into effective, scalable and affordable medical interventions that can help end this growing pandemic."

The Novo Nordisk Foundation committed up to USD

$25 MILLION

to CARB-X for three years.

Portfolio Strategy Review Results

IN THE SECOND HALF OF 2023, CARB-X CONDUCTED A REFRESH OF THE INITIAL 2020 PORTFOLIO STRATEGY REVIEW, INTENDED TO:

- augment our advisory pool to better represent our role as a global funder and supporter of R&D to prevent, diagnose and treat bacterial infections;
- update external stakeholder views of
  - highest-need syndromes,
  - pathogens that cause them,
  - modalities that are best suited for the job,
  - and performance characteristics that clinicians and patients need;
- analyze overlap (and gaps) with downstream-funder priorities; and
- prioritize recommended areas of focus for
  - refining existing portfolio and
  - shaping new funding calls.

THE FORMAT OF THE REVIEW INCLUDED TWO COMPONENTS:

- an online survey, which focused on syndromes, pathogens, modalities and performance characteristics; and
- a virtual panel discussion for each pillar (diagnostics, prevention and therapeutics).

In both cases, questions were included to underscore where there were similarities or areas of significant differences when considering priorities for High-Income Countries (HICs) and Low-and-Middle-Income Countries (LMICs).

Where diagnostics are concerned, the outcomes were very consistent with the prioritization set in the 2020 Review and included bloodstream infections (BSI) direct from whole blood, sexually-transmitted infections (STIs), enteric infections (*S. typhi*) and lower-respiratory tract infections (LRTIs). Additionally, the top priorities were the same, irrespective of World Bank economic categorization.

Our portfolio strategy review called upon advisors from around the world, as seen below.

SOME SALIENT POINTS FROM THE DIAGNOSTIC PANEL DISCUSSION:

- With BSIs, we still need rapid-triage tests, which rule-in a bacterial infection and rule-out other syndromes—turnaround time and sensitivity/specificity are critical.
- Diagnostics for neonatal sepsis, specifically, are lacking. Here, critical is the sample volume. In this category, rapid-triage, bacterial identification and rapid susceptibility testing are sought. This aligns well with the 2022-2023 omnibus solicitation for vaccines for neonatal sepsis.
- Where STIs are concerned, through the 2022-2023 omnibus solicitation CARB-X augmented the portfolio such that we are accelerating projects covering several levels of the health-care system. The recommendation is to invest in their advancement rather than seek more projects.
- With enteric infections, diagnostics are desired. Here, speed and cost are significant drivers. The antigen/antibody combination is important.
- There was no overwhelming feeling that we need diagnostics for LRTIs. Here, the critical work seems to be around identifying proper sample types, particularly to distinguish between colonization and infection. Because so many of our therapeutic programs focus on LRTIs, this diagnostic priority aligns well.

WHERE PREVENTION IS CONCERNED, THE TOP FOUR SYNDROMES AND SOUGHT-AFTER MODALITIES, ACROSS ALL REVIEWERS WERE:

Pathogen	Syndrome	Modality
Neisseria gonorrhoeae, 3rd gen ceph-R and/or FQ-R	Gonorrhea	Vaccine
Shigella spp, FQ-R	Diarrheal	Vaccine
Klebsiella pneumoniae, 3rd-gen ceph-R	Pneumonia	Other Preventative
Staphylococcus aureus, MRSA, VRE	Invasive	Other Preventative

IMPORTANT POINTS FROM THE PANEL DISCUSSION:

- Where *N. gonorrhoeae* is concerned, it was recognized that CARB-X now has 3 vaccine programs in the area, at several stages of preclinical development. As such, this was deprioritized as a high need for additional portfolio investments at this time.
- A focus on *K. pneumoniae* pneumonia is important for LMICs but not for HICs, where only special populations with co-morbidities are affected.
- When discussing *S. aureus*, what rose as priorities were vaccines for pathogens that cause invasive disease. In this light, and owing to the many failures in preclinical and clinical development, preventatives from non-vaccine and non-monoclonal antibody modalities were desired, for disseminated disease caused both by *S. aureus* and *E. coli*.

KEY POINTS FROM THE THERAPEUTICS PANEL DISCUSSION:

- The emphasis was on the need for therapeutics—particularly those with properties that allow development of an oral formulation—for serious infections caused by Gram-negative organisms.
- A heavy preference for direct-acting, small-molecule therapeutics (encourage development of non-traditionals, but there are many questions about when/whether/how best to use them).
- Novelty comes in many forms and does not necessarily require a new mechanism of action or a new chemical class.
- Developers should engage clinical-trial networks in regions where drug-resistant pathogens may be found (e.g. ADVANCE-ID, located in Southeast Asia).

With these, we framed the themes for the 2024 funding calls.

Acronym	Meaning
ceph-R	cephalosporin-resistant
FQ-R	Fluoroquinolone-Resistant
MRSA	methicillin-resistant *Staphylococcus aureus*
VRE	vancomycin-resistant Enterococci
HAP	hospital-associated pneumonia
VAP	ventilator-associated pneumonia
cUTI	complicated urinary tract infection
non-mAb	non-monoclonal antibodies
BAL	bronchoalveolar lavage
ETA	endotracheal aspirate

2024 FUNDING CALL THEMES

THERAPEUTICS FOR INFECTIONS CAUSED BY GRAM-NEGATIVE PATHOGENS

Required: direct-acting, small-molecule antibiotic

Preferred: properties to deliver both IV and oral forms

Target Indications: HAP/VAP, cUTI (and associated bacteremias)

DIAGNOSTICS FOR NEONATAL SEPSIS

Target Tests: (1) rapid triage (bacterial vs. other; host response); (2) bacterial identification; (3) genotypic typic or phenotypic susceptibility tests

Key Criteria: small sample volumes, time-to-result, cost-of-goods, proof of concept data on clinical or contrived samples

PREVENTION FOR INVASIVE DISEASE

Required: novel approaches, with supportive preliminary data

Preferred: non-vaccine, non-mAb

Target Pathogens: *S. aureus* and *E. coli*

NOVEL SAMPLE TYPES FOR DIAGNOSING LRTIs

Required: sample types other than BAL, ETA or sputum

Preferred: alternative sample type with demonstration of detection of at least one bacterial pathogen at a clinically-relevant threshold

2022-2023 Omnibus Funding Round Outcomes

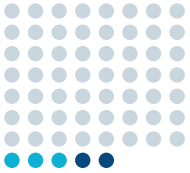
CARB-X received applications from a worldwide search for the best projects on three themes:

1 ORAL THERAPEUTICS

Oral therapeutics are essential to treat infections globally.
Several factors drive the need for new oral therapeutics:

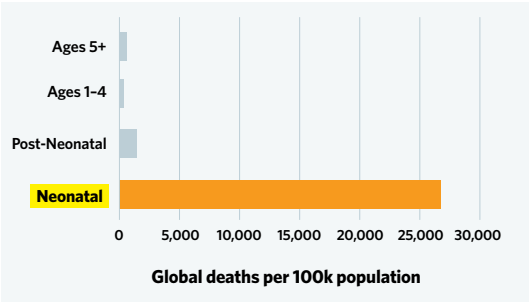
1/3 of the oral antibiotics on the WHO Essential Medicines List are marked as "Watch" due to a risk of resistance.

Of the 15 new antibiotics approved by the FDA in the last decade, only **1/3** have an oral option.



Of the 61 therapeutic programs supported by CARB-X since inception, **5** pursued an oral option, with **2** progressing.

2 VACCINES FOR NEONATAL SEPSIS



Neonates are 69 times more likely to die from sepsis than children in the 5+ age bracket.
Infections that cause neonatal sepsis are particularly burdensome in LMICs.

CARB-X requires neonatal sepsis vaccines to target top causative agents in LMICs where commercial indications would also be possible for HICs.

3 GONORRHEA PRODUCTS

Ceftriaxone is the only antibiotic left that can effectively treat drug-resistant strains of gonorrhea.

CARB-X requested all gonorrhea products–vaccines, rapid diagnostics and oral therapeutics–address drug-resistant strains with a focus on thinly-covered but important pathogens and syndromes.

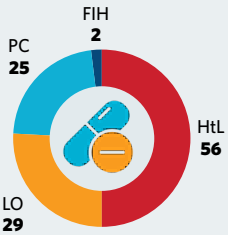
CARB-X received 237 expressions of interest.

185 were unique applicants

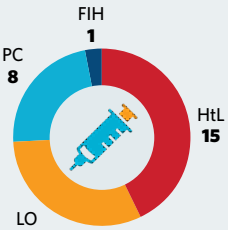
125 applied to CARB-X for the first time

Here's how the applications break down by theme and stage:

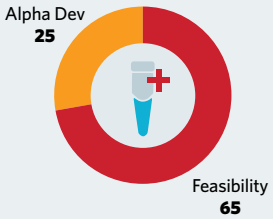
112 Oral Therapeutics



35 Vaccines for Neonatal Sepsis



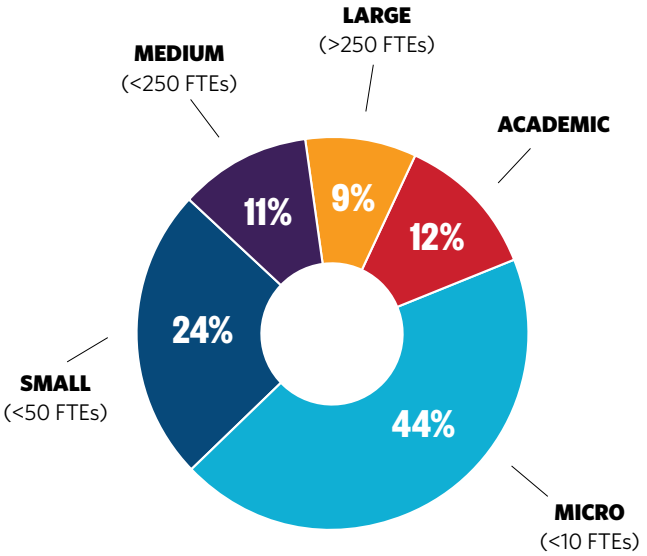
90 Rapid Diagnostics for Gonorrhea



FIH: First-in-human
PC: Pre-clinical
LO: Lead optimization
HtL: Hit-to-lead
Alpha Dev: Alpha Development

Demographics

APPLICANTS BY ORGANIZATION SIZE



FTEs = full-time employees

CARB-X received applications from 185 unique applicants—from small to large companies and non-profit organizations—based in countries around the world.

91%
were academic, and micro to medium and only

9%
were large.

Trends

Rapid diagnostics expanded during the COVID-19 pandemic.
Developers built rapid tests to detect the SARS-CoV-2 virus. This resulted in a significant increase in diagnostic products in use by customers, near point-of-care diagnostics, and fully established commercial and reporting infrastructures. As the pandemic winds down, product developers are poised to capitalize on their investments by embracing new sample types and pathogens, including *N. gonorrhoeae*.

Half of the therapeutics applicants were in the hit-to-lead stage.
This is consistent with the dearth of oral therapeutics in the clinical and preclinical pipelines, and the barriers that product developers face as they attempt to advance oral therapeutics to patients. CARB-X aims to help these programs advance to the clinical stage and replenish the pipeline with new oral therapeutics.

CARB-X received 35 expressions of interest from the vaccine community, who understand that there is a need for targeting pathogens of interest.
In 2021, the World Health Organization reviewed the pipeline of bacterial vaccines. Few are in clinical development for pathogens of interest. These include:

- **1 for *K. pneumoniae***
- **5 for Extraintestinal Pathogenic *E. coli***
- **11 for *S. aureus***
- **0 for *A. baumannii***
- **1 for *N. gonorrhoeae***

Historically, the pathogen *S. aureus* has posed challenges for vaccine developers, which has resulted in a high number of failed attempts. This is why CARB-X sought new approaches to develop an effective vaccine that can target *S. aureus* in our 2024 call.

The research team, led by Professor Christopher McDevitt, PhD, Laboratory Head at the Doherty Institute, investigates how pathogenic bacteria interact with the host environment and the specific role played by metal ions. Pictured from left to right: Dr. Aimee Tan, Dr. Jonathan Wilksch, Prof. Christopher McDevitt, Dr. Bliss Cunningham, and Dr. Stephanie Neville.

Australian Researchers are the First to Receive a New CARB-X Award in 2023

In October 2023, CARB-X awarded US$1.75 million to the University of Melbourne at the Peter Doherty Institute for Infection and Immunity (Doherty Institute) to develop an oral therapeutic that restores the activity of workhorse antibiotics used to treat community-acquired bacterial pneumonia (CABP).

Lower respiratory tract infections, including CABP, are among the world's most deadly communicable diseases. They are estimated to have killed 2.6 million people globally in 2019.

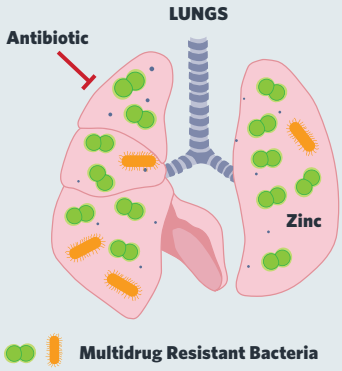
The Australian research team is developing PBT2, an ionophore therapeutic originally pursued as a treatment to restore brain activity in patients with neurodegenerative diseases, including Alzheimer's. Studies found that PBT2 can disarm key pathways involved in mechanisms by which bacteria become resistant to frontline antibiotics. The team aims to use the effects of PBT2 on drug-resistant bacteria to restore the ability of common antibiotics to eliminate those bacteria.

As bacteria that cause CABP are becoming increasingly resistant to antibiotics on the WHO model list of essential medicines, CARB-X is supporting the development of new oral antibiotics and other products that aim to restore the utility of the ones we already have. Oral therapeutics enable patients to be treated at home. This can reduce healthcare costs and increase access globally, including in low- and middle-income countries where the burden of antimicrobial resistance is highest.

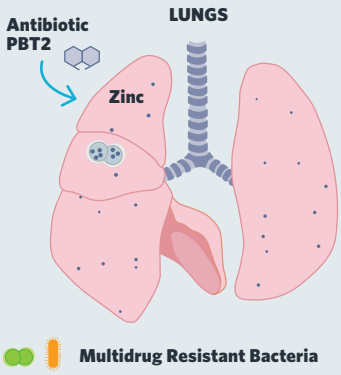
Additional CARB-X awards from the 2022-2023 funding rounds will be announced in 2024 after contracts have been finalized.

COMMUNITY ACQUIRED BACTERIAL PNEUMONIA

ANTIBIOTIC FAILURE



PBT2 + ANTIBIOTIC



Studies found that PBT2 harnesses host zinc to disarm key pathways involved in the mechanisms by which bacteria become resistant to frontline antibiotics, like amoxicillin or doxycycline.

Adapted from Brazel et al., 2022, Cell Reports https://doi.org/10.1016/j.celrep.2021.110202

PHOTO BY CESAR NICOLAS/DOHERTY INSTITUTE

CARB-X Portfolio Acceleration Tools

CARB-X is supporting several projects, called Portfolio Acceleration Tools (PATs), that aim to bridge gaps in the translation of novel antimicrobials to approved therapies. Below we highlight advancement of our lung model PAT this year.

Scan to view further examples of the Portfolio Acceleration Tools.

Animal lung model PAT

HEALTH IMPACT:

Lower-respiratory-tract infections remain the world's most deadly communicable disease.

They caused

2.6 MILLION DEATHS

in 2019

That is why 70% of CARB-X-supported therapeutic projects target this syndrome.

PURPOSE OF THE PAT:

Preclinical data from lung infection animal models do not always translate to the clinic. For example, tigecycline is an antibiotic that showed efficacy in mice, but not for human lung infections. CARB-X is collaborating with partners to advance a standard animal lung model for product developers, so their research will have translational value. This could help save time and money, while moving antibacterial products more quickly to patients. The PAT research will be published in open-access journals, so any team around the world could use the model and compare results across laboratories.

DESIGN:

CARB-X began with the IMI Antimicrobial Resistance (AMR) Accelerator standardized animal model, currently assessed across different laboratories, to determine whether clinical exposures are effective in this animal model. The Center for Anti-Infective Research and Development (CAIRD) tested humanized exposures of antibiotics that target lung infections and those that do not, to provide positive and negative controls. Several strains of *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* were tested, since these are two prominent bacteria that cause lung infections.

STATUS:

During 2023, humanized exposures were tested in the animal model and analyzed for two antibiotics, tigecycline (negative control) and levofloxacin (positive control). The results supporting the validation of the animal lung model are anticipated to be published in 2024 and three additional, clinically-used antibiotics will be studied to provide a fulsome model. All bacterial strains will become available to researchers through the Leibniz Institute DSMZ-German Collection of Microorganisms and Cell Cultures GmbH depository in Germany.

How CARB-X Benefits Vulnerable Individuals in LMICs

STEWARDSHIP AND ACCESS PLANS PUBLISHED

CARB-X's goal is to accelerate antibacterial products to patients around the world. To ensure products are appropriately stewarded and accessible globally, CARB-X contractually requires all product developers in our portfolio to develop Stewardship and Access Plans. This year, two product developers published their Plans:

bioMérieux's VITEK® REVEAL™ Rapid AST System is an automated *in vitro* diagnostic system for quantitative and qualitative phenotypic antimicrobial susceptibility testing directly from positive blood culture.

The T2Resistance® Panel is a direct-from-blood diagnostic designed to detect genetic markers associated with antibiotic-resistant gram-negative and gram-positive bacterial bloodstream infections.

CARB-X will continue to publish product developers' Stewardship and Access Plans as their products progress.

IN VITRO DIAGNOSTIC PRODUCT DEVELOPMENT SERIES

We have funded three Indian companies, one of them a diagnostic program. That experience prompted a six-part video series to help diagnostic companies from lower-resource settings to move forward with CARB-X. In previous funding rounds, CARB-X noticed a trend in award applications. While diagnostic developers of LMICs strongly described their core technologies, many struggled to articulate how they would translate them into meaningful products.

In April 2023, CARB-X developed a webinar series with FIND and C-CAMP to coach product developers from LMICs how to move their in vitro diagnostics (IVD) from concept through development.

The series aimed to help product developers:

- **strengthen their business plans,**
- **improve their applications to become more competitive for CARB-X funding, and**
- **increase access to diagnostics in LMICs.**

The free six-part video series is now available on CARB-X.org. In February 2024, C-CAMP hosted an in-person training sessions in India and Indonesia. CARB-X added modules on regulatory, procurement, and other advanced steps.

SIX-PART VIDEO SERIES

1. **Introduction to IVD Product Development**
2. **Product Development Process**
3. **Design Control**
4. **Quality Management System**
5. **Good Lab Practices**
6. **Why the Fundamentals Matter**

Scan to view the free six-part video series.

Q&A

Diane MacDonald
CARB-X Chief Operating Officer
2018–2023

Diane MacDonald was CARB-X Chief Operating Officer from 2018-2023 and Maria Uria-Nickelsen, an Alliance Director within the CARB-X Research & Development Team from 2019-2023. Both retired in 2023. Before they departed, we asked them to describe the most significant attributes of CARB-X, as it evolved over their tenures. Here's what they had to say.

How is CARB-X developing new tools to advance products and global partnerships?

Maria Uria-Nickelsen: CARB-X pursues Portfolio Acceleration Tools that impact product developers in the portfolio. CARB-X uses strategic reviews to debate science and strategy to push the envelope of innovation. Conditional milestones and units of work are created to minimize risk and improve study designs, and funding round decisions are thoroughly evaluated to enable selection of programs across a risk-value spectrum.

Diane MacDonald: Our financial innovation mirrors the research and development risk-based profile for overall portfolio progress. Data analysis and visualization improves decision making and performance evaluation.

Maria Uria-Nickelsen
Alliance Director, CARB-X Research & Development
2019–2023

We're also expanding the CARB-X partnership with new funders to leverage the funds invested to achieve patient-centered results.

What does the integration of deep antimicrobial expertise across disciplines and stages of development coupled with non-scientific capabilities to support the portfolio look like at CARB-X?

Maria Uria-Nickelsen: The CARB-X R&D Team has decades of experience leading projects in different settings. Our Scientific Advisory Boards are built with expertise across all disciplines. The Clinical Advisory Board selects the best plan and design based on innovative approaches and deep experience.

Diane MacDonald: CARB-X has staff in finance, research compliance, legal, project management, and communications that all provide direct assistance to product developers. There are standard operating procedures and tools developed to ensure CARB-X funding requirements are understood. Information platforms allow for the exchange of information between product developers and the CARB-X team in a secure, user-friendly manner.

How has CARB-X developed the most innovative portfolio across 3 different pillars and become the most effective global partnership to leverage funding and support?

Maria Uria-Nickelsen: CARB-X has funded the development of bacteriophage, antivirulence compounds, and antibiofilms in the therapeutics pillar. Within the preventatives pillar, there have been vaccines, bacteriophages, and live bio-therapeutic products, as well as genetic-based diagnostics in the diagnostics pillar of the CARB-X portfolio.

Diane MacDonald: In terms of global partnerships, CARB-X developed a consolidation of separate funding sources in a unified partnership. CARB-X leverages funding through jointly agreed strategic objectives and a uniform set of contractual terms. CARB-X has matured as a lean organization, leveraging funds invested to ultimately see results in patients.

CARB-X

Combating Antibiotic-Resistant Bacteria

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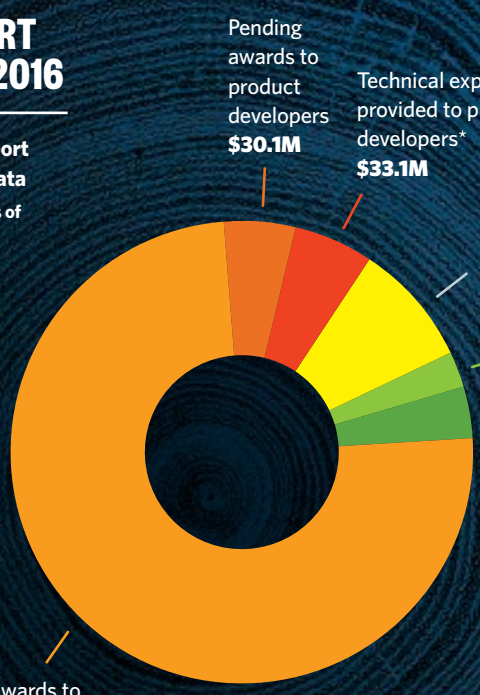
CARB-X is a global non-profit partnership that accelerates antibacterial research and development. CARB-X awards non-dilutive funding and provides scientific, regulatory and business expertise to support early-stage development of products that aim to prevent, diagnose and treat the most dangerous drug-resistant bacterial infections.

SUPPORT SINCE 2016

Annual Report Financial Data

Cumulative as of 12/31/2023



94%

of funding goes to product developers via direct awards or technical and in-kind support.

*Includes Global Accelerator Network, Portfolio Acceleration Tools, Advisory Boards, and external and in-house R&D technical experts

ASPR Administration for Strategic Preparedness and Response

BARDA Biomedical Advanced Research and Development Authority

wellcome

NIAID

Federal Ministry of Education and Research

UKaid from the British people

GAMRIF

Bill & Melinda Gates foundation

Canada

novo nordisk foundation Benefitting people and society

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