NIAID Support to Meet the CARB Challenge

NASEM, September 23, 2020

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Division of Microbiology and Infectious Diseases
NIAID/NIH

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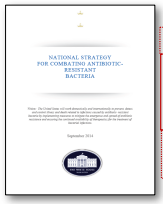
CARB National Strategy: NIH Role



- **Stewardship:** Slow the Development of Resistant Bacteria and Prevent the Spread of Resistant Infections
- **Surveillance:** Strengthen National One-Health Surveillance Efforts to Combat Resistance
- **Diagnostics:** Advance Development and Use of Rapid and Innovative Diagnostic Tests for Identification and Characterization of Resistant Bacteria
- **Countermeasures:** Accelerate Basic and Applied Research and Development for New Antibiotics, Other Therapeutics and Vaccines
- **International Collaboration:** Improve International Collaboration and Capacities for Antibiotic Resistance Prevention, Surveillance, Control, and Antibiotic Research and Development

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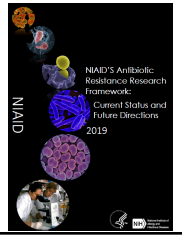
NIAID Antibacterial Resistance Program



- Basic Research
- Translational Research/ Product Development
- Clinical Research

Diagnosis, Prevention and Treatment

https://www.niaid.nih.gov/sites/default/files/AR2019.pdf

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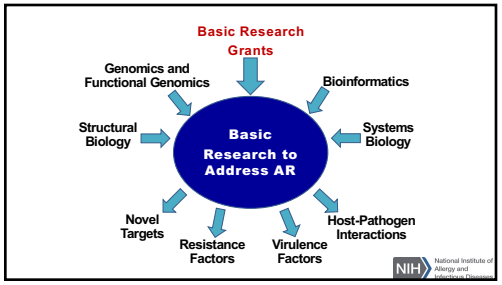

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Diagnostics Development

- Grant and Contract support, including targeted funding opportunities
- Antibacterial Resistance Leadership Group Activities
  - Master Protocol for Diagnostics
  - Host-based gene expression signatures
  - Resources for diagnostics developers
  - Clinical Outcomes Studies

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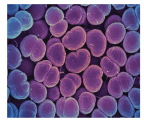
NIH National Institutes of Health
Turning Discovery Into Health

FOR IMMEDIATE RELEASE
Wednesday, August 5, 2020

News Release

Rapid Diagnostic for Gonorrhea Wins $19 Million Federal Prize Competition to Combat Antibiotic Resistance



- **Visby Medical diagnostic gives results ≤30 mins, allowing clinicians to treat patients immediately with the correct medication**

Credit: AS Fauci

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Antibacterial Development

- Hundreds of projects on basic, translational and clinical development of new therapeutics
- Numerous targeted funding opportunities
- Workshops
- Innovations on existing drug classes
- New classes of antimicrobials
- Non-traditional therapeutics

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Cefepime-taniborbactam (Venatorx)

- Combination of a novel serine and metallo-beta-lactamase inhibitor (taniborbactam) and a cephalosporin (cefepime) for treatment of carbapenem-resistant bacterial infections
- **NIAID Contribution**
  - Supported discovery and preclinical development of a new class of beta-lactam inhibitors (BLI)
  - Supported preclinical development of drug combination
  - Supported five Phase I clinical trials
- **Outcomes**
  - BARDA and DTRA support for advanced development
  - GARDP-supported Phase 3 clinical trial investigating efficacy and safety of the drug combination currently underway

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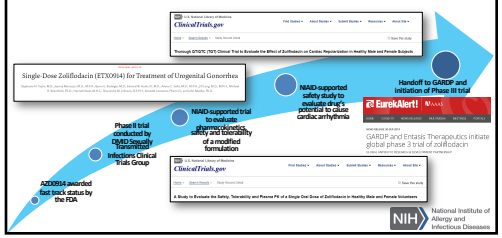
NIAID Support for Zoliflodacin



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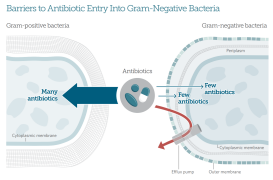
Priority: Gram-Negative Drug Discovery



- Partnerships for the Development of Tools to Advance Therapeutic Discovery for Select Antimicrobial-Resistant Gram-Negative Bacteria (R01)
- Chemistry Center for Combating Antibiotic-Resistant Bacteria (CC4CARB)
- Workshop

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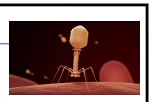
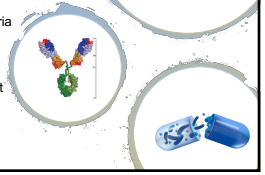
Priority: Non-Traditional Therapeutics



- Understanding Phage Biology to Support the Development of Bacteriophage Therapy (R21)
- Partnerships for the Development of Vaccines and Immunoprophylactics Targeting Multiple Antimicrobial-Resistant Bacteria
- Partnerships for the Development of Host-Targeted Therapeutics to Limit Antibacterial Resistance
- Non-Traditional Therapeutics that Limit Antibacterial Resistance



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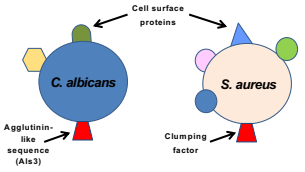
NDV-3: Vaccine Candidate Active Against *Candida* and *Staphylococcus aureus*



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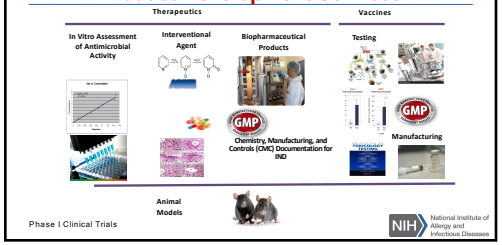
Product Development Services



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CARB-X

Combating Antibiotic Resistant Bacteria

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

FUNDERS

ALLIANCE PARTNER ACCELERATORS

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ARLG Renewed in FY2020

Maintain

- Overall scientific scope
- Ability to respond to new priorities
- Mechanism to solicit ideas from the global research community
- Mechanism to provide advice to companies on clinical development of drugs and diagnostics
- Focus on
  - Resistant Gram-negative studies
  - Diagnostics studies
  - Pragmatic/strategy trials
  - Innovations in statistical methodology
  - Mentoring

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Thank You

- To search for funded projects: https://projectreporter.nih.gov/reporter.cfm
- For a list of recent funding opportunities, visit NIAID's Drug Resistance website: https://www.niaid.nih.gov/research/recent-initiatives-antimicrobial-resistance

Contact:

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Jane.Knisely@nih.gov

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IV Fosfomycin (Contepo/ZTI-01)

- Broad spectrum antibiotic for Gram-positive and Gram-negative bacteria
- NIAID-funded Phase 1 trial demonstrated safety in healthy adults
- Zavante/Nabriva Phase 2/3 for cUTIs and acute kidney infections
- FDA Fast Track and QIDP designations for cUTIs, HABP, and VABP
- NIAID-funded Phase 1 trial to determine dosing for bacterial lung infections

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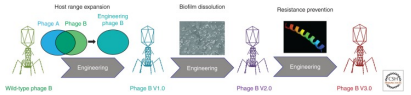
Engineered Phage

- Uses genetic engineering to construct lytic phage with desired therapeutic properties
- Creates a synthetic biology platform that allows rapid expansion of phage host range to construct phage with superior therapeutic efficacy against MDR pathogens



Awardee: Hubby, Bolyn

Phage Therapy in the Era of Synthetic Biology. Barbu et al. Cold Spring Harb Perspect Biol. (Oct 2016) 8(10):a023879.

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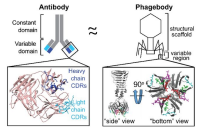
"Phage-body"

- Development of phage platforms that make engineering pathogen-specific phages easier (e.g. synthetic "phage-body" technology allows mutation of phage tail fibers to alter host range and prevent emergence of resistance)



Engineering Phage Host-Range and Suppressing Bacterial Resistance through Phage Tail Fiber Mutagenesis. Yehl et al. Cell. (Oct 2019) 179(2):459-469.

Awardee: Lu, Timothy

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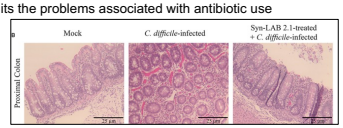
Probiotic for *C. difficile*

- Engineered Lactobacillus probiotic designed to prevent or treat CDI by competitive prevention of C. difficile establishment in the mammalian gastrointestinal (GI) tract
- Limits the problems associated with antibiotic use



An Engineered Synthetic Biologic Protects Against Clostridium difficile Infection. Vedantam et al. Front. Microbiol. (Sept. 2018) 9:2380.

Awardee: Vedantam, Gayatri

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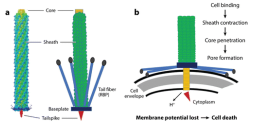
R-type bacteriocins

- Avidocin™ platform engineered from natural bacteriophage tail structures
- Potent antibacterial agents that puncture the bacterial membrane and can be engineered to specifically target almost any bacteria without damaging the microbiota



Phage Tail-Like Bacteriocins. Scholl, D. Annu Rev Virol. (Sept. 2017) 4(1): 453-467.

Awardee: Scholl, Dean (AvidBiotics Corp.)

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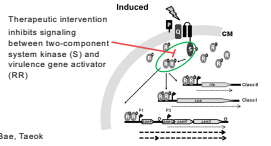
Targeting Virulence

- Inhibition of bacterial virulence systems by targeting two-component signaling systems that regulate virulence gene expression
- Reduces the pathogenic potential of the bacterium without killing or resistance development and complements conventional antibiotics



Identification of the P3 promoter and distinct roles of the two promoters of the SaeRS two-component system in Staphylococcus aureus. Jeong et al., J. Bacteriol. (Sept. 2011) 193(18): 4672-84.

Awardee: Bae, Taeok

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Phage Therapy

- Relies on the use of naturally occurring viruses (phage) to infect and lyse bacteria
- Therapeutic use in western countries in 1940's, but shelved as antibiotics developed
- Renewed interest with emergence of AMR: "Top 10 Drug Discoveries to watch in 2019"

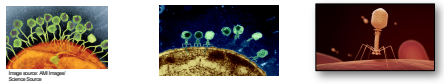

Image source: AMI Images/ Science Source

http://www.pharmexec.com/top-10-drug-discovery-trends-watch-2019

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nature

NATURE | ARTICLE January 21, 2017

A New Antibiotic Kills Pathogens Without Detectable Resistance

LL Ling, K Lewis et al.

- By screening uncultured bacteria, investigators identified a novel antibiotic, Teixobactin

Worm Guts May Hold a New Weapon Against Antibiotic-Resistant Germs

NIAID News | November 20, 2019

- By screening the microbiome of roundworms, investigators identified a novel antibiotic, darobactam

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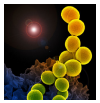
Eravacycline (XERAVA/TP-434)

- Novel synthetic tetracycline for the treatment of complicated intra-abdominal infections (cIAI)
- **NIAID contribution:**
  - Discovery and development of state-of-the-art chemistry
  - Supported synthesis of over 2,000 novel tetracyclines, including eravacycline
- **Outcomes:**
  - BARDA support for advanced development
  - Found to be well-tolerated & achieved high clinical cure rates in clinical trials (Tetraphase)
  - **FDA approval: August 27, 2018**



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