An Open Source Program for Rapid Pandemic Response

An Open Source Avenue for Discovery and Local Production of Neutralizing Antibodies

Background

Emerging pandemics create a medical and economic crisis that can kill millions of people and cripple economies

The development of new treatments and vaccines can take 2 years or more to have an impact on the disease spread

An approach to an immediate response to a pandemic is to develop neutralizing antibodies to the pathogen, and use them as therapeutics to prevent infection

This approach can be greatly accelerated and localized through an open-source approach

The Principle

In the early stages of a pandemic, there are patients who survive the initial infection by raising neutralizing antibodies against the pathogen

These neutralizing antibodies can be easily cloned from patient B-cells, and a set of neutralizing antibodies can be rapidly developed

Once these antibodies have been cloned and characterized, they can be quickly scaled up, run through an accelerated development process, and be ready to treat patients in as little as 60 days

Alternatively, humanized hybridoma based approaches can be used to isolate neutralizing antibodies in the laboratory

Since there are many possible solutions, driven by the diversity of the antibody response, many antibodies can be raised, even against specific strains of pathogen, and developed locally

Challenges

While the development of neutralizing antibodies as disease preventatives can be rapidly accomplished, there are number of key challenges

1. The antibodies will typically only be effective for about 2-3 months per dose
    a. Thus, they will need to be dosed 4-6 times per year per patient to be effective
2. Production of antibodies can be expensive
    a. The cost of producing therapeutic antibodies is more expensive than vaccines or small molecules
    b. Thus, they will likely be targeted to specific vulnerable populations
    c. Each locality can invest in its own antibody production, to meet its local needs.

Advantages

1. These antibodies can be developed and deployed rapidly
    a. From start to treatment can be as little as 60 days
2. These antibodies can be used to prevent disease in important populations
    a. First responders
    b. Healthcare Workers
    c. Essential Workers (supply chain and food supply)
3. These antibodies can bridge to the period when vaccines and drugs become available
4. Using a distributed ‘open source’ approach enables a focus on local needs with local resources

Proposal

OSPF proposes the development of a global network of open-source contributors to address the current needs of the COVID-19 pandemic, and to prepare for the next pandemic

The network will consist of

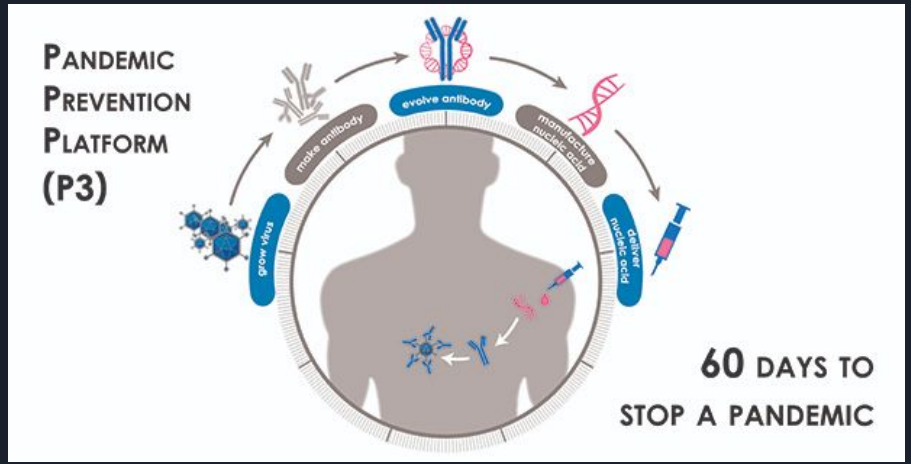
1. Discovery Laboratories
    a. Molecular Immunology groups that can rapidly discover, clone and characterize neutralizing antibodies
2. Development Laboratories
    a. Laboratories that can produce antibodies at a scale sufficient to produce materials for clinical trials
3. Clinical Trials Sites
    a. A number of local sites that can peform accelerated clinical trials to verify the safety and efficacy of these antibodies
4. Production Sites
    a. Commercial efforts that can rapidly produce, productize and distribute approved antibody therapies

Cloning Antibodies to Fight COVID-19

Objective

1. Rapidly deploy neutralizing antibody therapies for Pandemics
2. Use standard monoclonal antibody techniques to identify neutralizing antibodies
    a. Leveraging ‘Humanized’ monoclonal technologies
3. Clone the genes for the neutralizing antibodies
4. Produce therapeutic quantities of antibodies using bioreactors
5. Rapidly approve and deploy antibodies for prevention of disease

DARPA P3 Project



Pandemic Prevention Platform (P3)

- Launched in 2018
- Works with outside researchers to develop rapid response to emerging infectious diseases
- Goal is to deliver medical countermeasures within 60 days
- Current collaborators
  - Duke University
  - Vanderbilt University
  - Abcellera
  - AstraZeneca
- Would create immunity that would last several months
  - Would need additional treatments to maintain immunity

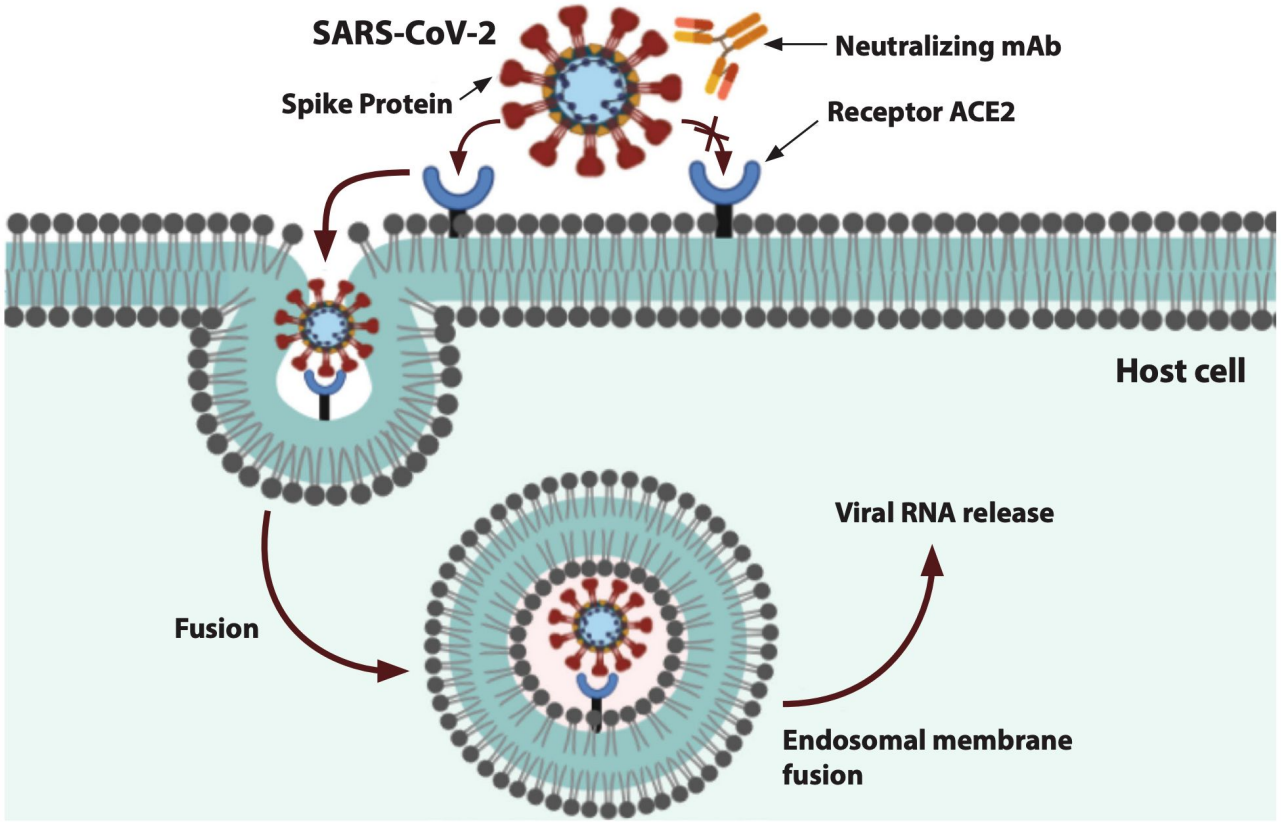


Figure 2. Schematic representation of SARS-CoV-2 neutralization mechanism.
Interaction of spike protein and the cellular receptor is required for membrane fusion and entry into the target cell. The monoclonal antibodies targeting spike protein of SARS-CoV-2 could potentially inhibit the virus binding to its cellular receptor thereby preventing its entry into the cell.

The process of discovering and developing an antibody-based treatment

AstraZeneca

Sources for antibodies against the SARS-CoV-2 virus

- Patients who have recovered from COVID-19
- Humanised mice immunised with the SARS-Cov-2 spike protein
- Laboratory techniques such as phage display

Harnessing multiple technology platforms

- Immune replica technology
- Hybridoma technology

Screening to assess the characteristics of the potential monoclonal antibodies

- Binding
- Neutralisation
- Developability

Testing, development, approval, manufacturing and distribution

- AstraZeneca is aiming for clinical evaluation in the next 3 to 5 months

Currently Identified anti-COVID-19 Neutralizing Antibodies

A human monoclonal antibody blocking SARS-CoV-2 infection

Chunyan Wang, Wentao Li, Dubravka Drabek, Nisreen M.A. Okba, Rien van Haperen, Albert D.M.E. Osterhaus, Frank J.M. van Kuppeveld, Bart L. Haagmans, Frank Grosveld, Berend-Jan Bosch

doi: https://doi.org/10.1101/2020.03.11.987958

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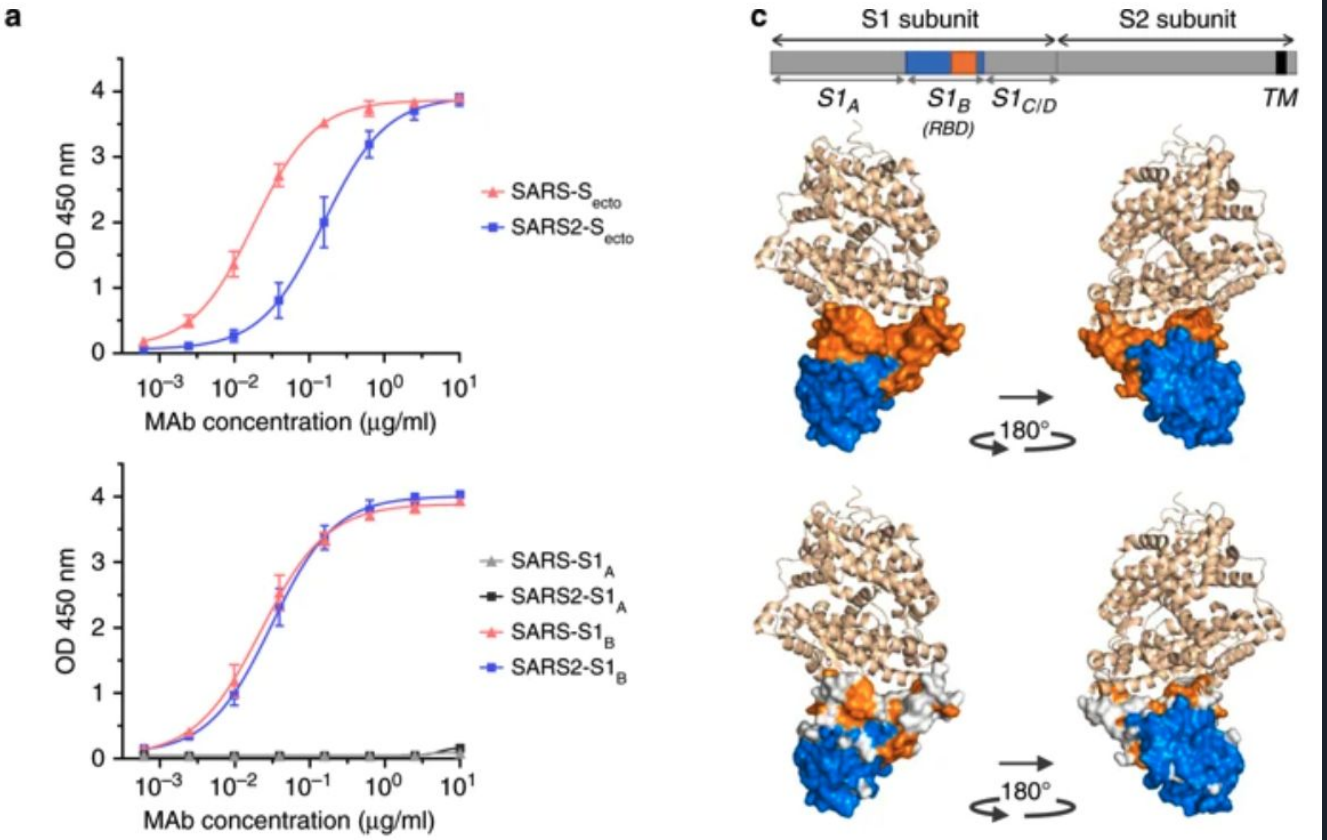
Abstract

The emergence of the novel human coronavirus SARS-CoV-2 in Wuhan, China has caused a worldwide epidemic of respiratory disease (COVID-19). Vaccines and targeted therapeutics for treatment of this disease are currently lacking. Here we report a human monoclonal antibody that neutralizes SARS-CoV-2 (and SARS-CoV). This cross-neutralizing antibody targets a communal epitope on these viruses and offers potential for prevention and treatment of COVID-19.

Fig. 2: The neutralizing 47D11 mAb binds SARS1-S and SARS2-S RBD without eliminating receptor interaction.



Chongquin Project

Approach

- Identify patients that have recovered from the disease
- Isolate B-cells
- Clone antibody genes
- Screen for neutralizing antibodies
- Develop as neutralizing antibody therapies

https://www.medrxiv.org/content/10.1101/2020.04.06.20055475v1

A human SARS-CoV neutralizing antibody against epitope on S2 protein

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Abstract

An immune antibody phage-display library was constructed from B cells of SARS convalescent patients. More than 80 clones were selected from the library by using the whole inactivated SARS-CoV virions as target. One human scFv, B1, was characterized extensively. The B1 recognized SARS pseudovirus in vivo and competed with SARS sera for binding to SARS-CoV with high affinity (equilibrium dissociation constant, K_d = 105 nM). The B1 also has potent neutralizing activities against infection by pseudovirus expressing SARS-CoV S protein in vitro. Finally, we found that the B1 recognized an epitope on S2 protein, especially within amino acids 1023–1189 of S2 protein. This study not only first made a human neutralizing antibody, which recognized an epitope on S2 protein like natural antibody in sera, but also may help us to better understand the immunological characteristics of SARS protein and SARS vaccine design.

Potent neutralization of severe acute respiratory syndrome (SARS) coronavirus by a human mAb to S1 protein that blocks receptor association

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PNAS February 24, 2004 101 (8) 2536-2541; https://doi.org/10.1073/pnas.0307140101

Edited by Robert A. Lamb, Northwestern University, Evanston, IL (received for review November 3, 2003)

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Abstract

Effective prophylaxis and antiviral therapies are urgently needed in the event of reemergence of the highly contagious and often fatal severe acute respiratory syndrome (SARS) coronavirus (SARS-CoV) infection. We have identified eight recombinant human single-chain variable region fragments (scFvs) against the S1 domain of spike (S) protein of the SARS-CoV from two nonimmune human antibody libraries. One scFv 80R efficiently neutralized SARS-CoV and inhibited syncytia formation between cells expressing the S protein and those expressing the SARS-CoV receptor angiotensin-converting enzyme 2 (ACE2). Mapping of the 80R epitope showed it is located within the N-terminal 261–672 amino acids of S protein and is not glycosylation-dependent. 80R scFv competed with soluble ACE2 for association with the S1 domain and bound S1 with high affinity (equilibrium dissociation constant, K_d = 32.3 nM). A human IgG1 form of 80R bound S1 with a 20-fold higher affinity of 1.59 nM comparable to that of ACE2 (K_d = 1.70 nM), and neutralized virus 20-fold more efficiently than the 80R scFv. These data suggest that the 80R human monoclonal antibody may be a useful viral entry inhibitor for the emergency prophylaxis and treatment of SARS, and that the ACE2-binding site of S1 could be an attractive target for subunit vaccine and drug development.

Neutralizing Antibodies to Sars-CoV

Monoclonal antibody	Mechanism of action	References
80R	• Binding to the conformational epitope (amino acid residues 426-492) on S1 fragment of SARS-CoV. • Blocking the interaction of S1 subunit protein with cellular receptor ACE2 using 6 complementary determining region (CDR) *in vitro* and *in vivo* (Mouse).	11,20,41,42
CR3014	• Binding to the amino acid residues 318-510 and amino acid residue 565 with high affinity on S1 fragment of SARS-CoV. • Blocking the interaction of S1 subunit protein with cellular receptor ACE2 *in vitro* and *in vivo* (Ferret).	43-45
CR3022	• Binding to the amino acid residues 318-510 on S1 fragment of SARS-CoV. • Blocking the interaction of S1 subunit protein (RBD) with cellular receptor ACE2 *in vitro*.	44
F26G18	• Binding to the linear epitope (amino acid residues 460-476) on S1 fragment of SARS-CoV. • Blocking the interaction of S1 subunit protein (RBD) with cellular receptor ACE2 *in vitro*.	42
F26G19	• Binding to the conformational epitope (amino acid residues 359-362, 391-392, 424-427, and 486-492) on S1 fragment of SARS-CoV. • Blocking the interaction of S1 subunit protein (RBD) with cellular receptor ACE2 *in vitro*.	42
m396	• Binding to the conformational epitope (amino acid residues 482-491) on S1 fragment of SARS-CoV. • Blocking the interaction of S subunit protein using CDR loops H1, H2, H3, and L3 with cellular receptor ACE2 *in vitro*.	42,46
1A9	• Binding to the Heptad repeat (HR) loops including heptad repeat 1 (HR1) and heptad repeat 1 (HR2) domain on S2 fragment of SARS-CoV. • Blocking the interaction of S2 subunit protein (amino acid residues 1111-1130) with cellular receptor *in vitro*.	47,48
201	• Binding to the amino acid residues 490-510 on S1 fragment of SARS-CoV. • Blocking the interaction of S1 subunit protein with cellular receptor ACE2 *in vitro* and *in vivo* (Mouse Syrian Hamster).	33,49
68	• Binding to the amino acid residues 130-150 of SARS-CoV *in vitro* and *in vivo* (Mouse)	33,49
4D4	• Binding to the amino acid residues 12-261 of SARS-CoV and N-terminal of RBD • Inhibiting the post-interaction in the viral penetration *in vitro*.	33,50
S230	• Binding to epitopes partially overlapping with receptor binding motifs on B domain of SARS-CoV. • Blocking the interaction of S1 subunit protein with cellular receptor ACE2 *in vitro*	51

Neutralizing Antibodies to Mers-CoV

Monoclonal antibody	Mechanism of action	References
MERS-4	• Binding to the C-terminal segment of the β5-β6, β6-β7 and β7-β8 loops on the receptor-binding subdomain in RBD of MERS-CoV with no overlap DPP4 binding surface. • Blocking the interaction of S1 subunit protein with cellular receptor DPP4 *in vitro* by inducing β5-β6 shallow groove on the RBD.	52-55
MERS-27	• Binding to the C-terminal segment of the β6-β7 loop and β7 strand on RBD of MERS-CoV and overlap with the DPP4 binding surface. • Blocking the interaction of S1subunit protein with cellular receptor DPP4 *in vitro*.	52-57
4C2	• Binding to the C-terminal segment of the β6-β7 loop and β7 strand on RBD of MERS-CoV and overlap with the DPP4 binding surface. • Blocking the interaction of S1 subunit protein with cellular receptor DPP4 *in vitro* and *in vivo* (Mouse).	52,53,56,58
m336	• Binding to the C-terminal segment of the β5-β8 strands, β5-β6 loop and β6-β7 loop in RBD of MERS-CoV and overlap with the DPP4 binding surface. • Blocking the interaction of S1 subunit protein with cellular receptor DPP4 by mimicking the interaction between RBD and DPP4 in the similar binding angle *in vitro* and *in vivo* (Mouse and rabbit).	52,53,56,59-61
G4	• Binding to the glycosylated surface on the S2 subunit protein *in vitro*.	52,62,63
D12	• Binding to the C-terminal segment of the β6-β7 loop and β7 strand on RBD of MERS-CoV and overlap with the DPP4 binding surface. • Blocking the interaction of S1 subunit protein with cellular receptor DPP4 *in vitro*	52,56,63,64
JC57-14	• Binding to the C-terminal segment of the β6-β7 loop and β7 strand on RBD of MERS-CoV and overlap with the DPP4 binding surface. • Blocking the interaction of S1 subunit protein with cellular receptor DPP4 *in vitro*.	52,56,64
MERS-GD27	• Binding to the C-terminal segment of the β5-β8 strands, β5-β6 loop and β6-β7 loop in RBD of MERS-CoV. • Blocking the interaction of S1 subunit protein with cellular receptor DPP4 by mimicking the interaction between RBD and DPP4 in the same binding angle *in vitro* and *in vivo* (Mice).	52,65
MERS-GD33	• Binding to the C-terminal segment of the β5-β8 strands, β5-β6 loop and β6-β7 loop in RBD of MERS-CoV. • Blocking the interaction of S1 subunit protein with cellular receptor DPP4 mimicking the interaction between RBD and DPP4 in the same binding angle *in vitro*.	52,66
LCA60	• Binding to the C-terminal segment of the β8 strand, β6-β9 loop, and β6-β8 loop on RBD of MERS-CoV. • Blocking the interaction of S1 subunit protein with cellular receptor DPP4 *in vitro*.	51
MCA1	• Binding to RBD with 6 complementarity-determining regions • Blocking the interaction of S1 subunit protein with cellular receptor DPP4 *in vitro* and *in vivo* (Mouse).	67,68
CDC2-C2	• Blocking the interaction of S1 subunit protein with cellular receptor DPP4 *in vitro* and *in vivo* (Mouse).	64
7D10	• Binding to N-terminal domain of S protein of MERS-CoV • Blocking the interaction of S1 subunit protein with cellular receptor DPP4 *in vitro* and *in vivo* (Mouse).	69
G2	• Binding to N-terminal domain of S protein of MERS-CoV • Blocking the interaction of S1 subunit protein with cellular receptor DPP4 *in vitro*.	69,70

Open Source Approach

Objective

1. To identify neutralizing antibodies for urgent response prior to vaccine availability
2. To develop, produce and distribute antibodies for local treatment of vulnerable populations

Process

1. Mobilize global laboratories to identify and clone neutralizing antibodies
2. Mobilize global laboratories to scale production of antibodies
3. Leverage local clinical infrastructures for rapid testing and approval
4. Leverage network of local manufacturers to scale and distribute in local areas