CARB-X

Combating Antibiotic-Resistant Bacteria

BOSTON UNIVERSITY

Considerations in the Development of Non-Traditionals : a CARB-X Perspective

Drug Development Considerations for the Prevention of HAIs

FDA Virtual Workshop August 30, 2022

Erin M Duffy

CARB-X accelerates innovative products for bacterial infections

Therapeutics, preventatives and diagnostics

Global partnership funds and advances high-risk projects with big-impact potential for patients

- Received $500M in 2016-22 to accelerate innovation addressing the global rise of antibiotic resistance
- Commencing next chapter with $370M committed by US Government and Wellcome
- Non-dilutive funding to product developers to drive innovation | Developers assume a cost-share
- Focused on infectious syndromes with highest mortality rates attributable to/associated with AMR
- World's most scientifically-diverse discovery & early-development portfolio

1,163 Expressions of Interest

92 funded projects

45 active projects

11 | 4
FIH | V&V
Tx/Pv | Dx

2 | 2
adv dev | CE marks
Tx/Pv | Dx

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

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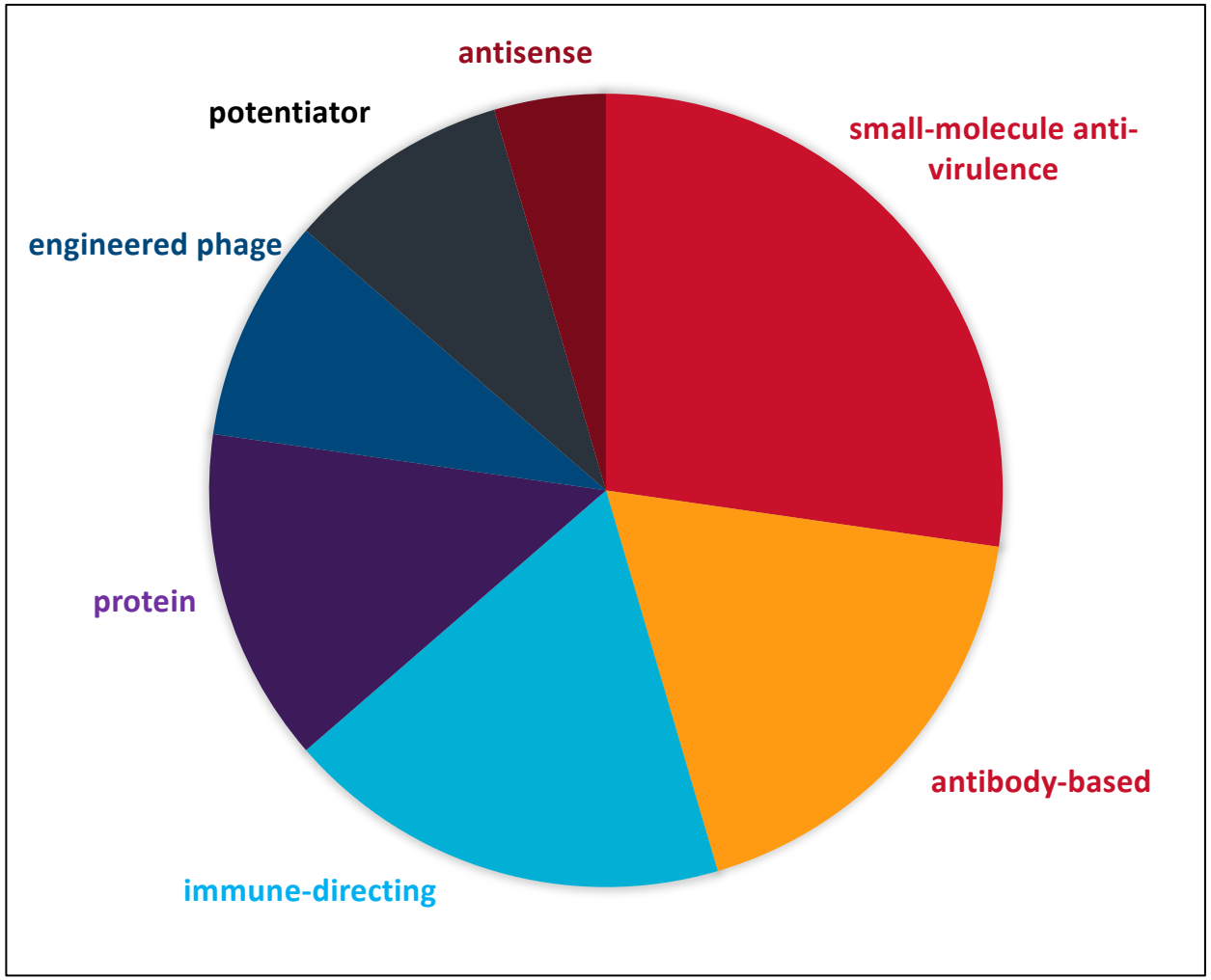
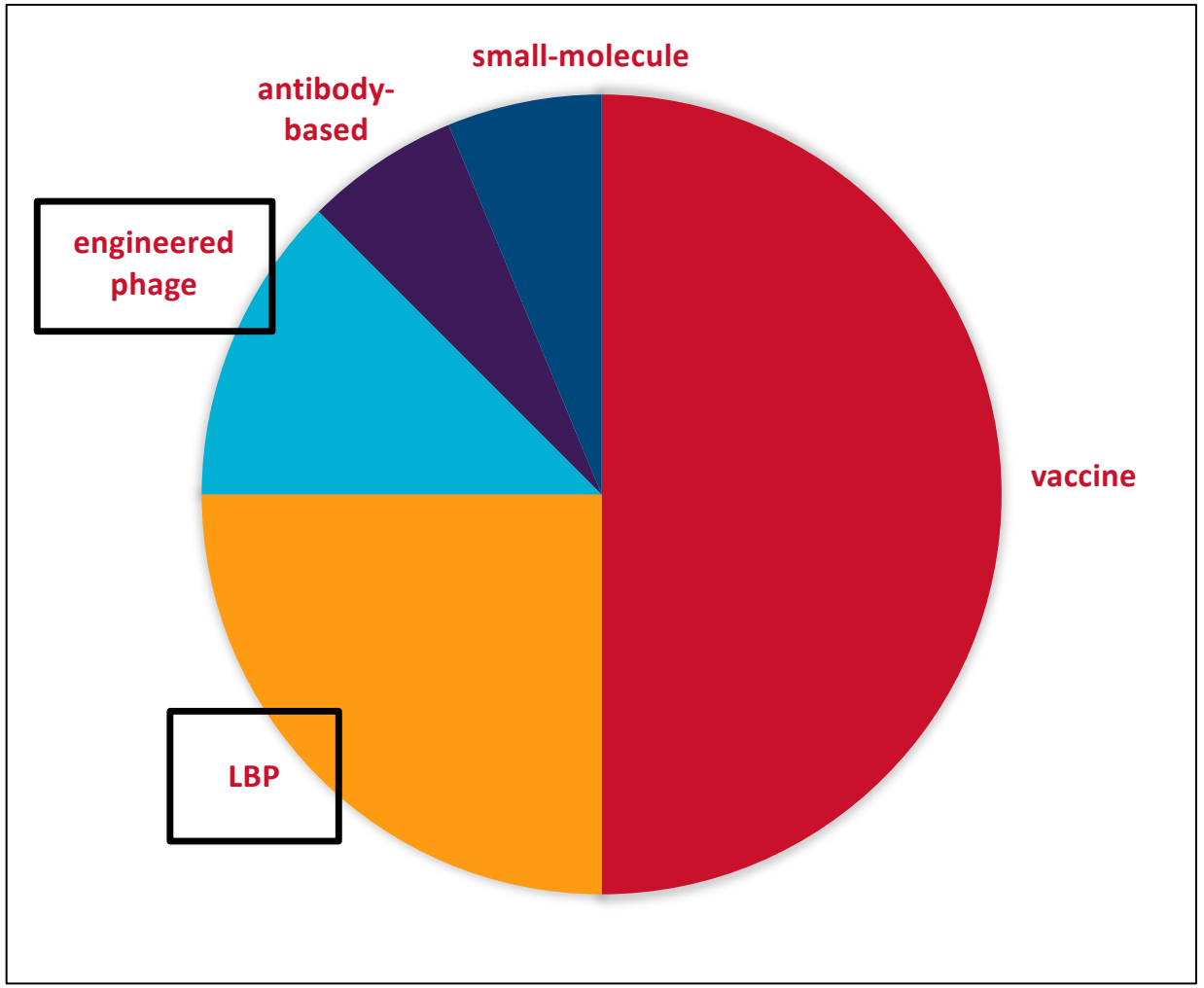
Non-traditional Portfolio with Multiple Modalities



Treatment



Prevention

Recently Held First of Decolonization Workshops

- Dr. Maxime Mallet, Groupe Hospitalier Universitaire APHP-Sorbonne Université, Site Pitié-Salpêtrière, Service de Pneumologie, Médecine Intensive et Réanimation (Département R3S)
- Dr. Eugene Katchman, Transplant ID Consultant, ID Division, Tel-Aviv Sourasky Medical Center
- Dr. Miriam Furst-Wilmes, Clinical Assessor for Antiinfectives, DZIF Office for Scientific and Regulatory Advice (OSRA), Federal Institute for Drugs and Medical Devices Unit 32 “Infectiology/Dermatology/Allergology“
- Dr. Mark Goldberger, former Medical Director Emerging and Pandemic Threat Preparedness, Director Office of Antimicrobial Products
- Dr. David Cook, SVP/CSO Forma Therapeutics, former EVP/CSO Seres Therapeutics

Some Questions Posed to Participants in a Decolonization Workshop

- Overall, what is your receptivity to decolonization strategies?
- What are the most important concerns and limitations to current decolonization procedures (lack of effectiveness?, recolonization rebound?, resistance development?, tolerability?, adverse re-population (ie *C. difficile*)?)?
- Do you or have you employed decolonization ahead of a procedure?
  - When, and what are the approaches you use?
  - Do you tailor how/if you treat high-risk populations, and if so what is your decision tree?
  - How is risk/tolerance or risk/benefit assessed for patients in different therapeutic areas (eg oncology patients versus patients with recurrent UTIs or *C. difficile*), and what drives this?
  - How does immune status impact decolonization considerations?
- What are the most important performance characteristics that might encourage uptake of a new decolonization product?
- What patient population(s) is(are) best suited to obtain early proof-of-concept?
- What are the preclinical/nonclinical data you feel are necessary to embrace a decolonization product?
  - What is the relevance of animal model data?
  - Are there guides, if you embrace animal models, for what success means in those models, including their predictive power for clinical outcomes?
  - Are there safety risks if these products breech a leaky gut barrier?
- What are endpoints in a clinical setting you feel are meaningful to show a benefit for a decolonization product? Relatedly, what is a timeframe where you would consider a patient sufficiently derisked from an infection perspective?
- Under what circumstances might decolonization negatively affect the patient?
  - When considering ecological succession, what is known or is needed to be known about "what moves in the neighborhood" after decolonization (either targeted or widespread removal)?
- Is "rebuilding the neighborhood" better than "clearing the neighborhood"? In this instance, we are talking about the difference between strategies that add good bacteria versus those that remove bacteria, either with laser precision or as a strafing run.

Several Key Themes Emerged

- Decolonization not employed routinely, but surgeons and ID consults need something – not using antibiotic prophylaxis given the extreme prevalence of colonization with ESBLs + FQ-R organisms.
- Working back from a label that might begin, “For the reduction of colonization in a [closed] population”…
  - For POC, a quantitative microbiology endpoint is good, but what is a sufficient measure of success?
  - For pivotal studies, there needs to be a link to clinical benefit. This might vary with the [closed] population.
- A biomarker strategy is desired, but what is relevant, and what is the signal/noise we can expect?
- An understanding of how broadly applicable results from one [closed] population to another is critical.
- An understanding of the effects of decolonization, how they manifest over time and what external variables might influence them is needed.

Thoughts on [Closed] Populations

1. Patients awaiting liver transplantation
   - often present with recurrent ascites
   - >30% are carriers of CRE+,ESBL+ and FQ-R organisms
   - at-risk for developing infection post-transplantation
   - most fragile in days following surgery (*not* from ICU)
   - ★ Study could involve decolonization at a timepoint prior to transplantation, with early and late readouts.
     - need understanding of the timecourse s/p transplant for development of infection
     - placebo-controlled, unless SOC requires preventative antibiotic therapy
     - need an understanding of impact on transplant list

Thoughts on [Closed] Populations

2. Cirrhosis patients hospitalized with ascites
   - reported to have a 10-30% likelihood of developing a spontaneous bacterial peritonitis
   - have a 40% (6-months) and 70% (12-months) recurrence rate, following Abx
   - ★ Study could be a small pilot to understand durability of antibiotic effect – treat at some point after discontinuation of Abx and follow-up
     - some patients eligible for preventive Abx – add decolonization on top? Compare decolonization to Abx? Study lower risk patients vs placebo?

Thoughts on [Closed] Populations

3. Patients awaiting induction chemotherapy
   - many of them
   - less complicated/fragile
   - many neutropenic and need Abx
   - ★ Study would likely be on top of SOC Abx versus Abx; benefit in mortality likely to be necessary

Thoughts on [Closed] Populations

4. Residents in nursing homes
   - high rate of MDRO colonization reported
   - potential transfer to hospital for higher level of care
   - ★ Study could randomize by facility but…
     - need to have similar demographics
     - need for decontamination of significant reservoirs
     - need to test staff as well as all new residents
     - decolonization product would need to be broad spectrum
     - ★ Best considered after POC had been shown in other populations

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Summary

- CARB-X is committed to bringing solutions across pillars and modalities to face the ongoing threat of AMR
- There are several challenges and opportunities in decolonization strategies
  - need for a closed population study is critical
  - need for microbiological and clinical endpoints clear
- A coordinated approach would be beneficial to the ecosystem

Thank you

emduffy@bu.edu