COVID-19 Therapeutic Development in Real Time
Roadblocks and Opportunities

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The Donnelly Centre
University of Toronto
You got to use what you got to get what you want

James Brown
COVID-19 and the Immune System

Antibody

SARS HCoV-2

Host receptor

Viral infection

Blockade of viral infection

Antibody-blocked host receptor
COVID-19 virus SARS-2: Spike infection protein

- SARS-2 is nearly identical to SARS-1 (80%)
- Spike protein mediates host recognition and entry (infection)
- RBD recognizes host receptor ACE2
- Most natural SARS-1 neutralizing antibodies bind to the RBD and compete for binding with ACE2
- Develop synthetic antibodies that bind SARS-2 RBD and compete for binding with ACE2
- THESE ARE PRIME CANDIDATES FOR BIOLOGIC THERAPEUTICS FOR COVID19
Natural Antibodies

**Immunization**
- Antigen
  - Isolate immune cells

**Antibody-forming cells**
- Fusion
  - Tumor cells
  - Hybridomas
    - Hybridomas screened for production of desired antibody
  - Monoclonal antibodies
    - Antibody-producing hybridomas cloned
    - Clonal expansion
Therapeutic mAb Generation

Antigen Immunization

1. Harvest Spleen
2. Immortalize
3. Screen Hybridoma clones for antigen binding

Evaluate biology of murine MAb

Humanized

Chimera

Presta & Carter
Highly Validated Technology
- a fully human protein
- Highly stable
- Long half-life (weeks)
- Highly potent
- Highly specific
- Low immunogenicity
- Identical to natural neutralizing antibodies
- A validated human therapeutic
  - (> 50 approved drugs)

- Single, highly validated human framework
  (Hereceptin, Avastin, Xolair, etc.)
- High stability and yield, low immunogenicity
- Minimal targeted synthetic CDR diversity
  → Diverse functions with fixed biophysics
  → Modular design
Integrated Discovery Platform: From Targets to Functional Antibodies

Cancer cell lines
- Pancreatic
- Ovarian
- Breast
- Head & Neck

Additional Cell lines

Literature & Public Databases

Genomics
- Next-generation sequencing

Functional Genomics
- Pooled lentiviral shRNA screens

Synthetic Lethality Screens

Patient tumors: Pancreatic, ovarian, breast, head & neck

Primary Xenografts

Matched Cell lines

Cell Surface Targets

Antibody Discovery
- Phage display
- know how

- Functional antibodies
- Mechanism of action
- Proof of concept data
- Companion biomarkers
- Multi-level IP
The Therapeutic Antibody War Chest

Functional genomics platform

Large-scale, industry-quality antibody generation

Preclinical biology in relevant models

>14,000 Antibodies
>1,300 Antigens

Color Group:
- CD
- Ephrin
- FGFR
- FZD
- GPCR
- Ion channel
- ITG
- Other
- PD
- PTP
- RTK
Key Questions

• Can we apply the TRAC pipeline to COVID-19?
  • YES WE CAN

• How quickly can we go from idea to drug?
  • PRETTY DAMN QUICK
Validated Antibody Platform for Anti-Virals

Synthetic Antibodies with a Human Framework That Protect Mice from Lethal Sudan Ebolavirus Challenge

- Similar to SARS-CoV-1/2, Ebola has an acute life cycle
- Developed humanized Abs to key epitope on Ebola virus
- Treatment with single Ab protected virtually all mice from Ebola challenge
- Surviving mice proved resistant to subsequent Ebola challenge
  - Ab cleared initial Ebola challenge and enabled host immune system to develop natural resistance
Effectiveness of convalescent plasma therapy in severe COVID-19 patients

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FDA Approved a Clinical Trial for Convalescent Plasma Therapy (CPT)

- Patients exhibited strong positive responses within days
- Success of CPT validates neutralizing Abs as effective therapy for COVID19
- Next-generation therapy should be a recombinant neutralizing Ab
- Recombinant Ab will enhance efficacy while obviating limits of CPT
  - Defined and consistent formulation and activity
  - Highly stable single agent optimized for neutralization
  - High purity guarantees high safety compared with undefined plasma

Chest CTs of two patients. (A) Chest CT of patient 9 obtained on February 9 (7 dpoi) before CP transfusion (10 dpoi) showed ground-glass opacity with uneven density involving the multilobal segments of both lungs. The heart shadow outline was not clear. The lesion was close to the pleura. (B) CT image of patient 9 taken on February 15 (13 dpoi) showed the absorption of bilateral ground-glass opacity after CP transfusion. (C) Chest CT of patient 10 was obtained on February 8 (19 dpoi) before CP transfusion (20 dpoi). The brightness of both lungs was diffusely decreased, and multiple shadows of high density in both lungs were observed. (D) Chest CT of patient 10 on February 18 (29 dpoi) showed those lesions improved after CP transfusion.
# Project Timeline

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Method</th>
<th>Numbers</th>
<th>Timeline</th>
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<tbody>
<tr>
<td>Pooled selections</td>
<td>Phage display</td>
<td>$&gt;10^{10}$</td>
<td>3/24 – 3/29</td>
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<td>Binding screen</td>
<td>Phage ELISA</td>
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<td>3/30</td>
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<td>Host receptor blocking screen</td>
<td>Phage ELISA</td>
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<td>3/30</td>
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<tr>
<td>IgG production</td>
<td>Mammalian cell expression</td>
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<td>Identification of unique IgGs</td>
<td>DNA sequencing</td>
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<td>IgG binding to virus</td>
<td>ELISA</td>
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<td>4/12</td>
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<tr>
<td>Receptor blocking confirmation</td>
<td>ELISA</td>
<td>~25</td>
<td>4/12</td>
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<tr>
<td>Affinity</td>
<td>Quantitative virus binding</td>
<td>~15 (sub-nanomolar)</td>
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<td>Biophysical characteristics</td>
<td>Yield, solubility, heterogeneity</td>
<td>3-4 (top leads)</td>
<td>4/13</td>
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<td><em>In vitro</em> cell assay</td>
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<td><em>In vivo</em> virus neutralization</td>
<td>Human trials</td>
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## Institutions: Roadblocks and Opportunities

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Questions

Answers