

NIAID and the National Strategy for CARB

CHI Re-entering Antibiotics Development

Rosemarie Aurigemma, PhD

Chief, Drug Development Section

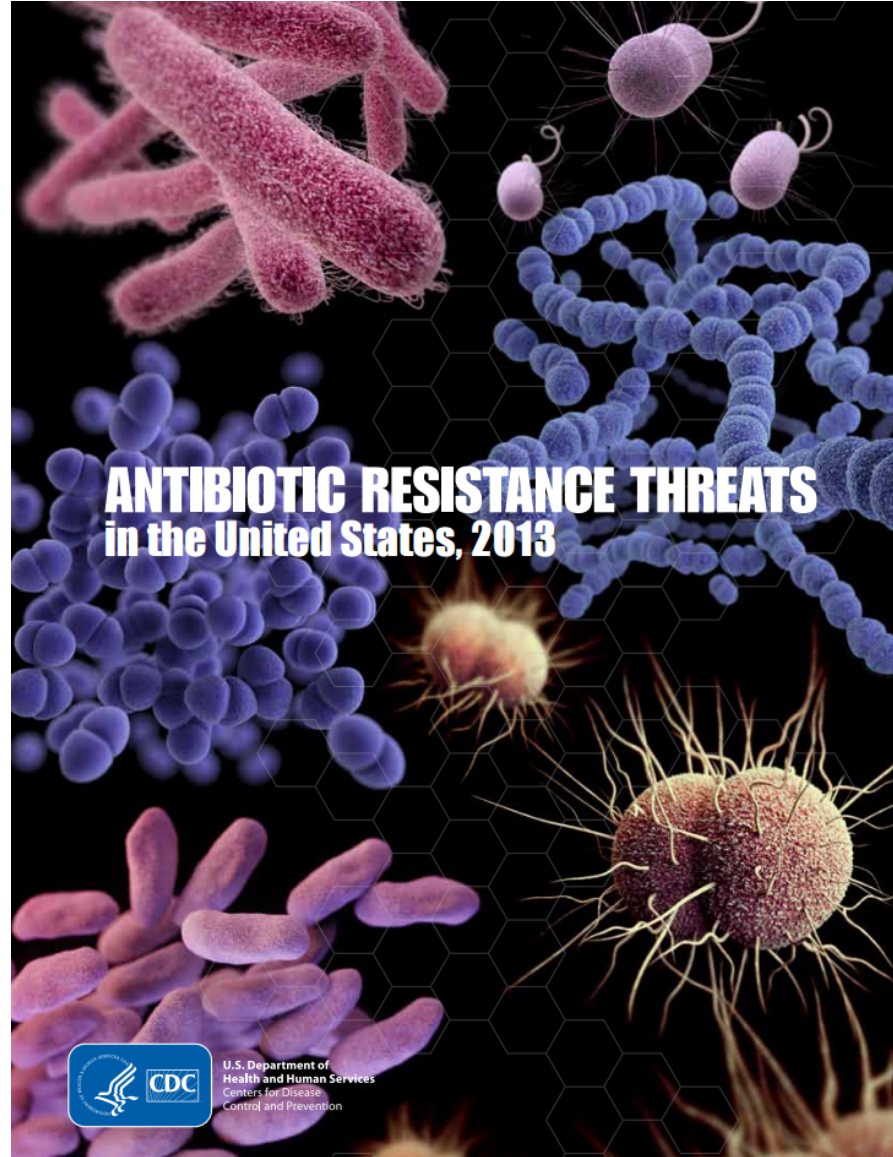
OBRRT, DMID, NIAID, NIH, DHHS

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NIAID: Support for R&D to Combat AMR

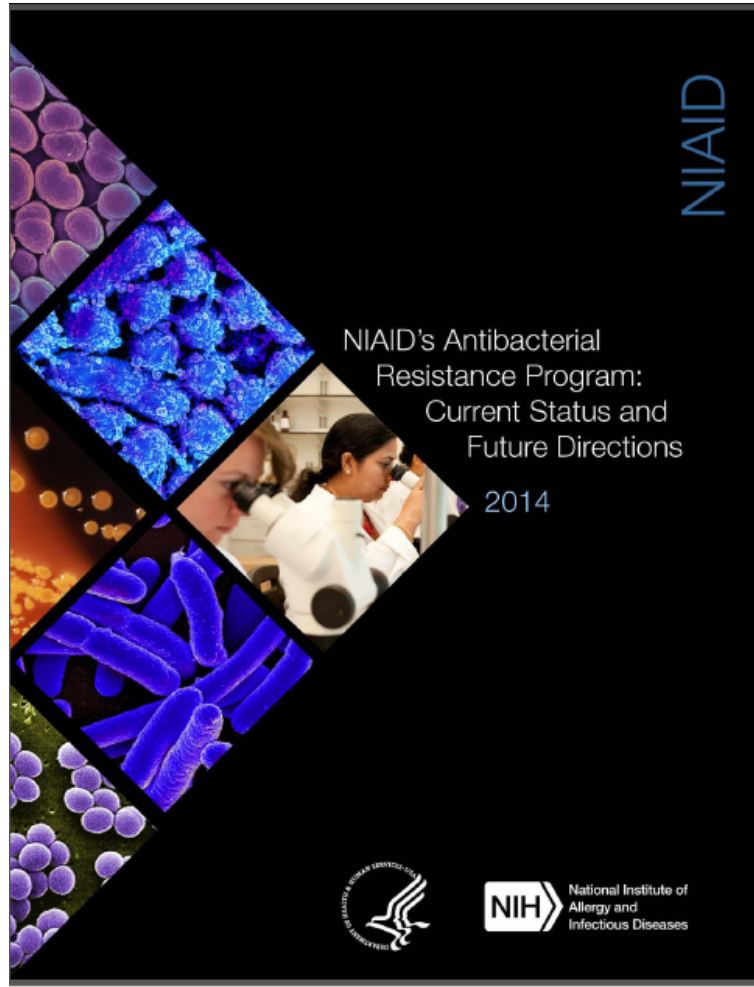
- ❑ NIAID-supported research on AMR facilitates translation of basic research discoveries from “bench to bedside”.
- ❑ The National Strategy for CARB has allowed all facets of this support to be boosted in order to drive investment and innovation.
- ❑ NIAID’s investment can result in an upwelling of novel products into the pipeline and lead to new licensed products in the future.
- ❑ This presentation will describe NIAID programs that support AMR product development, the results of the first year of the CARB initiative and the opportunities that lay ahead.

CDC Threat Report



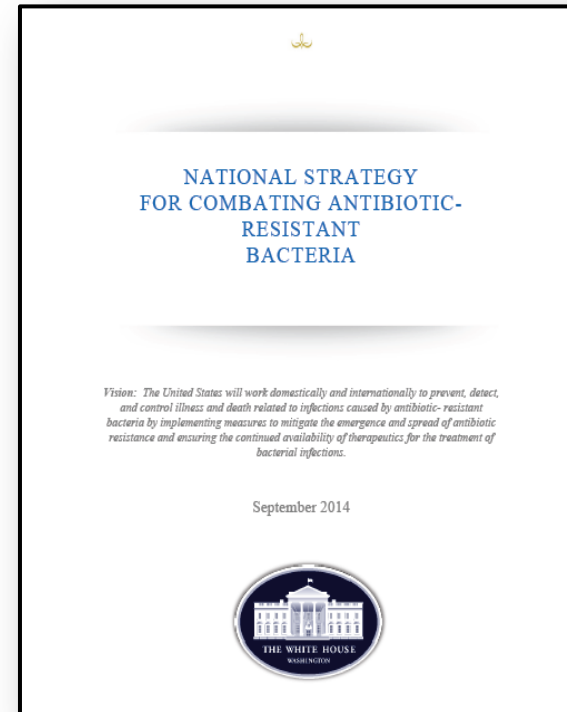
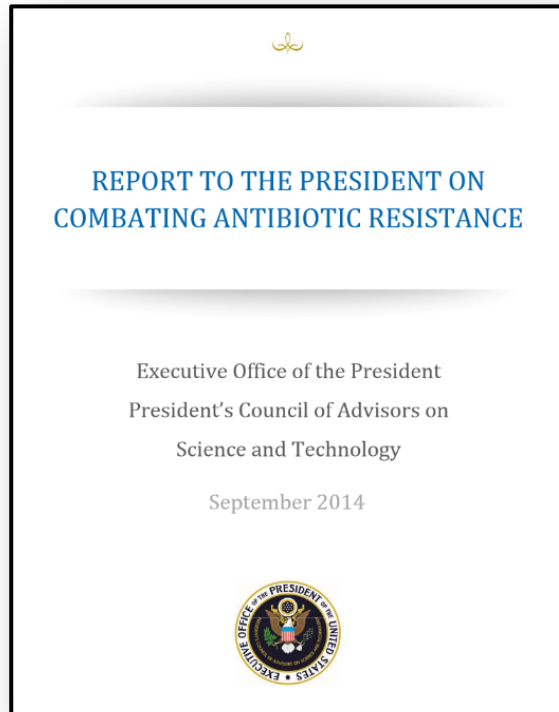
- **Urgent Threats**
- **Serious Threats**
- **Concerning Threats**

NIAID Antibiotic Resistance Program



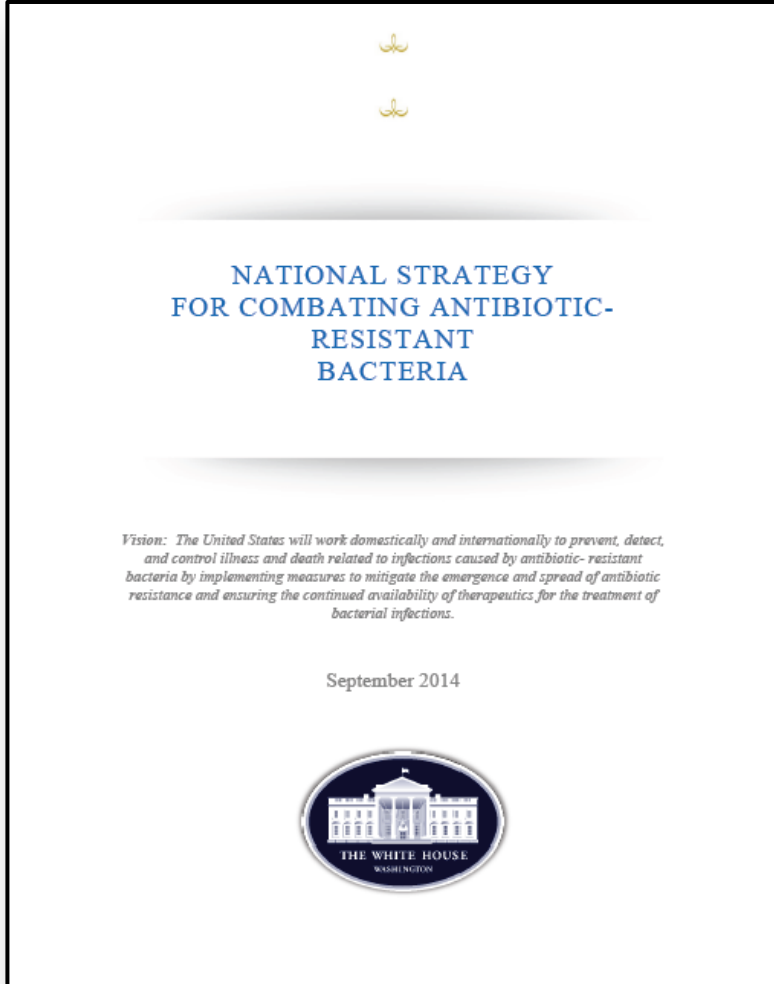
- **Systems Biology and Antibacterial Resistance:** New Directions for Drug Discovery
- **Teaching Old Drugs New Tricks:** Extending the Clinical Utility of Antibacterial Drugs
- **Disarm, But Leave Unharmd:** Exploring Anti-Virulence Strategies
- **Less is Better:** Diagnostics to Guide Use of Narrow-Spectrum Therapeutics
- **Exploiting Natural Predators:** The Specificity of Phage Therapy
- **Synthetic Microbiota:** An Ecobiological Approach
- **Harnessing the Immune System to Combat Bacterial Infections**

US Government and NIAID Antibiotic Resistance Initiatives



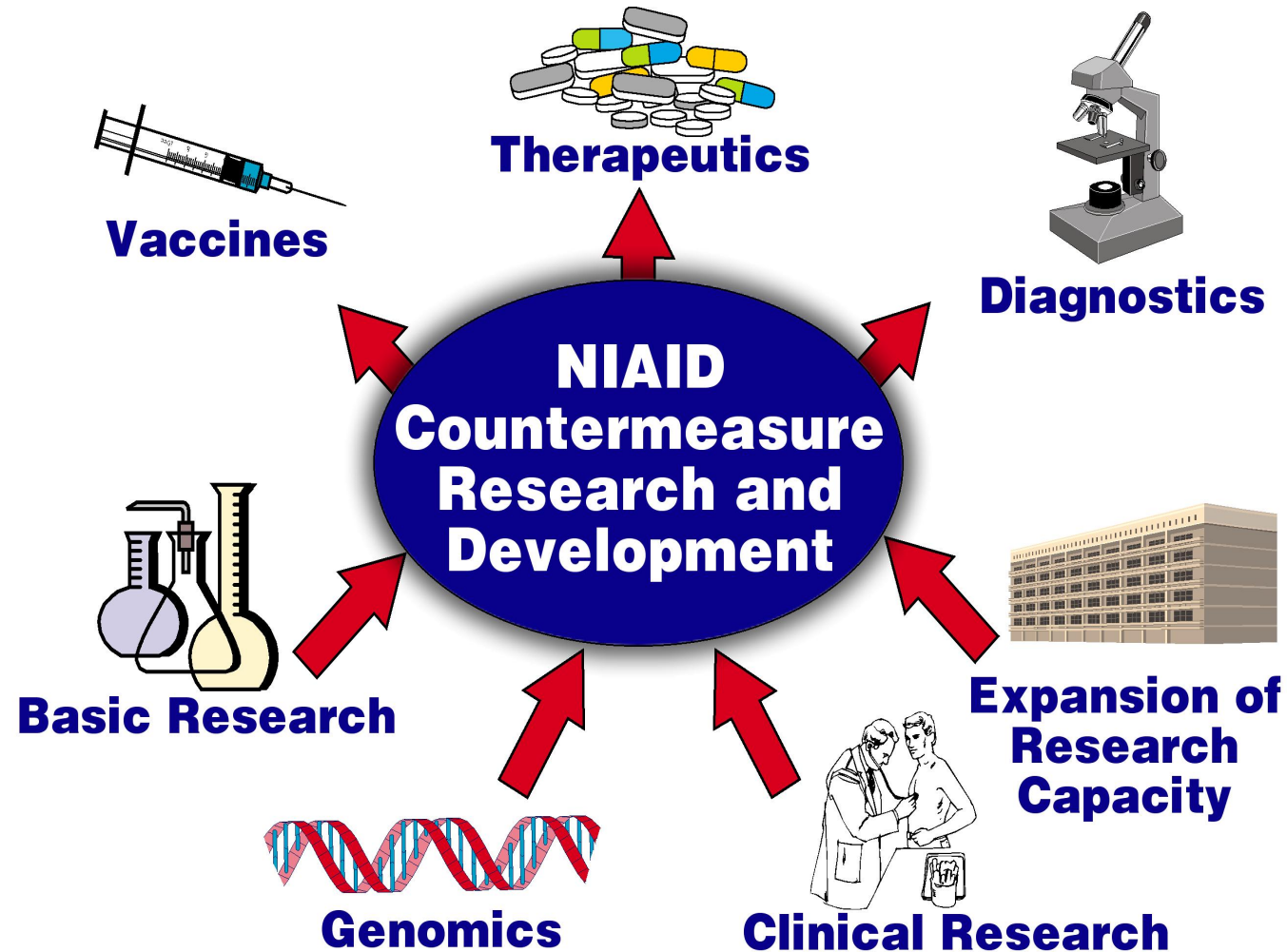
NIAID is supporting basic research, translational research, and clinical development of diagnostics, therapeutics and vaccines

CARB National Strategy: NIAID Role

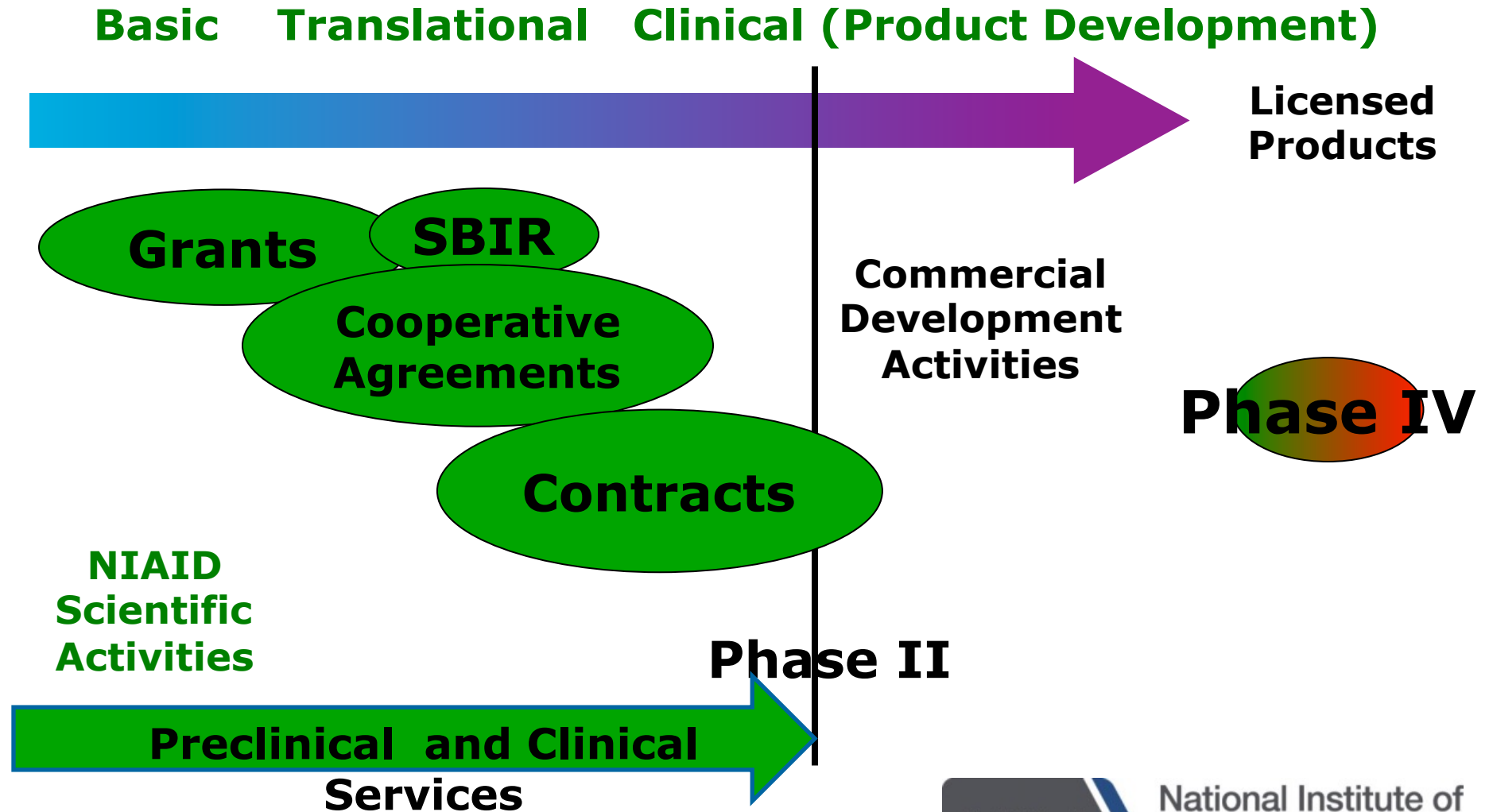


- **Stewardship:** Slow the Development of Resistant Bacteria and Prevent the Spread of Resistant Infections
- **Surveillance:** Strengthen National One-Health Surveillance Efforts to Combat Resistance
- **Diagnostics:** Advance Development and Use of Rapid and Innovative Diagnostic Tests for Identification 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

NIAID Support for Research and Development



Lowering Risk with Overlapping Mechanisms



Engaging with Stakeholders in Antibacterial Development

■ Workshops

- Development of New Antibacterial Products (with FDA; 2014)
- Staph vaccines (2010 & 2013)
- Bottlenecks in Drug Development (2012 & 2014)
- Coordinated Development of Diagnostics and Therapeutics (2014)
- GC Vaccines (2015)
- Phage Therapy (2015)
- Microbiota in Infectious Disease (2015)
- New Frontiers in Antibacterial Resistance and Clinical Trials in Antibacterial Resistance (2016)
- More coming in 2017.....

Seven Strategic Approaches to Antimicrobial Resistance Research

- **Systems Biology and Antibacterial Resistance: New Directions for Drug Discovery**
 - 5 Awards 2016 RFA-AI-14-064: **Systems Biology and Antibacterial Resistance** (U01)
- **Harnessing the Immune System to Combat Bacterial Infections**
 - RFA-AI-15-024: **Partnerships for the Development of Host-Targeted Therapeutics to Limit Antibacterial Resistance** (R01)
- **Disarm, But Leave Unharmful: Exploring Anti-Virulence Strategies**
 - RFA-AI-14-066: **Non-Traditional Therapeutics that Limit Antibacterial Resistance** (R21/R33)
- **Synthetic Microbiota: An Ecobiological Approach**
 - RFA-AI-14-066: **Non-Traditional Therapeutics that Limit Antibacterial Resistance** (R21/R33)
- **Less is Better: Diagnostics to Guide Use of Narrow-Spectrum Therapeutics**
 - RFA-AI-14-019: **Partnerships for Diagnostics to Address Antimicrobial Resistance of Select Bacterial Pathogens** (R01)
- **Exploiting Natural Predators: the Specificity of Phage Therapy**
 - RFA-AI-14-066: **Non-Traditional Therapeutics that Limit Antibacterial Resistance** (R21/R33)
- **Teaching Old Drugs New Tricks: Extending the Clinical Utility of Antibacterial Drugs**
 - BAA NIAID-DMID-NIHAI2010089: **Targeted Clinical Trials to Reduce the Risk of Antimicrobial Resistance**

Grant Awards to Support Antimicrobial Resistance Research

- **Development of Novel Therapeutics for Select Pathogens**
 - 14 Awards in 2015 for discovery and early stage development of novel strategies to treat Gram negative infections ([RFA-AI-14-026](#), R21/R33)
- **2016** there were **24 phased innovation awards** made to 18 academic institutions and three industrial organizations to support products such as: bacteriocin, bacteriophage strategies, microbiome-based strategies, nanoparticles, CRISPR-based biotherapeutics, anti-virulence strategies

CARB Funding Activities: Diagnostics

- Funded 9 grants under [RFA-AI-14-019: Partnerships for Diagnostics to Address Antimicrobial Resistance of Select Bacterial Pathogens \(R01\)](#)
- AMR Diagnostic Challenge Competition (\$20 million)
 - NIH and BARDA, with input from CDC and FDA
 - Stakeholder comments will be used to develop design and parameters of Challenge competition
 - Competition announced in 2016

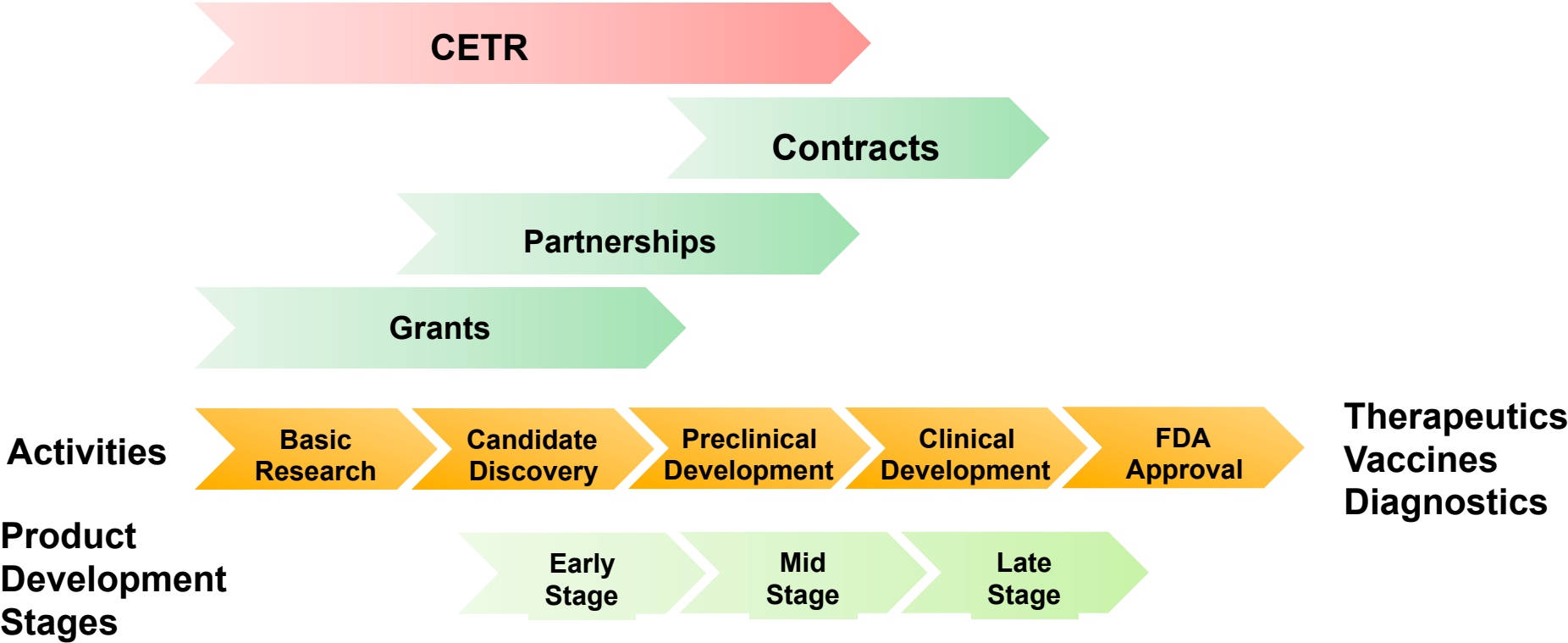
Grants to Support Antimicrobial Resistance Research

Current opportunity announcements:

- Systems Biology: The Next Generation for Infectious Diseases (U19) [RFA-AI-16-080](#) (due March 2017)
- Partnerships for the Development of Tools to Advance Therapeutic Discovery for Select Antimicrobial-Resistant Gram-Negative Bacteria (R01) [RFA-AI-16-081](#) (due May 2017)
- Platform Delivery Technologies for Nucleic Acid Therapeutics (R43/R44) [PAR-17-035](#)



Centers of Excellence in Translational Research

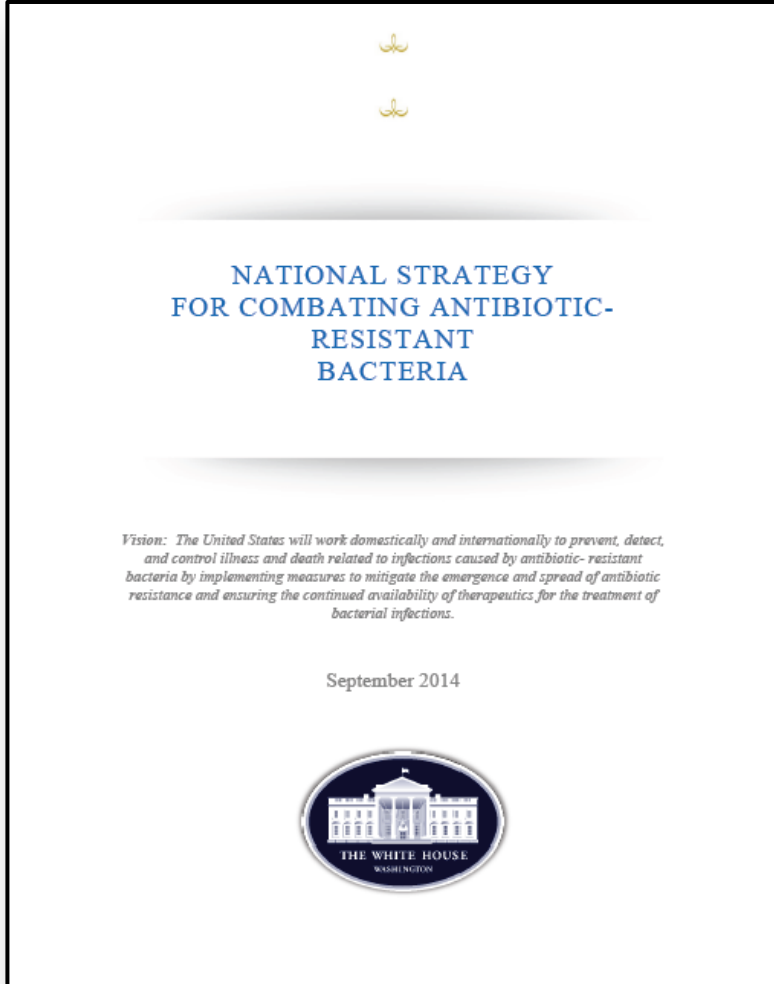


Centers of Excellence for Translational Research

CETRs focused on AMR to advance discovery, development, licensure and/or use of new or improved medical products; Technologies

- 1- Antimicrobial Drug Discovery from Coevolved Symbiotic Communities**
- 2- Innovative Platforms for Antimicrobial Therapy and Vaccine Development**
- 3- Immunoprophylactic Strategies to Control Emerging Enteric Infections**
- 4- Center to develop therapeutic countermeasures to high-threat bacterial agents**
- 5- Center for Research in Diagnostics and Discovery**
- 6- Integrated discovery and development of innovative TB Diagnostics**
- 7- Novel Nanoparticle Platform for the delivery of Vaccines and Adjuvants**
- 8- Autophagy Modulators as Novel Broad-Spectrum Anti-Infective Agents**

CARB National Strategy: NIAID role



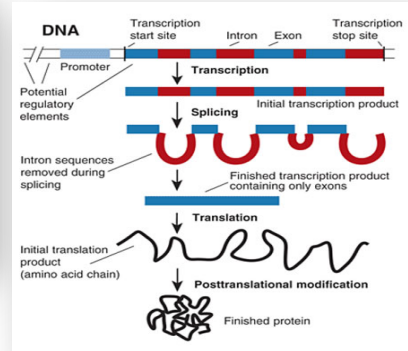
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NIAID/DMID Genomics Programs

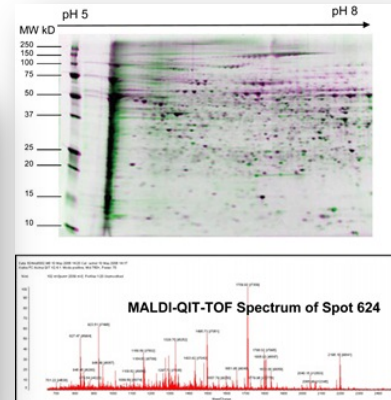
Sequencing



Functional Genomics



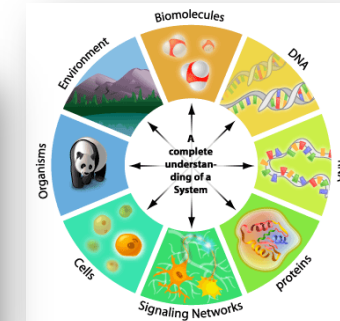
Proteomics



Structural Genomics



Systems Biology



Bioinformatics Resource Centers

Genomic Research Resources

Genomic/Omics Data Sets, Databases, Bioinformatics Tools, Biomarkers, 3D Structures, Protein Clones, Predictive Models

To address key questions in microbiology and infectious disease

To identify new targets and develop new strategies for vaccines, diagnostics and therapeutics

Genomic Centers for Infectious Diseases (GCIDs) Response to Antibiotic Resistance

J. Craig Venter™
INSTITUTE



BROAD
INSTITUTE



Sample
Processing
Method Develop

High
Throughput
Sequencing
Pipelines

Metagenomics
Transcriptomics

Bioinformatics
Tools
Data Analysis
Pipelines

Genomics
Bioinformatics
Training



GCID Understanding Antimicrobial Resistance

Generate large scale resources and data sets for > 4000 AMR organisms

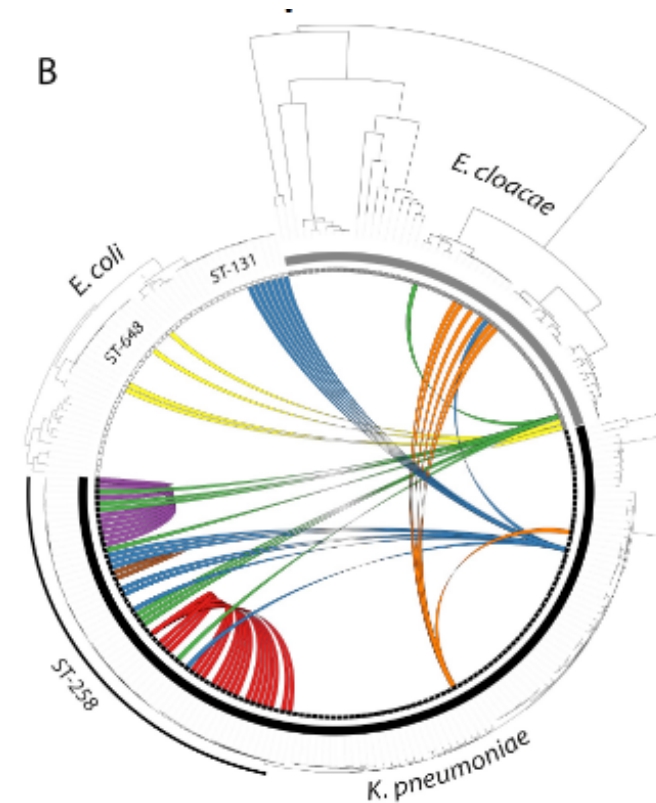
- genomics, transcriptomics, metagenomics, genome-wide screens
- Clinical samples domestic and international collaborations
- Hypothesis-driven experiments

Responding to PCAST and CARB recommendations

- Sequencing reference strains with CDC, FDA, NHGRI and NCBI to populate National Database of Resistant Pathogens

Diverse bacterial, fungal, and parasite pathogens

- CRE, ESKAPE, *Mycobacterium tuberculosis*, Infectious diarrhea, *Streptococcus pneumoniae*
- Azole resistance in *Candida* and *Aspergillus*



Cerquiera, GC, Earl, AM et al. PNAS under review

Antimicrobial Genome Resistance Projects

Enterococcus faecium

Staphylococcus aureus

Klebsiella pneumoniae

Acinetobacter baumannii

*Pseudomonas
aeruginosa*

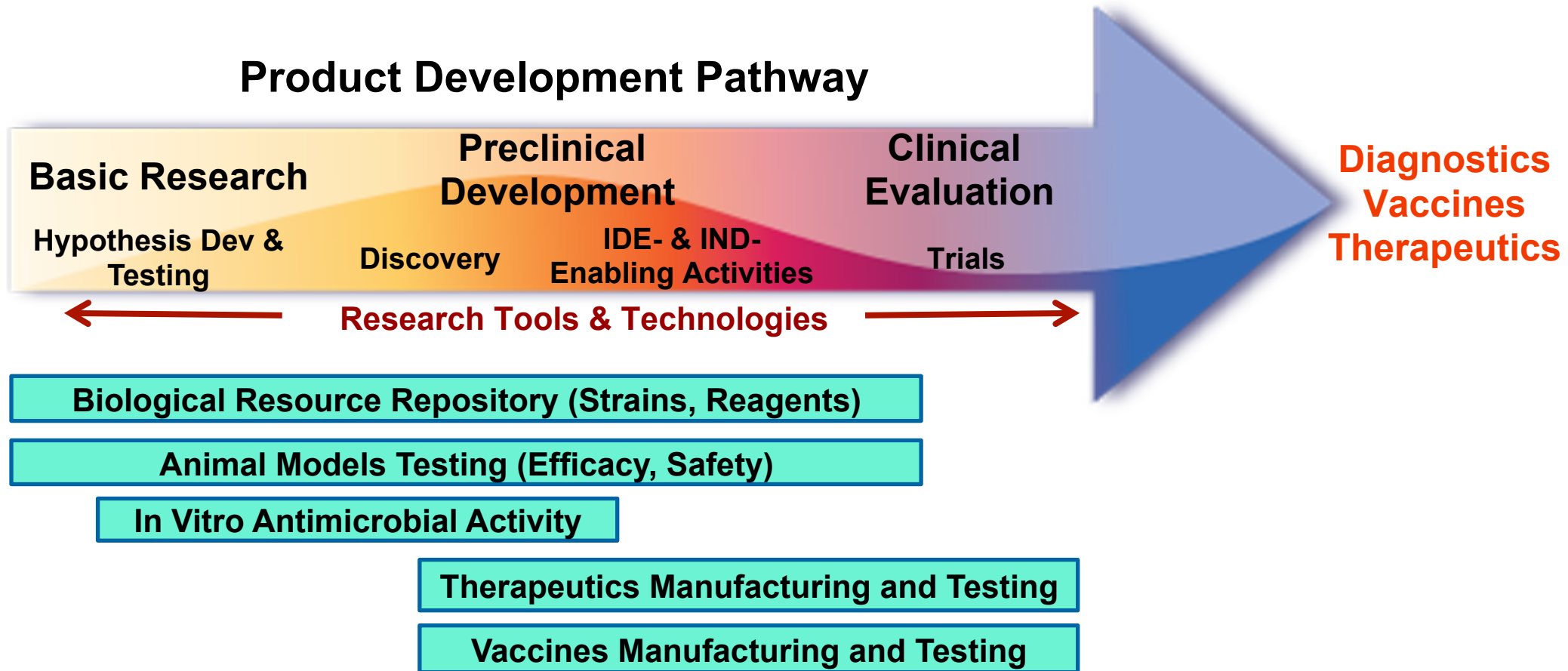
Enterobacter

*Streptococcus
pneumoniae, E. coli* and
other

NIAID/NIH will continue to work with CDC and other USG agencies to populate the *National Database of Resistant Pathogens* by sequencing high priority reference strains.

Well-characterized, fully sequenced isolate banks to help advance the development of diagnostics, therapeutics, and vaccines, as well as further basic research.

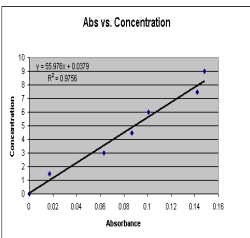
DMID Research Resources and Preclinical Services



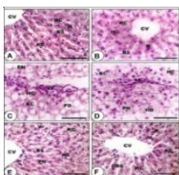
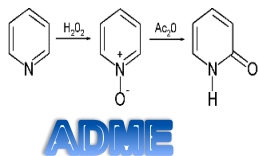
Product Development Services

Therapeutics

In Vitro Assessment of Antimicrobial Activity



Interventional Agent



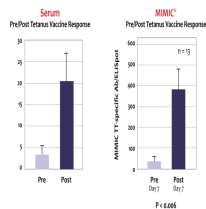
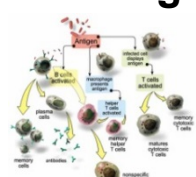
Biopharmaceutical Products



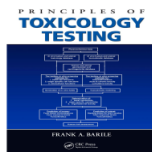
Chemistry,
Manufacturing, and
Controls (CMC)
Documentation for IND

Vaccines

Testing



Manufacturing



Animal Models



What do Preclinical Services Provide?

- Expertise/capability in product development
- Lower the risk for developers
- Helps move promising discoveries along the product development pathway
- Gap-filling, not intended as full development program support
- Confidentiality assured
- Sponsor maintains IP
 - Materials Transfer Agreement (MTA)
 - Non-Clinical Evaluation Agreement (NCEA)
 - Clinical Trial Agreement (CTA)

Who is Eligible for Support Services?

- Innovators from academia, non-profit organizations, industry, and government
- Domestic or foreign institutions
- Do not need to have NIH funding
- Services request process is available year-round
- Support determined based on:
Priority, Significance, Innovation, Preliminary Data, Value

In vitro Assessment for Antimicrobial Activity

- Screening for bacteria and fungi, viruses, parasites & vectors and toxins
- High throughput as well as specific and broad spectrum screens
 - MIC and MIC90
 - Public Health panels
 - *S. aureus*, *Enterococcus* sp., *S. pneumoniae*, *S. pyogenes*, *S. agalactiae*, *Klebsiella*, *A. baumannii*, *P. aeruginosa*, *Enterobacter* sp., *E. coli*
 - BioDefense panels
 - *B. anthracis*, *Y. pestis*, *F. tularensis*, *B. mallei*, *B. pseudomallei*
- To stimulate research towards discovery of improved antimicrobial therapies

Animal Models of Infectious Diseases

- Provision of a broad range of *in vivo* models (small animal, non-human primate and non-traditional)
- Development of novel models as needed
- Refinement of existing models (e.g. routes of delivery)
- Screening of products and efficacy testing to support FDA submission



Preclinical Development of Interventional Agents for Infectious Diseases

Core Service Task Areas

- Lead Identification, Development, Chemistry and Synthesis Services
- Chemistry and Manufacturing Services, Formulation (API, FDP)
- Pre-clinical Microbiological, Safety and PK Services (including GLP)
- Feasibility – GMP and GLP audits, Product Development Plans

Preclinical Development of BioPharmaceutical Agents

2016: Expanded scope; products supported **now includes diagnostic reagents**

Core task areas:

A: Feasibility Assessments, Audits

B: Product Assays, Bioanalytical Development

C: Process Development

D: Manufacturing, including pilot and cGMP

E: Regulatory documentation support

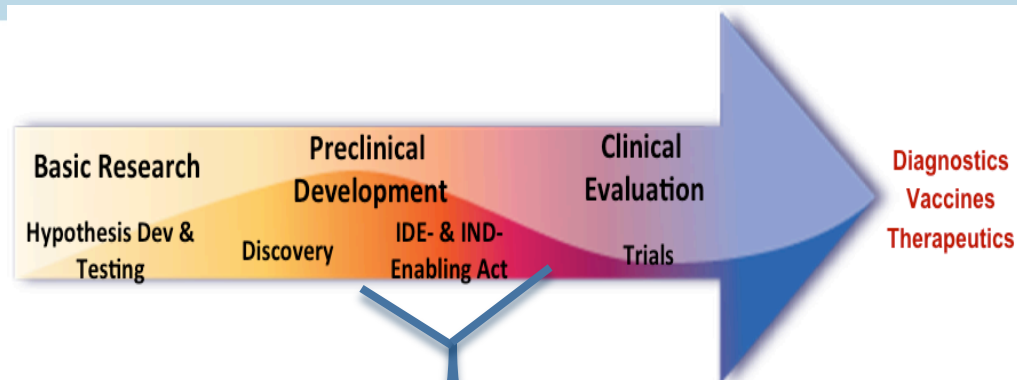
Goal: Filling Gaps and Extending Data Sets

Destiny Pharma Ltd. XF-73

A novel synthetic porphyrin for reduction of nasal carriage of *Staphylococcus aureus* (SA)

- Rapidly bactericidal prophylactic decolonization for those at risk of post-operative SA infection
- **MTD, NOAEL studies, intra-nasal, 14 day toxicity study in dogs**
- **NIAID September 2016 completed two-part Phase I Study for Safety and Local Tolerability of Nasal Formulations of XF-73 in the USA**

Lead Optimization: Critical Bottleneck in Rx Development



Lead Identification

- Chemical Starting Points
- Evaluate/Improve Potency
- Validate Mechanism
- Diversify Chem series
- Scope out SAR

Lead Optimization

- ID lead series for med chem
- Enhance drug-like phys props
- in vivo Efficacy & PK/PD
- ADME Optimization
- Tox Assessment
- Improve Potency/Selectivity

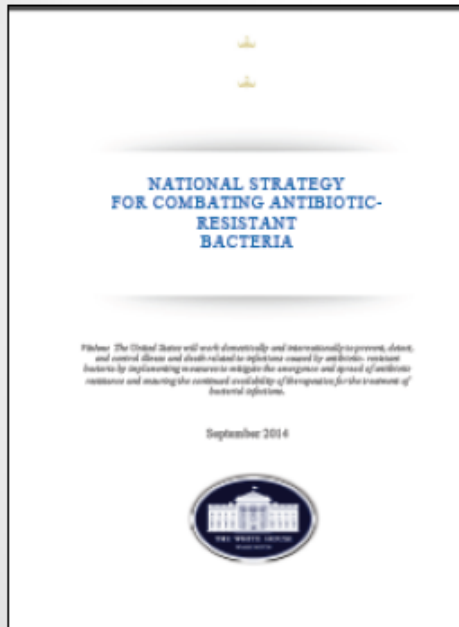
Candidate Drug ID

- Selection of candidate
- IND-enabling activities
- Phase 1

Task Order 4 Helps Fill Critical Need for Support of these LO Activities

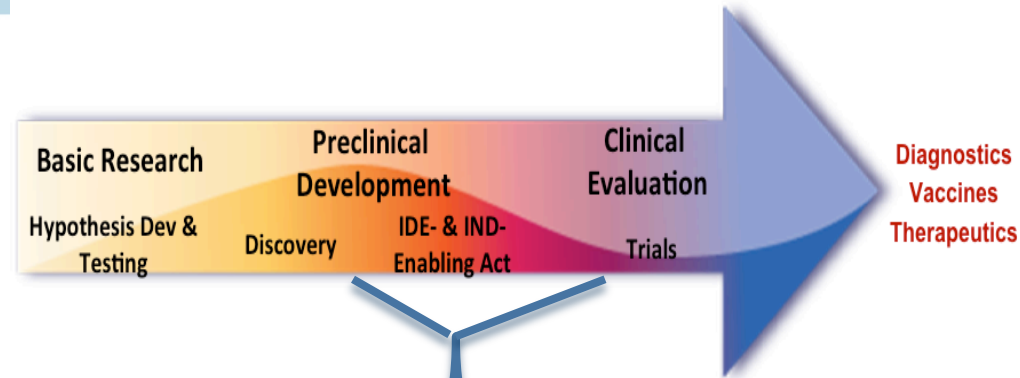
BARDA and NIAID Collaboration: CARB-X

■ GOAL 4: Accelerate Basic and Applied Research and Development for New Antibiotics, Other Therapeutics, and Vaccines



- 4.1 Conduct research to enhance understanding of environmental factors that facilitate the development of antibiotic resistance and the spread of resistance genes that are common to animals and humans.
- 4.2 Increase research focused on understanding the nature of microbial communities, how antibiotics affect them, and how they can be harnessed to prevent disease.
- 4.3 Intensify research and development of new therapeutics and vaccines, first-in-class drugs, and new combination therapies for treatment of bacterial infections.
- 4.4 Develop non-traditional therapeutics and innovative strategies to minimize outbreaks caused by resistant bacteria in human and animal populations.
- 4.5 Expand ongoing efforts to provide key data and materials to support the development of promising antibacterial drug candidates.
- 4.6 Enhance opportunities for public-private partnerships to accelerate research on new antibiotics and other tools to combat resistant bacteria.
- 4.7 Create a biopharmaceutical incubator—a consortium of academic, biotechnology and pharmaceutical industry partners—to promote innovation and increase the number of antibiotics in the drug-development pipeline.

BARDA and NIAID Collaboration: CARB-X



Accelerated access to preclinical development services

- Validate Mechanism
- Diversify Chem series
- Scope out SAR
- in vivo Efficacy & PK/PD
- ADME Optimization
- Tox Assessment
- Improve Potency/Selectivity
- Phase 1

Task Order 4 Helps Fill Critical Need for Support of these LO Activities

BARDA and NIAID Collaboration: CARB-X

FY17 CARB-specific Task Order

- CARB-X approved programs will not have to go through routine prioritization; Task Order already in place
- Goal is to address high-impact gaps
- CARB-X awards will include specified PCS support pending negotiation with awardee to ensure best use of resources

Broad Agency Announcements to Build a Pipeline of New Antibacterial Products

- 3 – 5 year contract awards
- \$3 – \$40M, based on scope
- Milestone driven: base + options
 - Clinical candidate optimization
 - Phase I program (occasionally phase I)

DMID/OBRRTR Advanced Therapeutics Development: FY2003 - present



BAA Contracts: A Pipeline of New Antibacterial Products

Fiscal Year	Contractor	Product/Indication	Scope
2011	CUBRC/Tetraphase	TP-271 IV/PO Tetracycline; CABP FastTrack and QIDP	IV SAD completed: Oral SAD and IV SAD/MAD 2017
2013	VenatoRx	VNRX-5133 IV serine and metallo BLI; cIAI and cUTI	IV SAD enrolling; IV MAD, DDI pending 2017
2015	Agile	2-Amino-imidazole; BS antibiotic potentiator	Candidate optimizing to clinical lead
2015	Cantab/Spero	Next-gen polymyxin; gram -	Candidate optimizing to clinical lead
2015	Crestone	PolC inhibitor; gram + infections	Candidate optimizing to clinical lead
2015	Achaogen	LpxC inhibitor; gram -	Candidate optimizing to clinical lead
2016	VenatoRx	BS Oral β -lactamase inhibitor	IND-enabling through Phase I program

Bench to Bedside CARB Support

- NIAID is supporting clinical trials to:
- Optimize the use of licensed drugs for treatment of drug-resistant infections, including GC, UTI, Gram-negative infections, and community-acquired methicillin-resistant *S. aureus* (CA-MRSA) infections.
 - NIAID is also supporting studies evaluating new ways to treat *Neisseria gonorrhoeae*, *Clostridium difficile*, Gram-negative bacteria, and *S. aureus*.
- ARLG
- DMID sponsored Phase I and VTEUs
- STI Cooperative Research Centers and STI Clinical Trials Group

The Antibacterial Resistance Leadership Group

Mission: To prioritize, design, and execute clinical studies that will reduce the public health threat of antibacterial resistance.



ARLG:

25 projects and counting since June 2013



Gram-negative

Gram-positive

Diagnostics

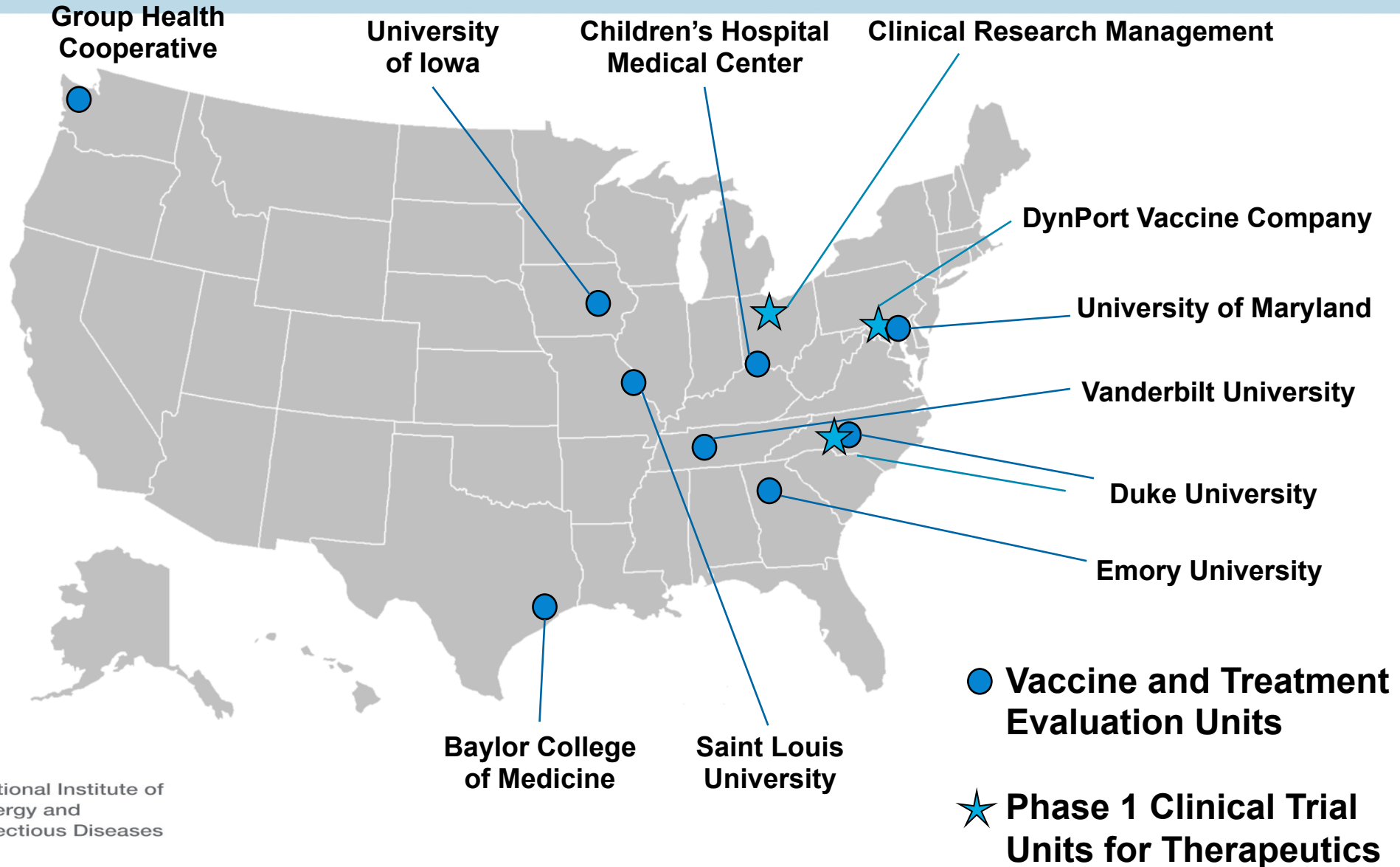
Stewardship

Antibacterial Resistance Leadership Group Diagnostics Activities

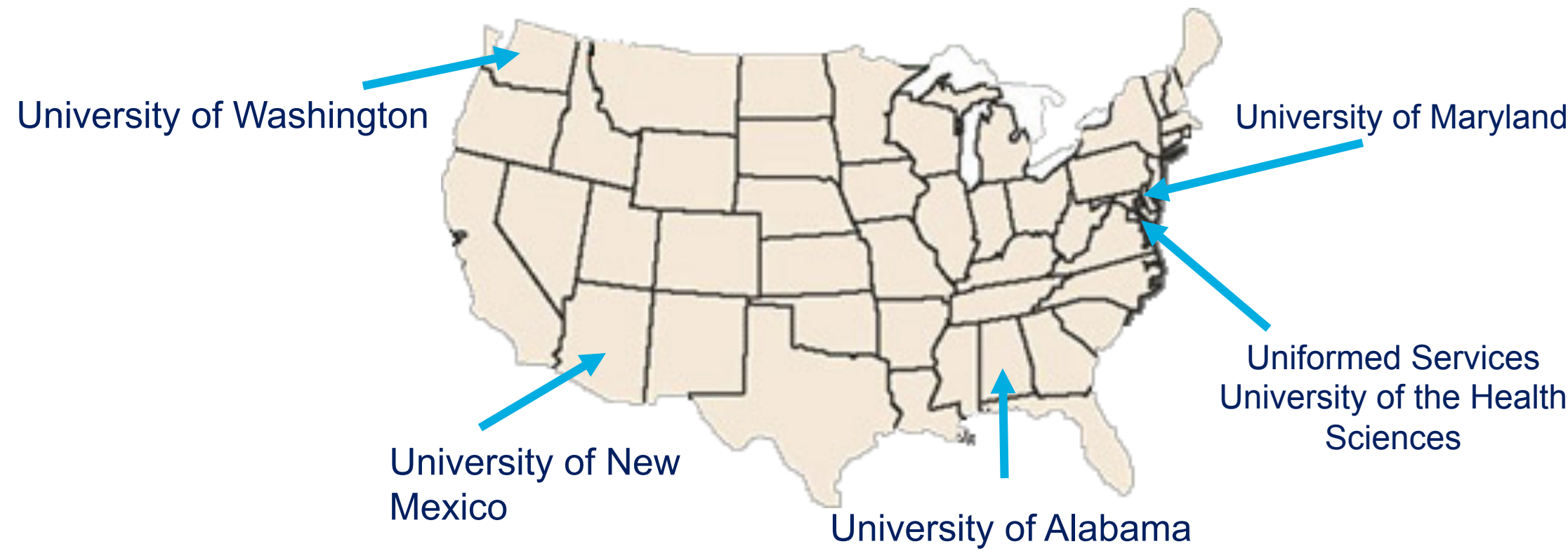
<http://www.arlg.org/>

- Host-based signature to distinguish viral from bacterial respiratory infections (Zaas, cont.)
- Virtual biorepository
- Capability to collect clinical specimens for diagnostics development
- Master protocol for validation of multiple diagnostics simultaneously
- Using procalcitonin levels to identify CAP patients who will not benefit from antibiotics

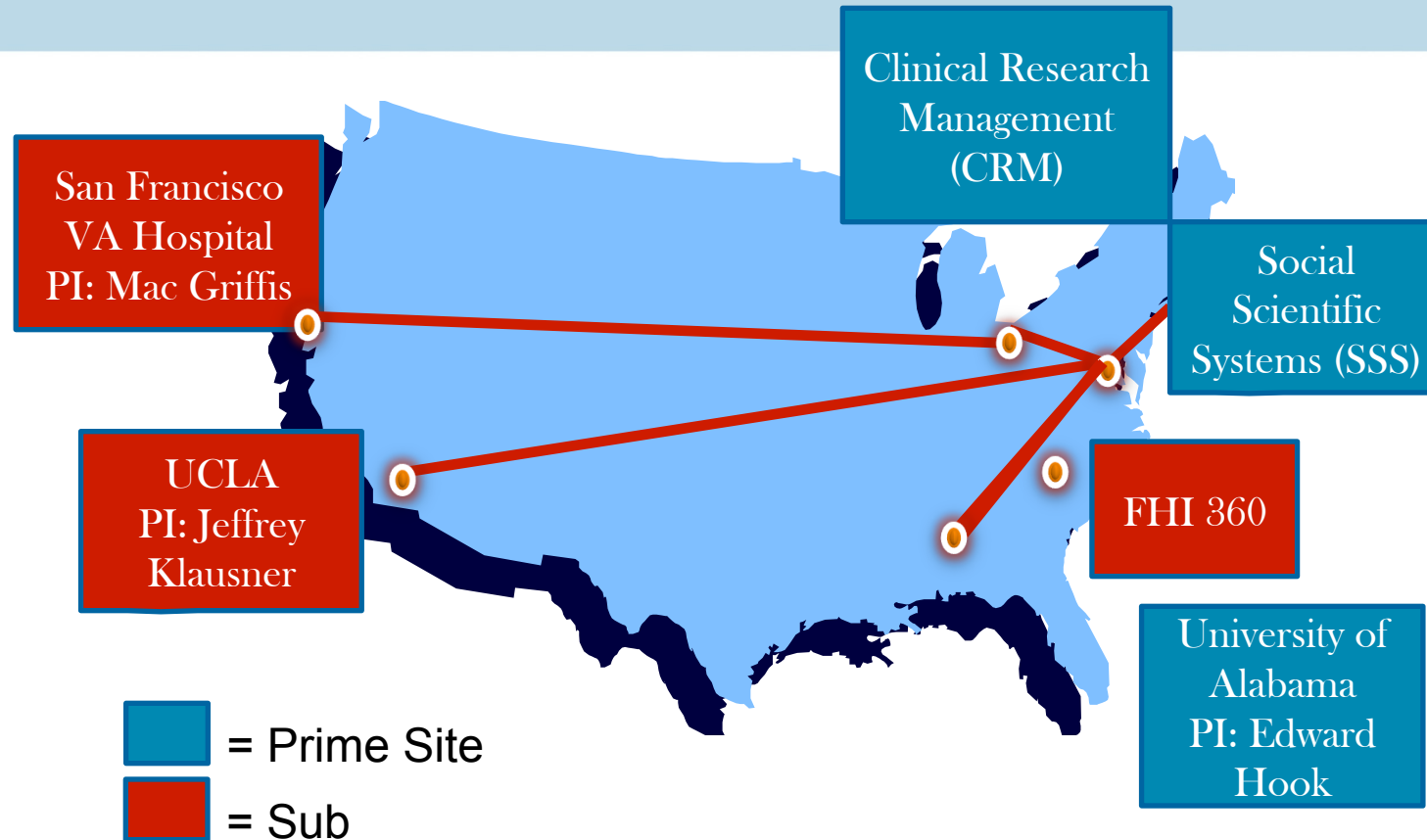
DMID-Supported Clinical Trial Units



Sexually Transmitted Infections Cooperative Research Centers



STI Clinical Trials Group <https://starstictg.s-3.net/>



NIAID is supporting several studies looking at new ways to treat gonorrhea, including:

- A Phase II trial examining safety and efficacy of an investigational oral antibiotic (AZD0914)

What's Coming in the Future?

- More workshops! (e.g. pK/pD modeling)
- Expansion of preclinical services to address unmet needs
- Development support for CARB-X
- BAA solicitations annually (at minimum) for Rx, Vx, Dx
- Check for FY2017 and FY2018 Funding Opportunities:
 - Program Announcements (grants)
 - FedBizOpps (contracts)
 - Concepts approved by NIAID council

Support for Antimicrobial Resistance Research

Concepts: Pot

DAIDS

DAIT

[September 2016](#)

[June 2016](#)

[January 2016](#)

[September 2015](#)

[May 2015](#)

[January 2015](#)

[September](#)

[June 2016](#)

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DISEASES & CONDITIONS

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CLINICAL TRIALS

NEWS & EVENTS

ABOUT NIAID

Grants & Contracts > Find a Funding Opportunity > NIAID Research Priorities > Concepts: Potential Opportunities

Find a Funding Opportunity

Opportunities & Announcements

Types of Funding Opportunities

NIAID Research Priorities

Concepts: Potential Opportunities

See Funded Projects

Timelines & Due Dates

September 2016 DMID Council-Approved Concepts

Concepts represent early planning stages for program announcements, requests for applications, or solicitations for Council's input. If NIAID publishes an initiative from one of these concepts, we link to it below. To find initiatives, go to [Find a Funding Opportunity](#).

NB: Council approval does not guarantee that a concept will become an initiative.

Table of Contents

Development of Medical Countermeasures for Biothreat Agents, Antimicrobial-Resistant Infections, and Emerging Infectious Diseases

Partnerships for the Development of Tools To Advance Therapeutic Discovery for Select Antimicrobial-Resistant Gram-Negative Bacteria

Partnerships for Development of Vaccines To Prevent *Mycobacterium tuberculosis* Infection and/or Tuberculosis Disease

Development of Multipurpose Prevention Technologies: A Strategy for the Prevention of STIs

Development of Medical Countermeasures for Biothreat Agents, Antimicrobial-Resistant Infections, and Emerging Infectious Diseases

Description:

This initiative is designed to advance high-priority, promising candidate therapeutics; vaccines and vaccine technologies; and diagnostics toward appropriate regulatory agency approval/licensure/clearance through a focused, milestone-based development approach for [NIAID Emerging Infectious Diseases/Pathogens-Category A, B, and C Priority Pathogens](#). It is anticipated that specific area(s) of focus will be announced annually.

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[s Diseases](#)

[ative Bacteria](#)

S

s, antimicrobial-

NIH

National Institute of Allergy and Infectious Diseases

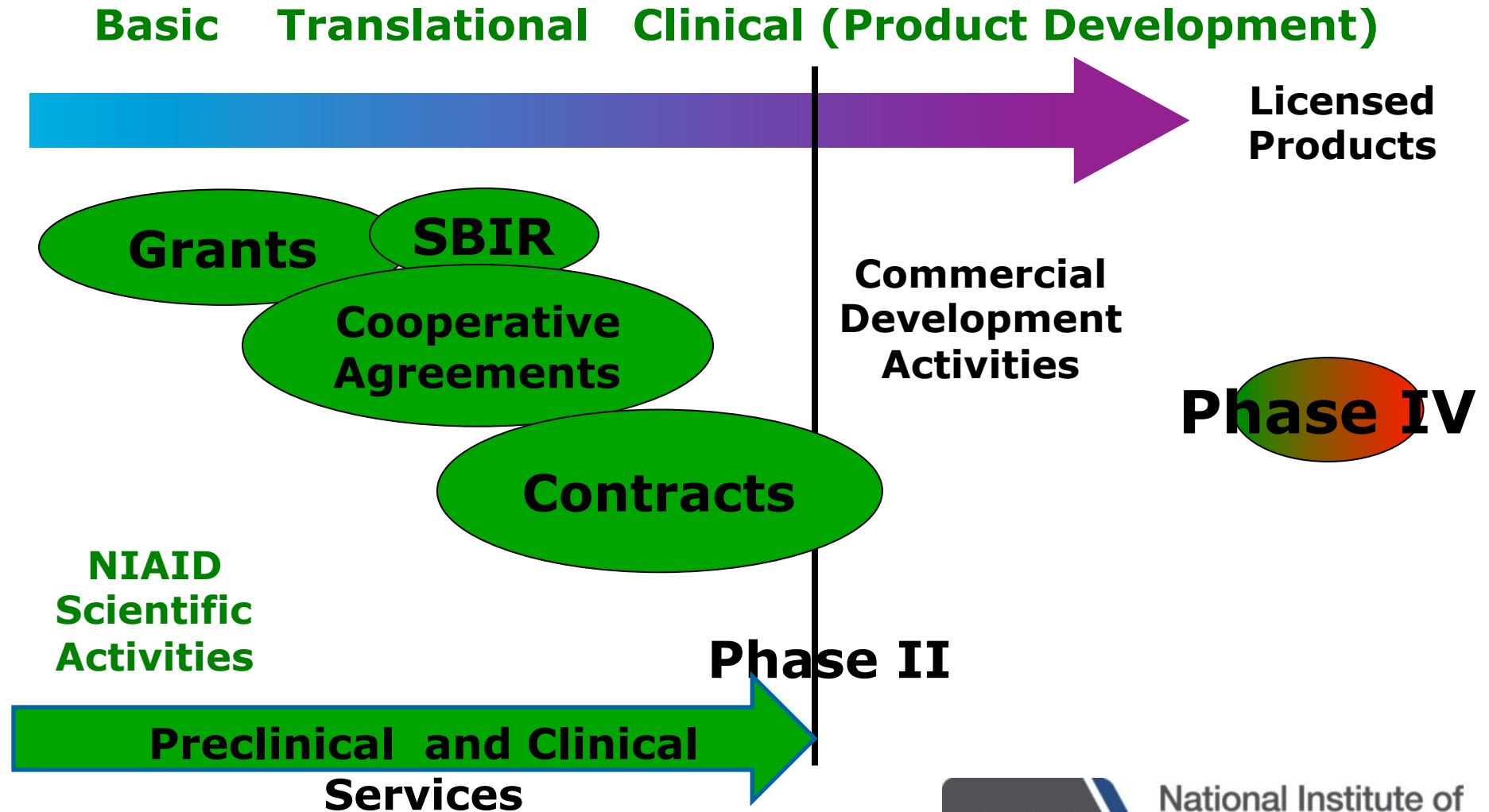
NIAID

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FY2017 Diagnostics Development Priorities

- Rapid, sensitive, specific, simple, and cost-effective diagnostics for primary healthcare settings (hospitals and point-of-care)
- Culture-independent diagnostics
 - Direct detection of pathogens in a clinical sample (blood, urine, CSF, pleural fluid, etc.)
- Multiplex platforms
 - Differential diagnosis (e.g. identify multiple/many pathogens)
 - Flexibility
- Diagnostics that facilitate antibacterial stewardship
 - Phenotypic and/or genetic information regarding pathogen antimicrobial sensitivity/resistance

Lowering Risk with Overlapping Mechanisms



DMID Resources for Researchers and Contacts

<http://www.niaid.nih.gov/LabsAndResources/resources/dmid/>

Resources for Researchers

Share this:      

Microbiology and Infectious Diseases Resources

The Division of Microbiology and Infectious Diseases (DMID) supports extramural research to control and prevent diseases caused by virtually all human infectious agents except HIV.

Funding Opportunities

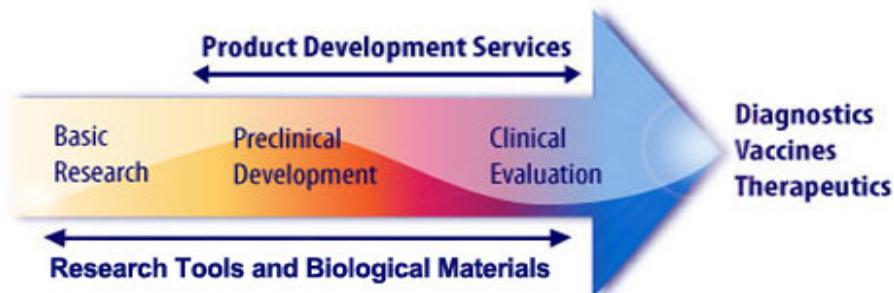
Apply for grants and contracts to conduct basic research, preclinical development, or clinical evaluation.

- [NIH-Wide Funding Opportunity Announcements](#)
- [NIAID Funding Opportunity Announcements and Requests for Proposals](#)


Product Development Services and Research Tools and Biological Materials

Request development by DMID-funded contractors of critical information needed to move a product through the product development pathway. Note: Services are contingent upon availability of required preliminary data.

Click on labels below to view information on services.



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