COVID-19 Update

Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) Therapeutics

Meeting of the NIH Advisory Committee to the Director

December 10, 2020
Order of Presentations

Preclinical ACTIVE, ACTIV-1, and Inpatient Convalescent Plasma RCTs
Christopher P. Austin, M.D. (NCATS)

ACTT, ACTIV-2, -3, -5, AND IVIg
H. Clifford Lane, M.D. (NIAID)

ACTIV-4, Outpatient Convalescent Plasma RCTs,
Community Engagement Alliance (CEAL) Against COVID-19 Disparities
Gary H. Gibbons, M.D. (NHLBI)
LAUNCH

On April 17, NIH announced the launch of a public-private partnership, Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV)

MISSION

Develop a coordinated research response to speed COVID-19 treatment and vaccine options
ACTIV Stakeholders

ACTIV is being coordinated by the Foundation for the National Institutes of Health (FNIH), and has brought together multiple partners from government, industry and non-profits.
The ACTIV partnership consists of four fast-track focus areas (Working Groups) with membership of both public and private sector representatives to oversee tactical operations:

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<td>+</td>
<td>Accelerate the evaluation of vaccine candidates to enable rapid authorization or approval</td>
<td>+ Develop a collaborative, streamlined forum to identify preclinical treatments</td>
<td>+ Improve clinical trial capacity and effectiveness</td>
<td>+ Accelerate clinical testing of the most promising COVID treatments</td>
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<th>Sub-Groups</th>
<th>Vaccines Clinical Trials</th>
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Preclinical Working Group

OBJECTIVE
Standardize and share preclinical evaluation methods and sharing testing resources in an open forum that allows for effective validation and comparison of therapeutic candidates.

ACCOMPLISHMENTS TO DATE

✔ Developed a master inventory of preclinical testing resources
✔ Established SOPs for accelerated preclinical agent development in response to a pandemic
✔ Developed a National Strategy for NHP Research and a process to coordinate NHP studies centrally through NIH, and “field guides” for the use of small animal testing models
✔ Created and published online 9 “field guide” videos for use of small animal models in COVID-19 preclinical development
✔ Established a process for prioritizing in vitro assays and evaluating preclinical compounds
✔ Created a public database for sharing preclinical data (NCATS Open Science Portal)

❑ Conducting a “matchmaking” process to pair promising compounds with available preclinical resources and funding, on an ongoing basis

❑ Assess the impact of emerging viral mutations on efficacy of vaccines and therapeutics

✔ Completed
❑ In progress
### Small Animals

<table>
<thead>
<tr>
<th>Species</th>
<th>Modification</th>
<th>Model Name/Nomenclature</th>
</tr>
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<tbody>
<tr>
<td>Ferret</td>
<td>Outbred Stock</td>
<td>Ferret</td>
</tr>
<tr>
<td>Guinea Pig</td>
<td>Wild Type</td>
<td>Guinea Pig</td>
</tr>
<tr>
<td>Hamster</td>
<td>Inbred Strain</td>
<td>Syrian Golden</td>
</tr>
<tr>
<td>Hamster</td>
<td>Transgenic</td>
<td>Tg(K18-hACE2)</td>
</tr>
<tr>
<td>Mouse</td>
<td>ACE2 Transduced</td>
<td>Adenovirus transduced hACE2</td>
</tr>
<tr>
<td>Mouse</td>
<td>Inbred Strain</td>
<td>BALB/c (adapted virus)</td>
</tr>
<tr>
<td>Mouse</td>
<td>Knock-In</td>
<td>C57Bl/6- Ace2mrtl(Ace2Yova)</td>
</tr>
<tr>
<td>Mouse</td>
<td>Transgenic</td>
<td>B6.Cg-Tg(K18-ACE2)2Pim1/J</td>
</tr>
</tbody>
</table>

### Non-Human Primates

<table>
<thead>
<tr>
<th>Species</th>
<th>Geographic Origin</th>
<th>Route of Exposure</th>
<th>Vaccines</th>
<th>Antibodies</th>
<th>Neutralizing Antibodies</th>
<th>Other Therapies</th>
<th>Imaging</th>
<th>Therapy</th>
<th>Disease Manifestation &amp; Pathology</th>
<th>Extent of disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>African Green</td>
<td>St. Kitts (wild-caught)</td>
<td>Intratracheal/intranasal, aerosol</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td>Y</td>
<td>TBD</td>
<td>Mild to moderate</td>
</tr>
<tr>
<td>Aged African Green</td>
<td>St. Kitts (wild-caught)</td>
<td>Intratracheal/intranasal, intratracheal, aerosol</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td>Y</td>
<td>TBD</td>
<td>Severe</td>
</tr>
<tr>
<td>Cynomolgus macaque</td>
<td>Cambodia</td>
<td>Intratracheal/intranasal, intratracheal</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td>Y</td>
<td>TBD</td>
<td>Mild</td>
</tr>
<tr>
<td>Rhesus macaque</td>
<td>China or India</td>
<td>Intratracheal/intranasal, intratracheal, ocular, oral, aerosol</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td>Y</td>
<td>TBD</td>
<td>Mild</td>
</tr>
</tbody>
</table>

[https://opendata.ncats.nih.gov/covid19](https://opendata.ncats.nih.gov/covid19)
Clinical Trial Capacity Working Group

The Working Group developed an inventory of clinical trial capacity, including networks of NIH ICs, industry, and other organizations, that will serve as a guide for how and where to implement effective COVID-19 clinical trials.

- ✔ 3 unique clinical trial capacity surveys developed for Networks, Sites, and Clinical Research Organizations (CROs) and Site Management Organizations (SMOs)
- ✔ 63 Networks completed the survey*
- ✔ 725 total Sites completed the survey*
- ✔ 39 CROs/SMOs completed the survey*
- ✔ Identified 52 novel and scalable enhancements / efficiencies for therapeutic clinical protocols and vaccine protocols
- ✔ A Tableau-based dashboard was created to query and visualize survey data
- ✔ Clinical Trial network, site, and CRO/SMO survey data is combined in one comprehensive view
- ✔ Dashboard includes overlay of COVID-19 infection data with collected survey data to inform decisions around optimizing site selection for therapeutic and vaccine trials

*Additional organizations will be surveyed as identified
TransNIH 2: Bringing Clinical Trial Networks Together

Clinical Trial Network Inventory

- Central repository of NIH clinical trial network information for improved response planning to current and future pandemics and health threats

Highlights

- Coordination with OER and NIAID
- Jump-started ACTIV Clinical Trial Capacity Working Group and rapid identification of sites and special populations

COVID-19 Clinical Trials “Data Lake”

- Curated database combining information from several large clinical trial registries to provide a unified view of the global clinical trials landscape for COVID-19

Highlights

- Successful transfer of system from Operation Warp Speed to NCATS

TransNIH 8: Preclinical Therapeutic Discovery

COVID-19 NIH Intramural Program Inventory Dashboard

Version 1.0 – Built in April with the COVID SIG, included forms to collect information that populates a visualization dashboard – primarily, project dashboard & reagent registry

Version 2.0 – Rolled out in Nov

- Enable updating of IRP entries and establish cadence of updating projects
- Improve search and data extraction functionality
- Improve dashboard layout and user instructions to make more user friendly

Review & Prioritization Activities

The WG members have gone through 2 rounds of project reviews to date, reviewing all 370 projects in the 1.0 dashboard. The first review cycle occurred in May; the second occurred in July. To date, 32 projects have been prioritized.
Therapeutics – Clinical Working Group

OBJECTIVE
Prioritize promising therapeutic candidates and accelerate their clinical evaluation by establishing large-scale master protocol trials.

ACCOMPLISHMENTS TO DATE

✔ Developed and continuously enhanced a world-class process for prioritizing clinical agents for rapid testing

✔ Evaluated ~500 available agents with potential relevance for COVID-19 therapies and prioritized the most promising agents for further study (agent prioritization continues on a rolling basis)

✔ Assessed, designed, and harmonized seven master protocols for ACTIV clinical trials, focusing on candidates selected through the agent prioritization process

✔ Selected clinical trial networks best suited to execute these master protocols and supported NIH efforts to launch them; six protocols have been launched to date

❑ Actively working with NIH and OWS across all protocols to ensure they are effectively coordinated, efficiently managed, and meet recruitment targets

✔ Completed

❑ In progress
**Current Portfolio of ACTIV Master Protocols**

ACTIV Therapeutics has been taking a portfolio approach to address the dramatic health and economic challenges posed by the pandemic, with harmonized “master protocol” trials.

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Desired Outcomes</th>
<th>Status</th>
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| **ACTIV-1** | • Phase III trial of 3 host-targeted immune modulators  
• Inpatient (hospitalized) patient population  
• NCATS Trial Innovation Network + CRO | • **Trial launched October 16**  
• First 3 agents selected – Abatacept, Infliximab, and Cenicriviroc |
| **ACTIV-2** | • Phase II/III trial of up to 5-7 Neutralizing Antibodies and Oral Antivirals  
• Outpatient population  
• NIAID ACTG network + CRO | • **Trial launched August 3**  
• Initial agent: nAb from Lilly; onboarding other agents |
| **ACTIV-3** | • Phase III trial of 5-7 Neutralizing Antibodies and Oral Antivirals  
• Inpatient population  
• NIAID INSIGHT + NHLBI PETAL + NHLBI CSTN + VA networks + CRO | • **Trial launched August 4**  
• Initial agent: nAb from Lilly (halted for futility Oct. 26); onboarding other agents  
• Preliminary results submitted to NEJM on Nov 9 |
| **ACTIV-4** | • Phase III trial of anticoagulants (heparin, aspirin) and antiplatelet drug  
• Three different populations: pre-hospitalized, hospitalized, & post-hospitalized  
• NHLBI-NINDS CONNECTS network | • **Hospitalized and Pre-Hospitalized cohorts launched on Sept 17**  
• **Post-hospitalized cohort launching early December**  
• First agents – LMWH and UFH (hospitalized) and low dose aspirin, high dose aspirin, and apixaban (pre-hospitalized) |
| **ACTIV-5 (Big Effect Trial)** | • Phase II “proof of concept” study to identify multiple promising treatments  
• Inpatient population  
• NIAID networks + CRO | • **Trial launched October 12**  
• Two initial agents selected – Risankizumab + Lenzilumab  
• Prioritizing additional agents |
**ACTIV-1: Immunomodulators**

NCATS CTSA Trial Innovation Network/Hubs + CRO
Launched October 16, 2020

**Design:** Randomized, placebo-controlled adaptive master protocol trial

**Patient population:** Moderately or severely ill hospitalized patients with COVID-19 cytokine storm

**Recruitment goal:** 2200

**Sites:** 15 active, expanding to 50

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**INITIAL STUDY AGENTS**

- Infliximab (Remicade): anti-TNFα mAb
- Abatacept (Orencia): CTLA-4-Ig fusion protein
- Cenicriviroc (CVC): SM CCR2/CCR5 antagonist

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**OUTCOME MEASURES**

- 1°: Time to Recovery by Day 29
- 2°: Clinical Status on day 15 & Day 29 defined by 8-point ordinal scale
- 2°: Mortality
NCATS Convalescent Plasma RCTs
*Multisite trials run through CTSA network*

- Two independent but coordinated trials, begun in April and expanded in August
- Patient population: *inpatients* early in disease course
- Intervention: 1 unit *high-titer convalescent plasma* vs crystalloid placebo
- Outcomes: *improvement on ordinal scale*, hospitalization duration, mortality
- Enrollment targets: 1000 participants in each trial (total enrollment = **2000**)
- **CONTAIN COVID-19** (NCT04364737)
  - Current sites = 8, expanding to 14 as needed
    - *NYU, Einstein*, Milwaukee, Iowa, Michigan, Univ Illinois Chicago, Johns Hopkins, Oregon
  - Current total enrollment (as of December 4): **546**
- **PassItOnII** (NCT04362176)
  - Current sites = 14, expanding to 30 as needed
    - *Vanderbilt*, Univ Colorado Denver, Univ Utah, Univ Mississippi, Our Lady of the Lake (Baton Rouge, LA), Univ Washington, Newton-Wellesley Hospital, Univ Minnesota, Univ Kansas, State Univ New York Buffalo, Virginia Commonwealth Univ, Scripps Research Institute, Univ Maryland, Ohio State Univ
  - Current total enrollment (as of December 4): **297**

*Supported with NCATS CURES and Operation Warp Speed funds*