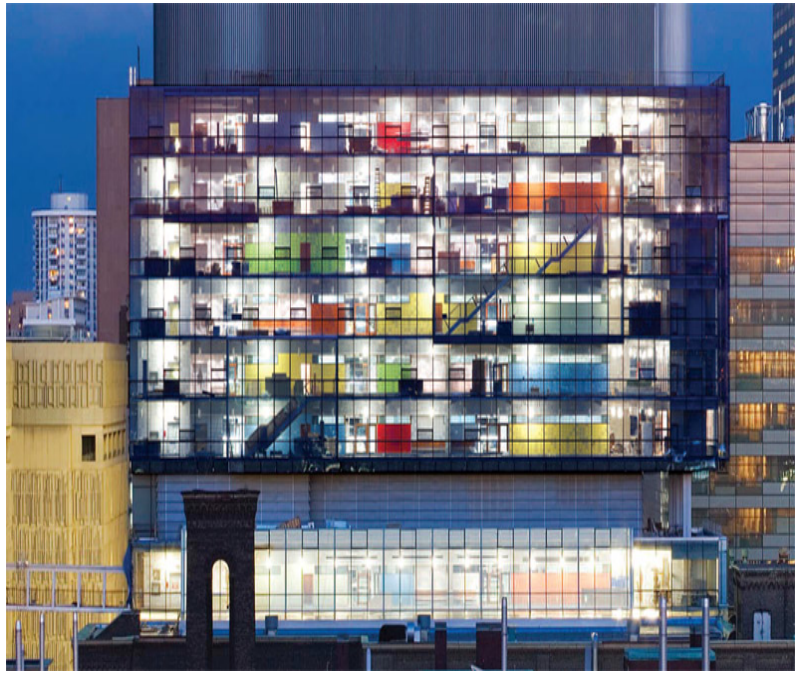
COVID-19 Therapeutic Development in Real Time Roadblocks and Opportunities

Sachdev Sidhu
Toronto Recombinant Antibody Centre
The Donnelly Centre
University of Toronto



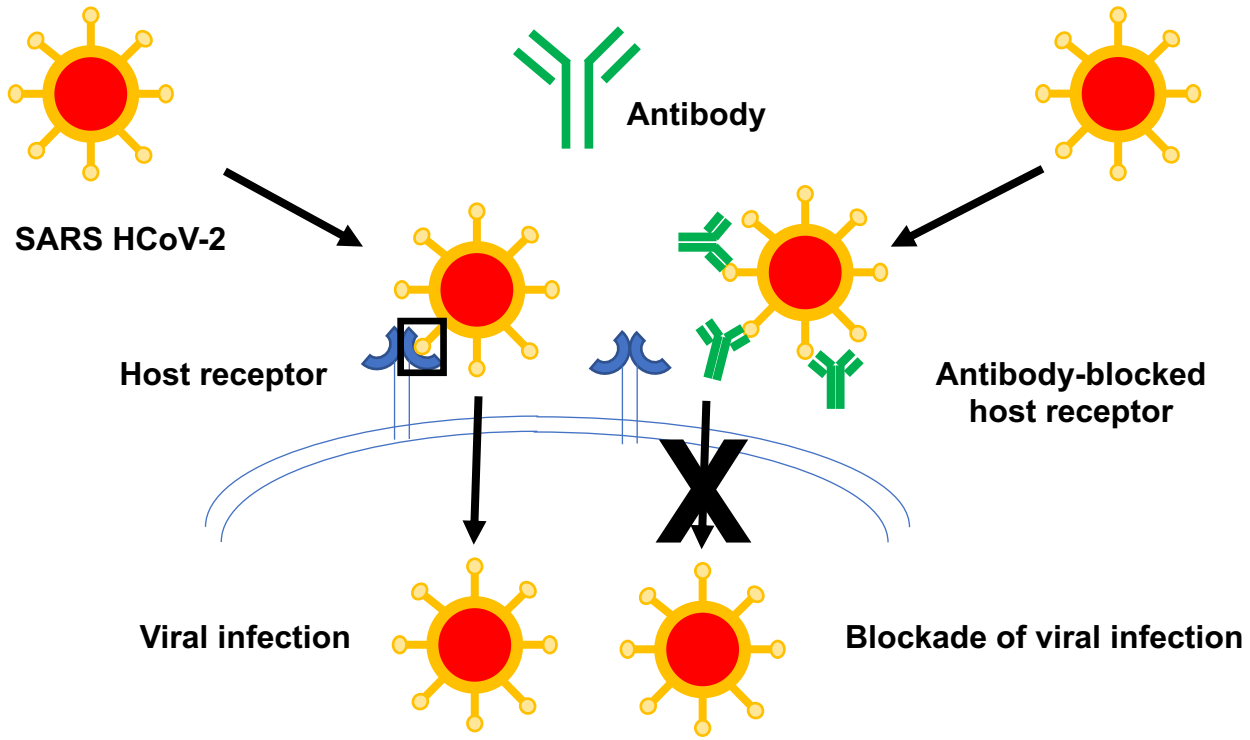
TRAC Mission Statement

MWA: Medicine with Attitude

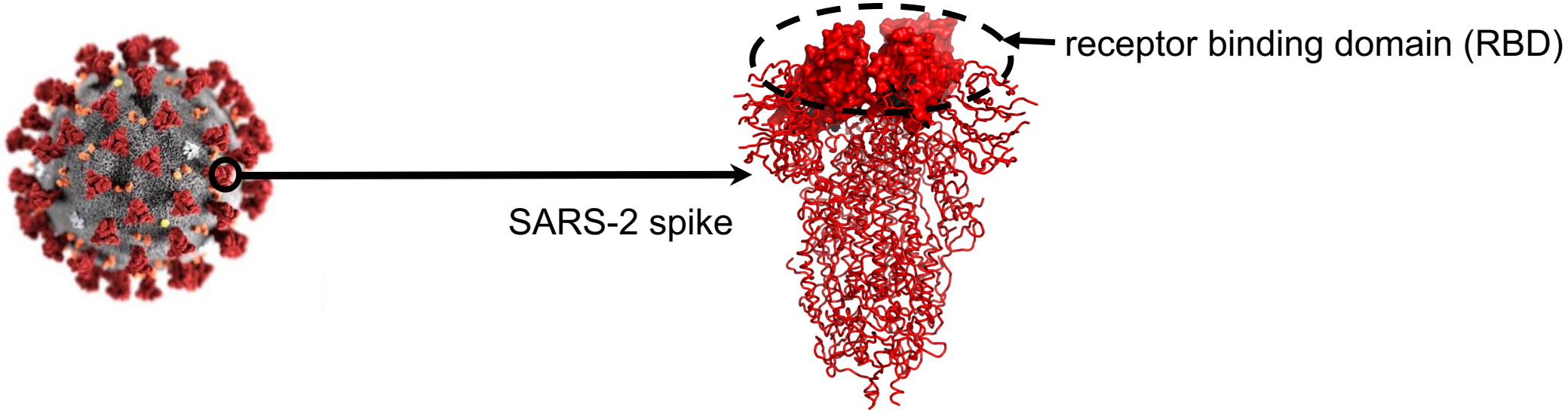
You got to use what you got to get what you want

James Brown

COVID-19 and the Immune System

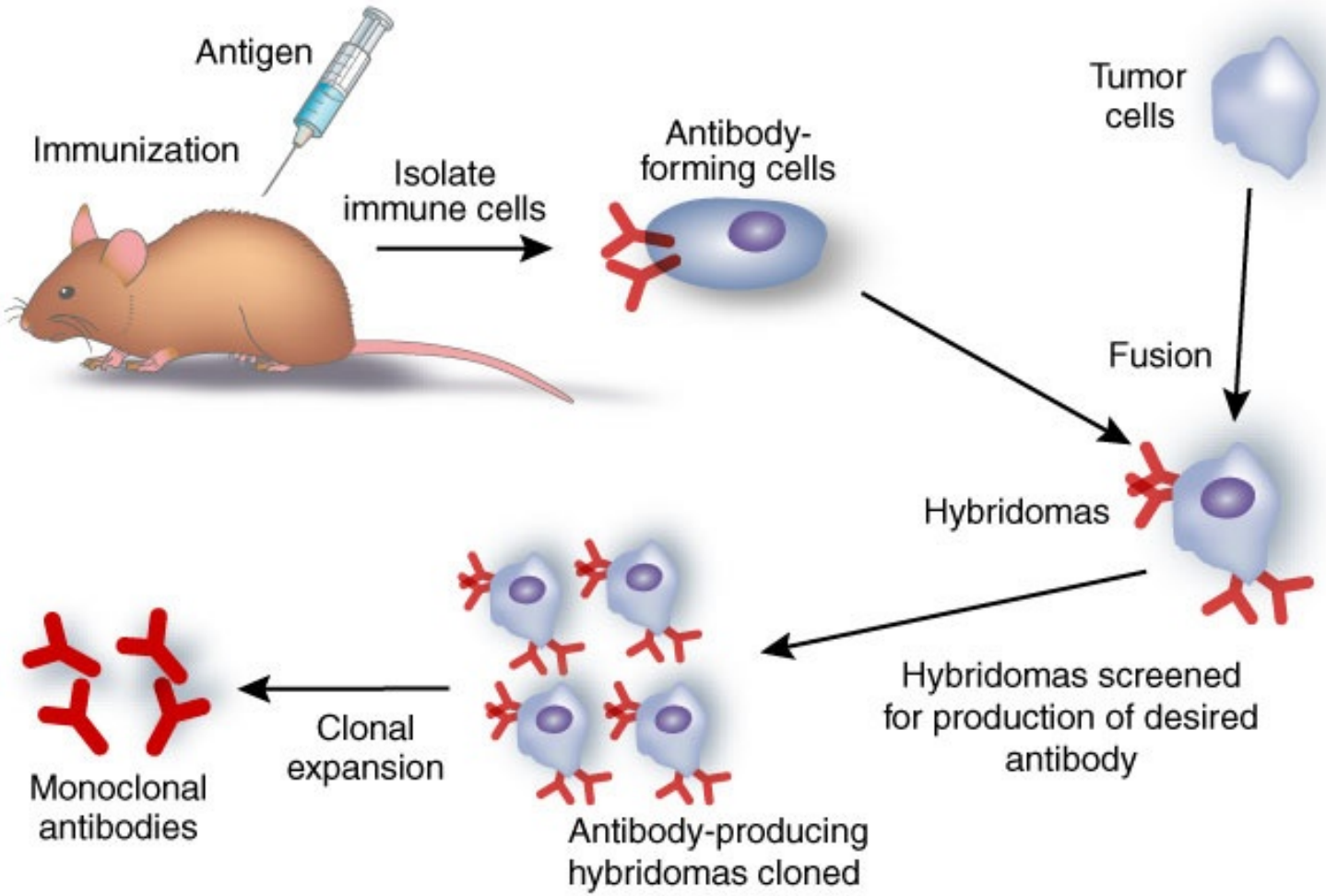


COVID-19 virus SARS-2: Spike infection protein



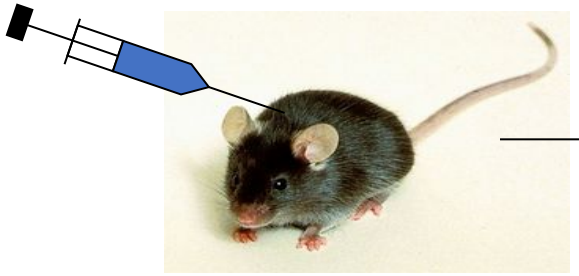
- **SARS-2 is nearly identical to SARS-1 (80%)**
- **Spike protein mediates host recognition and entry (infection)**
- **RBD recognizes host receptor ACE2**
- **Most natural SARS-1 neutralizing antibodies bind to the RBD and compete for binding with ACE2**
- **Develop synthetic antibodies that bind SARS-2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

Natural Antibodies

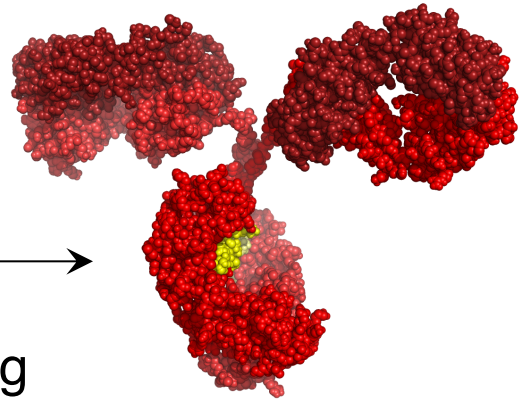


Therapeutic mAb Generation

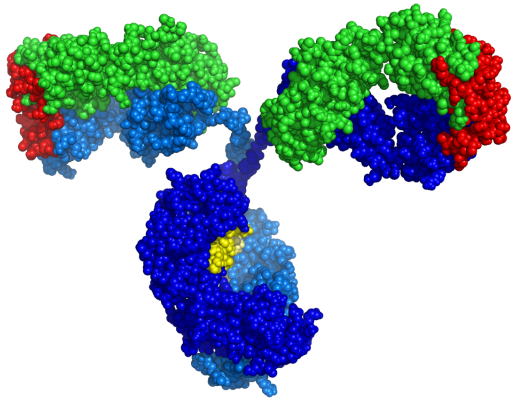
Antigen Immunization



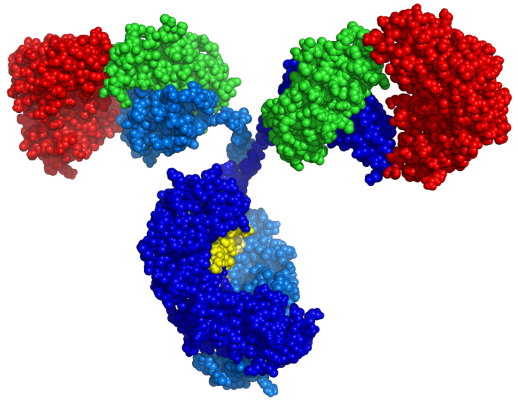
1. Harvest Spleen
2. Immortalize
3. Screen Hybridoma clones for antigen binding



Evaluate biology of murine MAb



Humanized



Chimera

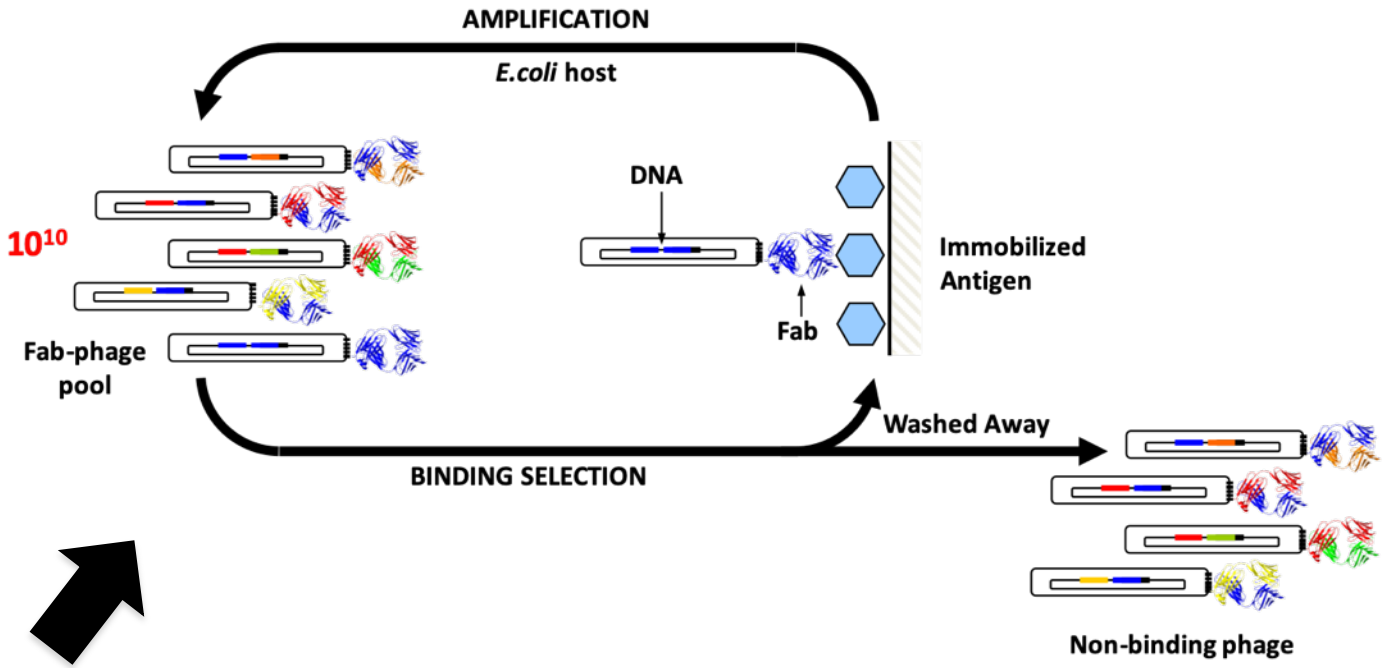
Presta & Carter

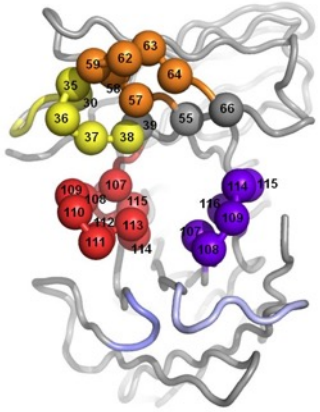
Toronto Recombinant Antibody Centre

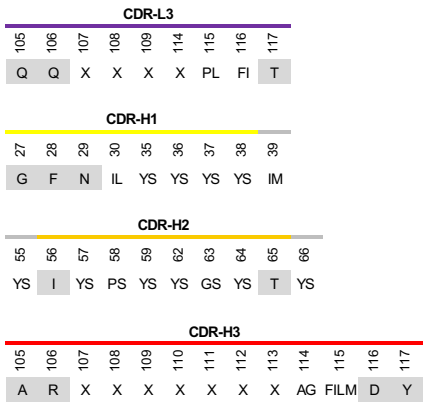
A High-throughput synthetic antibody platform

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.)

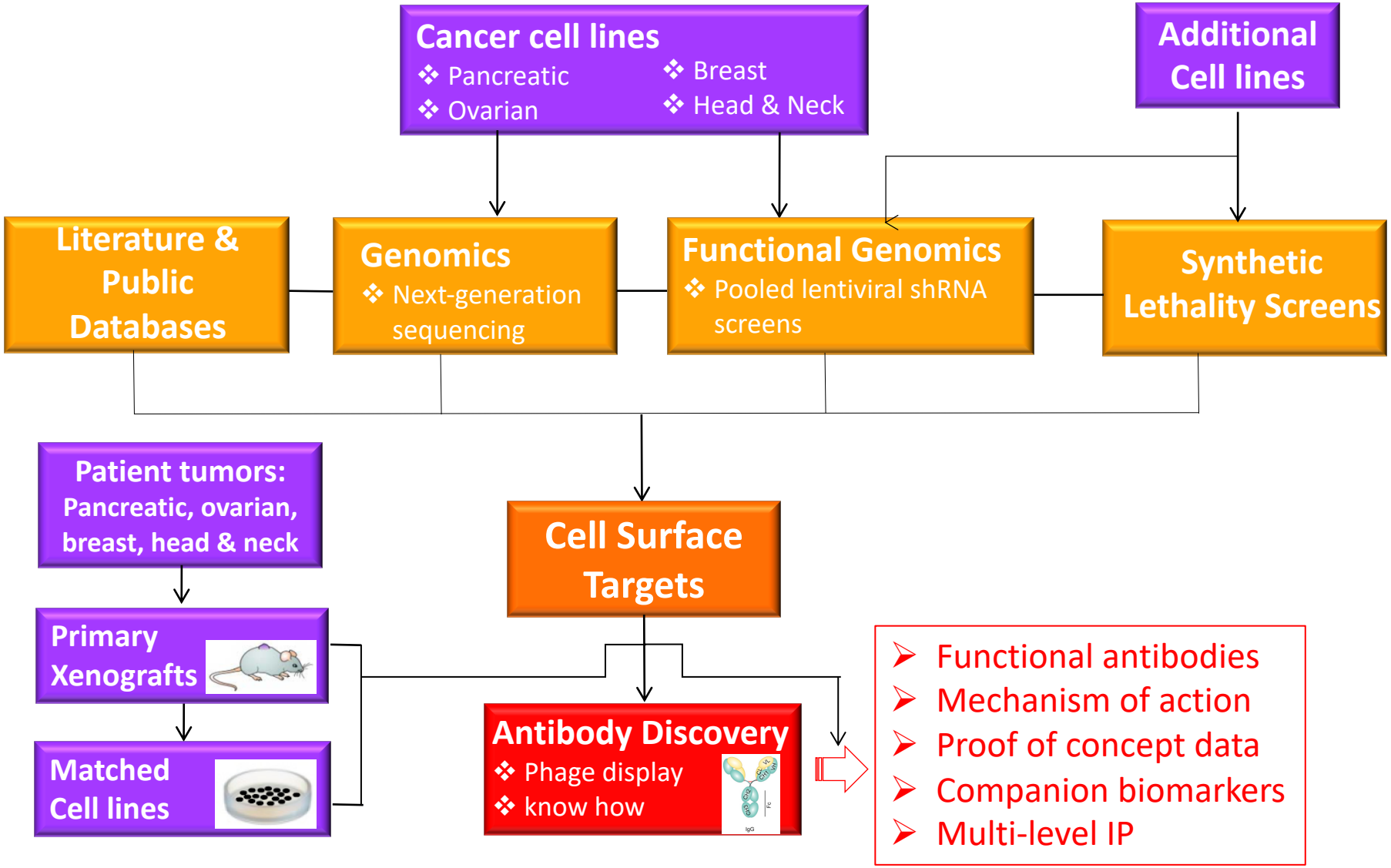
-High stability and yield, low immunogenicity

-Minimal targeted synthetic CDR diversity

→Diverse functions with fixed biophysics

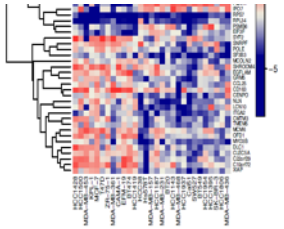
→Modular design

Integrated Discovery Platform:
From Targets to Functional Antibodies

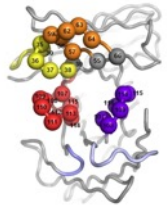


The Therapeutic Antibody War Chest

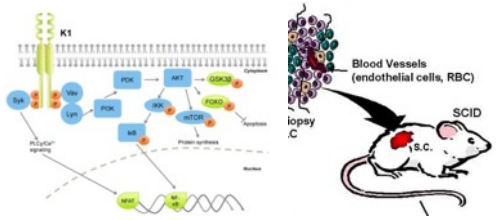
Functional genomics platform



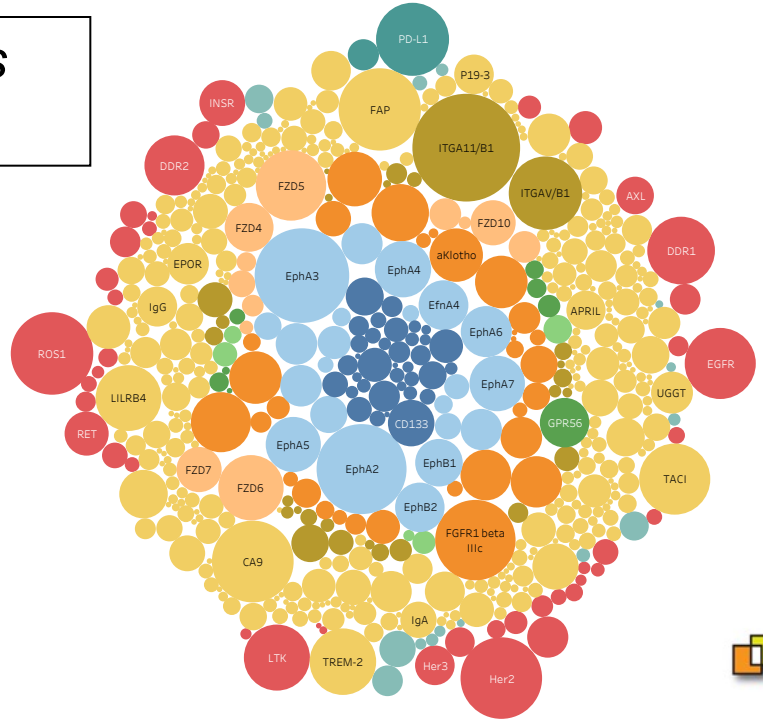
Large-scale, industry-quality antibody generation



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

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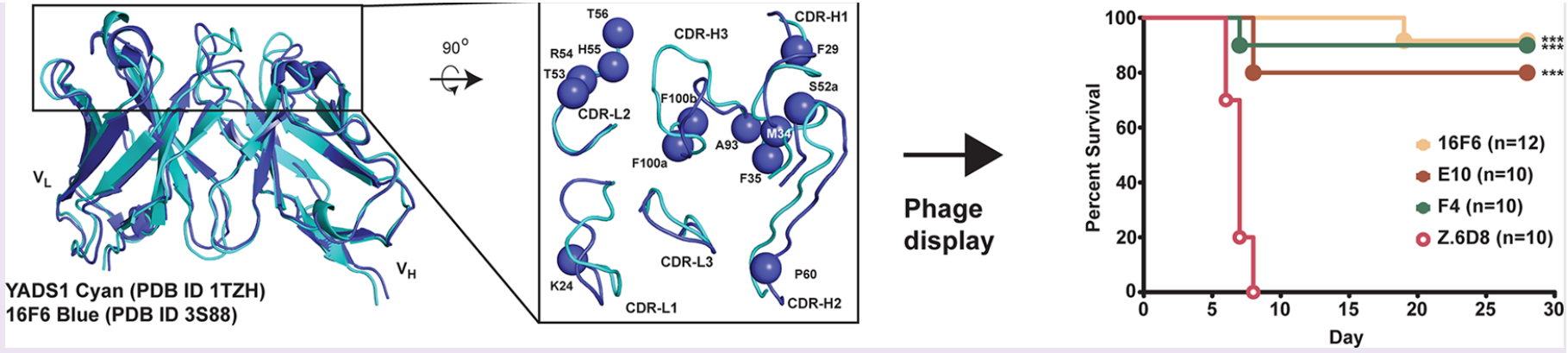
Key Questions

- 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



Sidhu and colleagues:*dx.doi.org/10.1021/cb5006454 | ACS Chem. Biol., 2014*

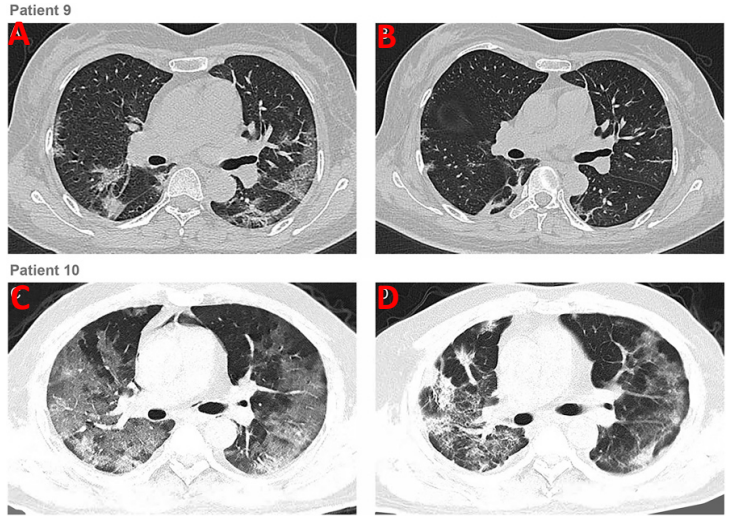
-Similar to SARS-CoV-1/2, Ebola has an acute life cycle
-Developed humanized Abs to key epitope on Ebola virus
-Treatment with single Ab protected virtually all mice from Ebola challenge
-Surviving mice proved resistant to subsequent Ebola challenge
-Ab cleared initial Ebola challenge *and* enabled host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

Synthetic Neutralizing Antibodies – Proven Stability and Efficacy
-Rapid Development and Scalable Cost-effective Production

Effectiveness of convalescent plasma therapy in severe COVID-19 patients

Kai Duan[a,b,1], Bende Liu[c,1], Cesheng Li[d,1], Huajun Zhang[e,1], Ting Yu[f,1], Jieming Qu[g,h,i,1], Min Zhou[g,h,i,1], Li Chen[j,1], Shengli Meng[b], Yong Hu[d], Cheng Peng[e], Mingchao Yuan[k], Jinyan Huang[l], Zejun Wang[b], Jianhong Yu[d], Xiaoxiao Gao[e], Dan Wang[k], Xiaoqi Yu[m], Li Li[b], Jiayou Zhang[b], Xiao Wu[d], Bei Li[e], Yanping Xu[g,h,i], Wei Chen[b], Yan Peng[d], Yeqin Hu[b], Lianzhen Lin[d], Xuefei Liu[g,h,i], Shihe Huang[b], Zhijun Zhou[d], Lianghao Zhang[b], Yue Wang[d], Zhi Zhang[b], Kun Deng[d], Zhiwu Xia[b], Qin Gong[d], Wei Zhang[d], Xiaobei Zheng[d], Ying Liu[d], Huichuan Yang[a], Dongbo Zhou[a], Ding Yu[a], Jifeng Hou[n], Zhengli Shi[e], Saijuan Chen[l], Zhu Chen[l,2], Xinxin Zhang[m,2], and Xiaoming Yang[a,b,2]

www.pnas.org/cgi/doi/10.1073/pnas.2004168117, March 2020



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

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

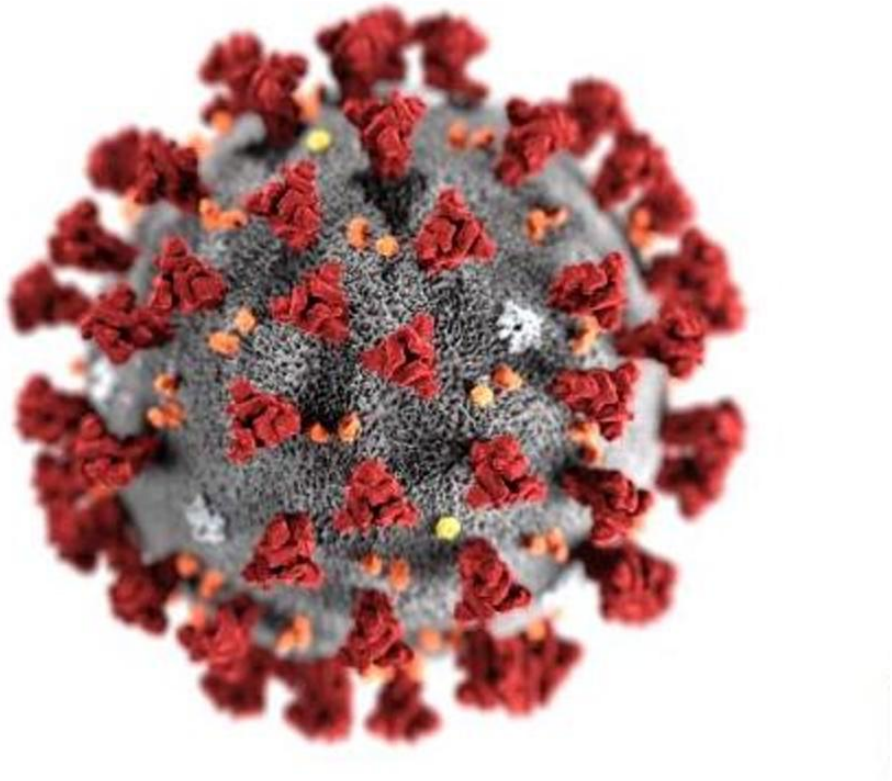
Project Timeline

Parameter	Method	Numbers	Timeline
Pooled selections	Phage display	$>10^{10}$	3/24 – 3/29
Binding screen	Phage ELISA	384	3/30
Host receptor blocking screen	Phage ELISA	358	3/30
IgG production	Mammalian cell expression	66	3/31 – 4/11
Identification of unique IgGs	DNA sequencing	>50	4/8
IgG binding to virus	ELISA	~50	4/12
Receptor blocking confirmation	ELISA	~25	4/12
Affinity	Quantitative virus binding	~15 (sub-nanomolar)	4/13
Biophysical characteristics	Yield, solubility, heterogeneity	3-4 (top leads)	4/13
In vitro virus neutralization	*In vitro* cell assay	2	4/30
In vivo virus neutralization	Human trials	1	7/1

Institutions: Roadblocks and Opportunities

Institution	Roadblock	Opportunity
Finance	Greed	Investment
Government	Politics	Mobilization
Academics	Bureaucracy	Clarity
Science	Conservatism	Innovation
Humanity	Nationalism	Globalism

Questions



Answers