Two-pronged approach to catalyze the development of a robust pipeline of antivirals

**Discovery**

Build a sustainable platform to discover new antivirals by:

- Establishing multi-investigator, and multi-disciplinary discovery groups (AViDD Centers)
- Using structural and systems methods to identify potential drug targets shared across key viral pathogens
- Progressing promising candidates to IND\(^1\)-enabling work

**Development**

Accelerate clinical testing of promising antiviral candidates by:

- Supporting key non-clinical and early clinical studies
- Establishing public-private partnerships to supplement private sector capabilities (including facilitating third-party collaborations)
- De-risking candidates for further late-stage development

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1. IND – Investigational New Drug
7 viral families in-scope for the APP

**Coronaviridae** – MERS, SARS-CoV-2

**Bunyavirales** – Lassa, Junin, Rift Valley Fever Virus, Andes, Sin Nombre, LaCrosse, California Encephalitis, Crimean Congo Hemorrhagic Fever

**Filoviridae** – Ebola, Marburg

**Flaviviridae** – Dengue, Zika, West Nile

**Paramyxoviridae** – Nipah, Hendra

**Picornaviridae** – EV-D68, EV-A71

**Togaviridae** – Chikungunya, EEE, VEE, WEE
Multiple mechanisms of targeted support coordinated across the drug Discovery-Development pipeline

**Basic research and discovery**
- Target ID & Validation
- Hit ID
- Lead Screening & Optimization

**Non-Clinical development**
- Lead Candidate and IND-Enabling

**Early Clinical development**
- Early Clinical Evaluation (Phase 1/2a)

**Late Clinical development**
- Late Clinical Evaluation (Phase 2b/3)

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**NIAID**
- AViDD Centers (U19 Cooperative Agreements)
- Preclinical Services (PCS) Contracts
- Early Clinical Phase Contracts
- Product Development/Public-Private Partnership Contracts

**NCATS**
- Screening & Drug Development Collaborations

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**BARDA**
- Contracting for Early Clinical CMC
- Contracting for Advanced Clinical Dev.

1. CMC – Chemistry and Manufacturing Controls
Progress on Discovery Pillar

- Published Antiviral Drug Discovery Centers (AViDD) on July 9, 2021
  - Applications received October 22, 2021
  - 38 applications passed initial review for being within scope and completeness

- Created a portal to capture and track requests for preclinical support
  - 3,691 queries reviewed to date
  - 22 submissions of bona fide leads from labs and companies identified

- Established a database of sequence variants for the 3CL Pro. Mapped these variants into the 3D structure of the protein. Looking at binding patterns of drug leads into the structure.
  - Good news, both Pfizer or Shionogi compounds are potent against currently circulating variants (Omicron not known as of 12/02/2021)

- Expanded the preclinical services to make them scalable for significant increase in demand for support

- Worked with all APP partners to harmonize activities
Objective: To establish multidisciplinary Centers focused on discovery and development of antivirals against coronaviruses (CoVs) and one or more select RNA viruses with pandemic potential
Role of Industry

- Active industry participation is *required* for projects and activities involved in optimization of novel antiviral candidates to ensure input of medicinal chemistry and pharmacology expertise.
  - For the purpose of this FOA, "industry" is defined as a large or small, domestic or foreign, pharmaceutical, biotechnology, bioengineering, or chemical company, or a related non-profit entity.

- Early target identification and validation efforts in the Centers may be accomplished without industrial participation.
Progress on the Development Pillar

- Advancing candidates into clinical trials
- Assisted Pfizer in nonclinical evaluations, designed the protocol that Pfizer successfully implemented for Paxlovid
- ACTIV-2 will not be evaluating AT527, the polymerase inhibitor from ATEA/Roche
  - Drug failed in phase 1 and Roche pulled out of the collaboration
  - BARDA cancelled the contract with company
  - APP Discovery Team is working with ATEA to evaluate their alternative leads
- New data submitted for the 11/30 FDA meeting on molnupiravir is quite concerning, FDA committee voted 13-10 for approval (11/30/2021)
- Shionogi trial to be performed in ACTIV-2B with the 3CL protease inhibitor S-216622, submitted to FDA and enrollment will begin in January 2022. Trial currently on FDA clinical hold
- Ongoing conversations with other companies
  - Enanta—3CL PI
  - Pardes—3CL PI
  - Cocrystal Pharma—3CL PI, Polymerase inhibitor
  - Norvartis—3CL PI
Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV)

**ACTIV1 (NCATS)**
Inpatient, Ph. 3 Master Protocol
Immunomodulators: infliximab, abatacept, cenicriviroc

**ACTIV2 (NIAID)**
Adapt Out COVID (A5401), Ph. 2/3 Outpatient RCT;
mAbs: (Lilly, Brii Bio, AZ, RU/BMS), pABs (SAB), interferon-beta, DARPin, S-217622 and more to come

**ACTIV3 (NIAID, NHLBI)**
Tx for Inpatients w/COVID-19
Ph. II/III Inpatient RCT;
mAbs: (Lilly, Brii Bio, GSK-Vir, AZ), DARPin, Pfizer PI, aviptadil

**ACTIV4 (NHLBI)**
Antithrombotics, antiplatelets: Inpatient: UF/LMW heparin, P2Y12 inhibitors
Outpatient: apixaban, aspirin
Host Tissue: Inpatient: TXA127, TRV027

**ACTIV5 (NIAID)**
Big Effect Trial (BET)
Inpatient; proof-of-concept study in hospitalized adults: Risankizumab, lenzilumab, danicopan

**ACTIV6 (NCATS)**
Outpatient; Phase III master protocol, re-purposed agents:
Ivermectin, fluvoxamine, fluticasone
Pandemic Preparedness - Vaccines
Vaccine Development for Pandemic Preparedness

- Priority-Pathogen Approach
- Platform Approach
- Prototype-Pathogen Approach
Vaccine Development for Pandemic Preparedness

- Priority-Pathogen Approach
- Platform Approach
- Prototype-Pathogen Approach
Priority Pathogen Approach Will Focus On the Same Seven RNA Virus Families With Pandemic Potential

<table>
<thead>
<tr>
<th>Family</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronaviridae</td>
<td>e.g. SARS-Cov-2, MERS</td>
</tr>
<tr>
<td>Bunyaviridae</td>
<td>e.g., Hemorrhagic fevers,</td>
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<tr>
<td></td>
<td>Hantavirus, Lassa fever</td>
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Vaccine Development for Pandemic Preparedness

- Priority-Pathogen Approach
- Platform Approach
- Prototype-Pathogen Approach
Vaccine Platform Technologies

- **Genetic immunization** (DNA and RNA vaccines)
  - SARS, MERS, West Nile, Zika, RSV

- **Viral vector** (e.g., VSV, adenovirus)
  - Ebola, Marburg, Zika

- **Recombinant protein**
  - Influenza, RSV

- **Nanoparticles** (viral protein on particle)
  - Influenza, Malaria, RSV

- **Virus-like particle (VLP)** (no RNA or DNA; non-infectious)
  - Chikungunya, Zika, WEVEE

- **Adjuvants** (e.g., AS01, MF59)

**Selected Examples**
Vaccine Development for Pandemic Preparedness

- Priority-Pathogen Approach
- Platform Approach
- Prototype-Pathogen Approach
Genus Flavivirus

Japanese encephalitis
West Nile virus
Zika virus
Dengue virus
Yellow fever virus
Tick-borne encephalitis virus
Applying Strategies and Tools from One Virus to Inform Vaccine Design for Related Viruses

- Basic virology (e.g., neutralization mechanisms)
- Assays for preclinical and clinical settings
- Animal models
- Antigenic targets
- Optimal platforms
- Potential immune correlates
- Manufacturing strategies
To Vaccine Development

Build on Prior Experiences
Monoclonal Antibodies

- An output from the vaccine development for pandemic preparedness will be monoclonal antibodies
- Monoclonals serve as a bridge between antivirals and vaccine efforts
- As an incredibly useful, virus-specific biologic, these can:
  - Serve as reagents to assess vaccine responses
  - Be developed and deployed as first wave of treatment and prevention
- Can be selected for breadth and matured for potency
Questions