Translational Research for Emerging Infectious Diseases

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NIAID Infectious Disease Research: A Dual Mandate

Maintain and “grow” a robust basic and applied research portfolio in microbiology, infectious diseases, immunology, and clinical research

New/Improved Interventions

Respond rapidly to new infectious disease threats

Source: A S Fauci
NIAID Countermeasure Research and Development

- Therapeutics
- Novel Vector Control
- Vaccines
- Diagnostics
- Basic Research
- Expansion of Research Capacity
- Genomics
- Clinical Research

Source: A S Fauci
DMID supports extramural basic through applied research to control and prevent diseases caused by virtually all human infectious agents except HIV.

- Understand microbiologic influences on health and disease
  - Internal exposure (e.g., microbiome)
  - Antimicrobial resistance and mechanisms by which antimicrobial resistance occurs
  - Emergence of new diseases (e.g., from such viruses as Zika, MERS-CoV, and Ebola)
  - Long standing and re-emergent zoonotic diseases (e.g., influenza, rabies, dengue fever, chikungunya, tuberculosis and leprosy)
  - >300 infectious disease pathogens
Global Examples of Emerging and Re-Emerging Infectious Diseases

- Antimicrobial-resistant threats: CRE, MRSA, C. difficile, N. gonorrhoeae
- H1N1 influenza
- Cyclosporiasis
- E. coli O157:H7
- Measles
- Human monkeypox
- Listeriosis
- 2009 H1N1 influenza
- Adenovirus 14
- Anthrax bioterrorism
- Chikungunya
- Hantavirus pulmonary syndrome
- Dengue
- Zika virus
- Yellow fever
- Cholera
- Human African trypanosomiasis
- Marburg hemorrhagic fever
- MDR/XDR tuberculosis
- Plague
- Ebola virus disease
- HIV
- Hantavirus pulmonary syndrome
- Dengue
- Zika virus
- Yellow fever
- Cholera
- Human African trypanosomiasis
- Marburg hemorrhagic fever
- MDR/XDR tuberculosis
- Plague
- Ebola virus disease

Legend:
- Newly emerging
- Re-emerging/resurgine
- “Deliberately emerging”

January 2018
Centers of Excellence for Translational Research

- Established in 2014 to advance discovery, preclinical development, production, licensure and/or use of new or improved countermeasures for emerging and re-emerging infectious diseases.

- Multi-project, organized around a specific theme.

- Supported translational activities will range from very early discovery-based efforts to late-stage preclinical development.

- Builds on Regional Centers of Excellence for Biodefense and Emerging Infectious Diseases Research (RCE) program
Centers of Excellence in Translational Research

Activities
- Basic Research
- Candidate Discovery
- Preclinical Development
- Clinical Development
- FDA Approval

Product Development Stages
- Early Stage
- Mid Stage
- Late Stage

Grants

Contracts

Partnerships

CETR

Therapeutics Vaccines Diagnostics
CETR Ebola Response

Viral Hemorrhagic Fever Immunotherapeutic Consortium (VIC)

- Identification and development of novel monoclonal antibodies (mAbs) and combinations of mAbs to treat filoviruses and arenavirus
  - 44 labs, 5 continents, 15 countries
  - 230 antibodies vs EBOV, SUDV, MARV

compare the antibodies, compare the assays
VIC Antibody Epitope Distribution

**MBP-134** - Cocktail of 2 human mAbs
- Active in ferret and nonhuman primate models of EBOV, SUDV, and BDBV

**MBP-091** (MR191-N) - Single human mAB
- 100% survival of Marburg-Angola or Ravn virus-infected rhesus macaques and guinea pigs when given 5 days post-inoculation when clinical signs of disease were evident

**BARDA contract to advance to Phase 1**

CETR Diagnostic Development

- **CII- Arboviroplex rRT PCR-** detects viral RNA matching Zika virus, dengue virus types 1-4, chikungunya, and WNV

- **TBD-Serochip-** detects 8 *phagocytrophilum*, *Babesia microti*, *Borrelia burgdorferi*, *Borrelia miyamotoi*, *Ehrlichia chaffeensis*, *Rickettsia rickettsii*, Heartland virus and Powassan virus.

- **Vir-Cap-Seq-** broadly screen for all viral infections in vertebrates including humans in serum, blood, tissue.

- **Bac-Cap-Seq-** simultaneously screens for all 307 known human pathogenic bacteria as well as biomarkers for virulence and antibiotic resistance
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- Integrated discovery and development of innovative TB Diagnostics
6- Novel Nanoparticle Platform for the delivery of Vaccines and Adjuvants
7- Autophagy Modulators as Novel Broad-Spectrum Anti-Infective Agents
NIAID Partnerships Program for Translational Research

- Established in 2003 under NIAID BioD Initiative
- Support product-focused research and development activities
- 44 RFAs (BioD and Emerging Infectious Diseases)
- $440M
- 689 Awards (Multiple Mechanisms) assigned to Branch PCCs
- 10-20% Application Success Rate
- Numerous Accomplishments
## Recent Partnerships

<table>
<thead>
<tr>
<th>Fiscal Year</th>
<th>Projects</th>
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| **FY2014**  | Drug Target Development and Validation for AR Pathogens  
Category A-C Pathogens |
| **FY2015**  | Novel Therapeutics for Select Anaerobic Protozoa  
Novel Therapeutics for Select Pathogens  
Diagnostics to Address AR of Select Bacterial Pathogens |
| **FY2016**  | Innovative Diagnostics for Acute Febrile Illnesses  
Non-Traditional Therapeutics that Limit AR  
Host-Targeted Therapeutics to Limit AR  
Novel Assays to Predict Vaccine Efficacy |
| **FY2017**  | Select Emerging Pathogens  
Structure-Based Vaccine Design  
Novel Therapeutics for Eukaryotic Pathogens |
| **FY2018**  | Tools for Therapeutic Discovery for Select AR Bacterial Pathogens  
Vaccines/Immunotherapeutics for MDR Bacterial Pathogens  
Clinical Diagnostics for AR Bacterial Pathogens  
Vaccines for Mtb and TB |
| **FY2019**  | Select Emerging Pathogens  
Target-based Pharmaceutical Libraries for Discovery of Therapeutics against Eukaryotic Pathogens |

### Grant Mechanism
- **R21/R33**
- **R01** (Candidate Product and Substantial Industrial Investment Required)
Partnerships Program supported the development of the Equivac® HeV-sG subunit vaccine licensed for horses

- Hendra virus (HeV) appeared first in Australia in 1994
- Transmitted to humans from infected horses
- Severe and often fatal respiratory disease and encephalitis in horses and humans
- BSL-4 select agent

- No approved vaccines for humans
- HeV-sG subunit vaccine can limit the transmission of HeV from horses to humans
Partnerships (cont.)

- BioFire® FilmArray® -nested multiplex polymerase chain reaction and amplicon melt curve analysis- GI, ME, BCID, RP EZ, Pneumonia panel
- ID93-GLA-SE TLR4 agonist adjuvant- TB vaccine candidate- Ph1 complete
- Advax™ adjuvant derived from delta inulin
- Brincidofovir- nucleotide analog with antiviral activity.
  - FDA Fast Track CMV and small pox, Orphan Medicinal Product Designation for adenovirus and small pox treatment and for CMV prevention
- Novel phage based T4 nanoparticle-based dual viral vaccine that protects animals from both anthrax and plague.
NIAID- DMID

Influenza Surveillance

- Focused active surveillance
  - Human & animal
  - Domestic & international animal reservoirs
- Interspecies transmission
- Evolutionary dynamics
- Antiviral research
- Viruses for vaccine development
- Avian & swine viruses
- Detection of emerging pathogens

Pathogenesis and Host Responses

- Adaptation, antigenicity, reassortment, pathogenicity & inter/intra-species transmission
- Host factors & disease outcomes
- Human immune responses to vaccines & infection

>30,000 samples characterized
Middle Eastern Respiratory Syndrome Coronavirus

- Virus spreads from bats to camels, then to people
- Developed mouse and camel models of MERS to demonstrate transmission from animals to humans
- Development of methods to stop the introduction of these viruses in the human population

2266 laboratory confirmed cases, 804 deaths, 27 countries

Source: Munster et al., *Scientific Reports* (2016)

Source: Adney, *EID* (2014)
MERS-C0V

- Immunotherapeutics
  - Trans-chromosomic (Tc) bovines
    - genetically modified to produce large quantities of fully human polyclonal IgG
    - DCR Phase 1
  - Spike-protein blocking antibodies-
    - REGN3048 and REGN3051,
    - NIH-sponsored Phase 1 clinical and BARDA support
In the United States, Antimicrobial Resistance Results in Lost Lives and Dollars

- 2 million drug-resistant infections, 23,000 deaths/yr
- Annual costs:
  - $20 billion in excess healthcare expenditure
  - $35 billion in lost productivity
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 Unharmed**: 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**
• **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
Other DMID Zoonotic Disease Activities

- **Mycobacterial diseases-** *M. tb*, Leprosy, *M. bovis* (zoonotic tuberculosis)
  - Many Hosts of Mycobacteria Meetings- 2008, next meeting scheduled at AECOM in March 2019.

- **Enteric diseases**
  - *Campylobacter*, *Salmonella*, *E.coli*, *C.difficile*

- **Bacterial zoonotic diseases**
  - Leptospirosis
  - Melioidosis
  - Anthrax
DMID Research Resources and Preclinical Services

Product Development Pathway

- Basic Research
  - Hypothesis Dev & Testing
- Preclinical Development
  - Discovery
  - IDE - IND - Enabling Activities
- Clinical Evaluation
  - Trials

Research Tools & Technologies

- Biological Resource Repository (Strains, Reagents)
- Animal Models Testing (Efficacy, Safety)
- In Vitro Antimicrobial Activity

Therapeutics Manufacturing and Testing

Vaccines Manufacturing and Testing

Diagnostics

Vaccines

Therapeutics
Product Development Services

In Vitro Assessment of Antimicrobial Activity

Interventional Agent

Biopharmaceutical Products

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

Testing

Manufacturing

Animal Models
Preclinical Services Goals

- Lower the risk for product developers
- Advance promising discoveries along product development pathway
- Gap-filling services, not intended to take a product to licensure
- Provide expertise/capability in product development
- Provide data to support/address:
  - Research/knowledge gaps
  - New/continued funding
  - Go/no-go decisions
  - Investigational New Drug (IND) Applications
  - Lifting of FDA clinical hold
- Sponsor maintains IP
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
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*
DMID-Supported Clinical Trial Units

- Group Health Cooperative
- University of Iowa
- Children’s Hospital Medical Center
- Clinical Research Management
- DynPort Vaccine Company
- University of Maryland
- Vanderbilt University
- Duke University
- Emory University
- Baylor College of Medicine
- Saint Louis University

Vaccine and Treatment Evaluation Units

Phase 1 Clinical Trial Units for Therapeutics
Resources for Funding Opportunities

- For updates on **Funding Opportunities**, subscribe to **NIAID Funding News** at [https://www.niaid.nih.gov/grants-contracts/funding-news-2018](https://www.niaid.nih.gov/grants-contracts/funding-news-2018)

- For Resources for Researchers: [http://www.niaid.nih.gov/LabsAndResources/resources/dmid/](http://www.niaid.nih.gov/LabsAndResources/resources/dmid/)

- **NIAID Council-cleared concepts** – information on upcoming potential opportunities: [https://www.niaid.nih.gov/grants-contracts/potential-opportunities](https://www.niaid.nih.gov/grants-contracts/potential-opportunities)
Thank you!