Coronavirus Immunotherapeutics Consortium

COVIC-19 Therapeutics Accelerator:
The Bill & Melinda Gates Foundation, Mastercard,
The Wellcome Trust and others

NIAID U19 AI142790-02S1
and the GHR Foundation
We are praying for vaccines.

But, there will be those who are not vaccinated,
not vaccinated yet,
who can’t be vaccinated,
or in whom vaccines didn’t take or didn’t last
One goal of a vaccine is production of antibody.

You can deliver antibody right away, as a drug “Antibody therapy or Immunotherapy”
Use cases of antibody therapy

**Treatment**
- Mild to moderate COVID-19
- Treatment for individuals who are at high risk for severe disease

**Prophylaxis**
- Health Care Workers and First Responders
- High risk Groups
- Disease Outbreaks

Immediate protection for:
- Health care workers and first responders
- High risk groups (e.g., pregnant women)
- Ring vaccination-type response to disease outbreaks
Millions of possible antibodies, which 1 or 2 are best? What makes them the best? How do we know? (Which assays/features) Cocktail: what’s the best pairing? Different labs’ assays, different results?
Goals of CoVIC

**Primary - Translational**

- Evaluate promising therapeutic candidates against SARS-CoV-2 in independent, standardized platforms
- Identify cocktail of human neutralizing monoclonal antibodies against Spike to prevent severe COVID-19 in low and middle income countries

**Secondary - Basic**

- How do anti-SARS-CoV-2 antibodies work? Landscape of activities: CoVIC-DB database
- Which features at which epitopes? which features correlate with protection?
- Evaluate current assays for future use (i.e. do in vitro assays and animal models adequately correlate with success in humans? If not, why not?)
Why do a broad study?
ATTENTION! EBOLA!
2013:

**KZ52 monotherapy**

CHO cell production

50 mg/kg days -1, 4

0% survival

(Oswald et al)

**MB-003 cocktail**

CHO or Nicotiana

50 mg/kg (CHO) or

16.7 mg/kg (Nicotiana) days 0,4,7

50% (CHO) or 100% (Nicotiana) survival

(Pettitt, Olinger et al)

**Neutralizes, Didn’t protect**

**Protected, Don’t neutralize**

Need a combination? Something about Fc?
Neutralization not enough?
Not measuring neutralization properly?
Found the exceptions so far, and not the rule?
Ebola virus: “VIC”

43 labs, 5 continents
academic-industry-government
168 mAbs - 32 features measured side-by-side
Three different neut. assays & un-neut. %

Incubate virus with mAb
Infect Vero cells

Detect
sGP

Group

Authentic EBOV
Ebola-ΔVP-Luc
rVSV-EBOV GP

KZ52
2′ Alexa-Fluor

LUC

EGFP

BSL-4
BSL-2/3
BSL-2+

Dye
Kawaoka
U Wisc.

USAMRIID
Chandran
Einstein

(Micrographs: EBOV: Golding et al. Sci Rep. PMID: 27212232; DVP30: Halfmann et al. PNAS, PMID: 18212124; VSV: Ivanov et al. Virus Res. PMID: 21963863; images are scaled relative to rVSV)

Saphire et al. Cell 2018 PMID: 30096313
Relationship between Ebola virus neutralization and protection

(1) Bin by epitope
  Cap
  GP1/Head
  Mucin
  Base
  Fusion
  GP1/Core
  GP1/2
  HR2
  Unknown
Saphire et al. Cell 2018 PMID: 30096313
Binned by epitope, compared by assay

Cap       GP1/Head       Mucin

Base       Fusion       GP1/Core

GP1/2       HR2       Unknown

Saphire et al., Cell 2018 PMID: 30096313

John Dye, USAMRIID
Yoshihiro Kawaoka, Wisc.
Kartik Chandran, Einstein
Relationship between Ebola virus neutralization and protection

- **None/Weak**
- **Moderate**
- **Strong**

### Table

<table>
<thead>
<tr>
<th>rVSV % unneut</th>
<th>ΔVP30</th>
<th>EBOV Protect</th>
<th>Frac. unneut (% GFP+ cells)</th>
<th></th>
</tr>
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<tbody>
<tr>
<td>&gt;50</td>
<td></td>
<td></td>
<td>&gt;50</td>
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</tr>
<tr>
<td>5-50</td>
<td></td>
<td></td>
<td>5-50</td>
<td></td>
</tr>
<tr>
<td>≤5</td>
<td></td>
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<td>≤5</td>
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</table>

### Diagram

- **Cap**
- **Base**
- **Fusion**

### Authors
- John Dye
- Yoshihiro Kawaoka
- Kartik Chandran

**References**

Saphire et al. Cell 2018 PMID: 30096313
Relationship between neutralization and protection

Saphire et al. Cell 2018 PMID: 30096313

John Dye, USAMRIID
Yoshihiro Kawaoka, Wisc.
Kartik Chandran, Einstein
Fc function contributes to \textit{in vivo} protection

Saphire et al. \textit{Nature Immunology} 2018 PMID: 30333617
Antibody features that predict protection

Logistic regression: 17 features together predict protection (AUC 0.958)

Feature

Coefficient

BSL-4 Neut
BSL-2 fraction un-neut.
BSL-2/3 Neut
Fc
Fc glycan
Fc glycan
(2nd gen.)
(1st gen.)
BSL-2 Neut
Fc
Fc
Fc
Binding
Fc
Epitope
Epitope

Kristian Andersen, TSRI
Bette Korber, LANL

Saphire et al. Cell 2018 PMID: 30096313
We want both features in cocktails

SARS-CoV2? Complementary resistance patterns, synergistic binding and neutralization…
Clinical testing: PALM trial

ZMapp cocktail

- Fc 13C6
- Neut 2G4
- Neut 4G7

Survival: 50% (85/169)

mAb 114 monotherapy

- Neut. + Fc 114

Survival: 65% (113/174)

REGN-EB3 cocktail

- Neut + Fc 3471

Survival: 66% (103/155)
COVIC-19 Therapeutics Accelerator:
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Launch:

COVIC-19 Therapeutics Accelerator: NIH/NIAID U19 AI142790-02S1 and the GHR Foundation

Expansion:

• Evaluate therapeutics heading to clinical trials
• Find therapeutics we can mobilize to low- and middle-income countries
CoVIC workflow

intellectual property protected
Can use data for IND

donated antibodies

therapeutic antibody cocktails
sequence optimization
analyze & downselect
catalog in CoVIC-DB database
potency, efficacy, structural analyses
 aliquot & distribute
sample blinding
Binding (on/off rates) to forms, regions and variants of spike

High-Resolution epitope binning

High-Resolution structural biology by cryoEM, X-ray

Fc activities, enhancement, protection via effector

Neutralization: pseudovirus and BSL-3 systems

Escape location and propensity

In vivo protection

Novel combinations, optimization
High-resolution structural analyses

Cryo-electron Microscopy

mAb Fab domains in complex with:
- Full-length S
- RBD or NTD
- transmembrane surface spike

Intact mAbs in complex with FcR and Spike

X-ray Crystallography

Erica Ollmann Saphire

La Jolla Institute for Immunology

Life Without Disease
Binding analyses

- Binding kinetics analyses and epitope binning using standardized, structural biology-grade antigens (reference strain, D614G and other variants of S) in a GLP setting (Tomaras lab, Duke)

Georgia Tomaras

Daniel Bedinger
Pseudovirus neutralization

VSVΔG expressing SARS-CoV-2 S (reference strain or D614G) and GFP

Vero cells

Measure fluorescence

Calculate IC\textsubscript{50}, IC\textsubscript{90}, fraction neutralized

Lentivirus platform is licensed to Nexelis by NIAID Vaccine Research Center

Luc Gagnon
Authentic virus neutralization

- Neutralization assays at BSL-3 with authentic virus
- Data will be compared against neutralization of pseudovirus systems
Immune profiling of mAbs against SARS-CoV-2 Spike

- mAb-FcR binding profiles
- mAb glycosylation
- mAb-dependent phagocytosis
- NK cell degranulation
- Innate immune effector cell activation
- Complement deposition

High-throughput systems serology to profile Fc-driven activities of anonymized mAbs.

Galit Alter
Cellular studies: Fc function and resistance of to ADE

Bio-layer interferometry (BLI) to determine binding kinetics and affinity of mAbs for FcRs

Effect of blocking FcγR on mAb inhibition of infection by SARS-CoV-2

Propensity to infect primary human myeloid cell types

Determine phagocytic score and complement deposition

Alexander Bukreyev

*Xie et al. Cell Host Microbe 2020 PMID 32289263
In vivo efficacy

- Syrian golden hamster
- hACE2 tg
- NHPs

Treat with mAbs

mAb delivery Pre- or Post-Exposure

Infect with SARS-CoV-2

Survival
Weight loss
Lung titer (at peak replication)
Histopathology
Serum PK

- mAbs will be delivered either pre- or post-SARS-CoV-2 infection
- Initial testing in hamsters and mice transgenic for hACE2
- A subset of mAb combinations will be tested in NHPs
In vivo analyses of antibody half-life and ADE resistance in human Fc-FcRn binding setting*

Triple knock-in mice expressing human ACE2, FcRN and TMPRSS2

- Evaluate novel mouse model for predictive efficacy
- Viral load, kinetics and histopathology
- Half-life, efficacy without ADE

*Antibody owners may opt-in to this study
Mapping escape site, resistance in vitro

Vero E6 + TMPRSS2

Incubate cells with $10^2$-10$^5$ virus particles and 0.1-10 µg/mL mAbs

Harvest virus particles

Sequence S protein to identify mutations

Yoshihiro Kawaoka
Tracking Spike mutations in global human-to-human transmission

- GISAID: recurrent spatial, regional changes
- New tools for mutational tracking
- Keep researchers abreast of emerging mutations
- Suggest therapeutic candidates that remain responsive to emergent mutations
CoVIC database: a profile of therapeutic antibodies against SARS-CoV-2 Spike protein

Contributors can view
- Unblinded data for their mAbs
- How their mAbs compare with other blinded mAbs in the panel

Contributors will receive
- Email confirmation of mAb submission
- Email alerts when new data are available
- Data that can be used for IND filings

Data generated by partner reference labs

Data analysis Landscape of activities of anonymized mAbs

Bjoern Peters, LJI
And we’re off!

Thank you Contributors!

Academics
Non-profits
Small biotechs
Large biotechs
Major corporations

on four continents
Preliminary SARS-CoV-2 neutralization data for VSV pseudovirus

Some mAbs have clear matches across pseudoneut backbones (VSV and HIV) and with authentic virus

<table>
<thead>
<tr>
<th>COVID ID</th>
<th>VSV backbone Nexelis</th>
<th>HIV backbone (reported)</th>
<th>Authentic virus (reported)</th>
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<tr>
<td>COVIC-30</td>
<td>0.009</td>
<td>0.008</td>
<td>0.007</td>
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<tr>
<td>COVIC-32</td>
<td>0.009</td>
<td>0.008</td>
<td>0.009</td>
</tr>
</tbody>
</table>
Affinity landscape of CoVIC antibodies (1-47)
Spread of functional ability among CoVIC mAbs
Antibody contribution

- CoVIC PI and all reference labs are blinded to mAb name and source.
- OWS and BMGF Program Officers and CoVIC Program Manager are unblinded (but keep data confidential)
- Contributors know code names of their own mAbs, can view data as it is collected, can request re-analysis if data not as expected
- Contributors retain all IP and may publish and develop as they wish
Experiments in progress. More data to come!

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