

ACCADEMIA NAZIONALE DEI LINCEI



«CONFERENZE ISTITUZIONALI»

RINO RAPPUOLI

Monoclonali per la cura e la prevenzione del COVID-19

Venerdì 12 marzo 2021, ore 11



In Siena, my city, Covid-19 is not the first pandemic



Siena 14th century

In the 14th century Siena, a city located on the way from Rome to northern Europe, had one of the most powerful economies of its time. It had wealth, flourishing arts, and a population of 100,000 inhabitants (Paris had only 70,000 at that time).



Ambrogio Lorenzetti
1330

The city was rich, had a flourishing culture
and had a dream:

Build the largest cathedral ever

they started building the cathedral,
the tall facade had to intimidate those approaching the city from Rome



... In Siena, the unfinished cathedral is the largest existing monument to Infectious Diseases, standing reminder of a flourishing economy and culture wiped out forever in just three months by the 1348 PLAGUE



Manaus, Brazil



By 2021 we can control Covid-19

thanks to vaccines and human monoclonals

2020

So far we have the same tools of 700 year ago to fight the pandemic:

- quarantine
 - social distancing
 - hygiene
- non pharmaceutical interventions

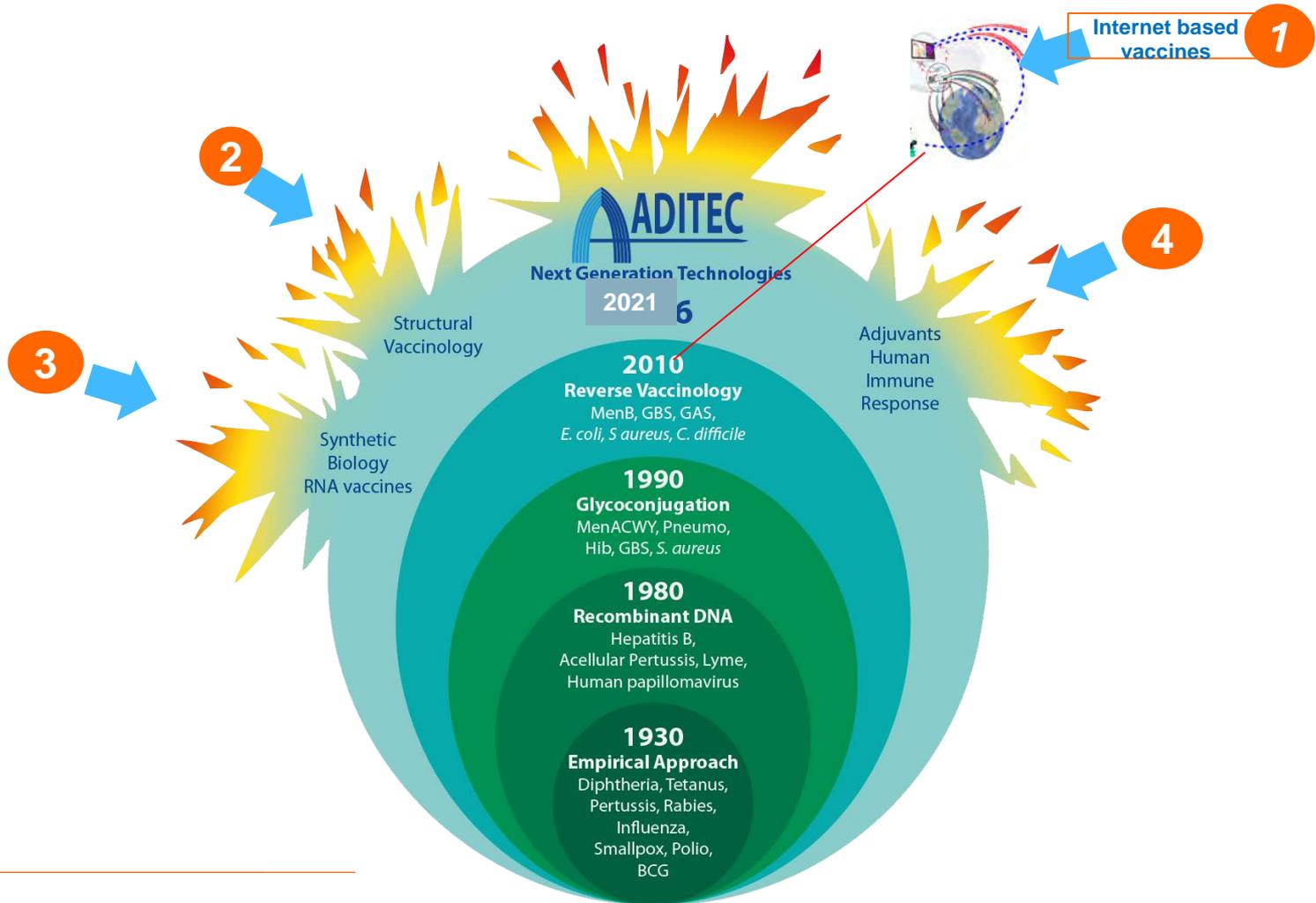
2021 -

Vaccines and human monoclonal antibodies will control Covid-19
They will be made at pandemic speed thanks to:

- Technology
- Unprecedented investment in development and manufacturing

Technologies

4 technologies allowed fast development of Covid-19 vaccines

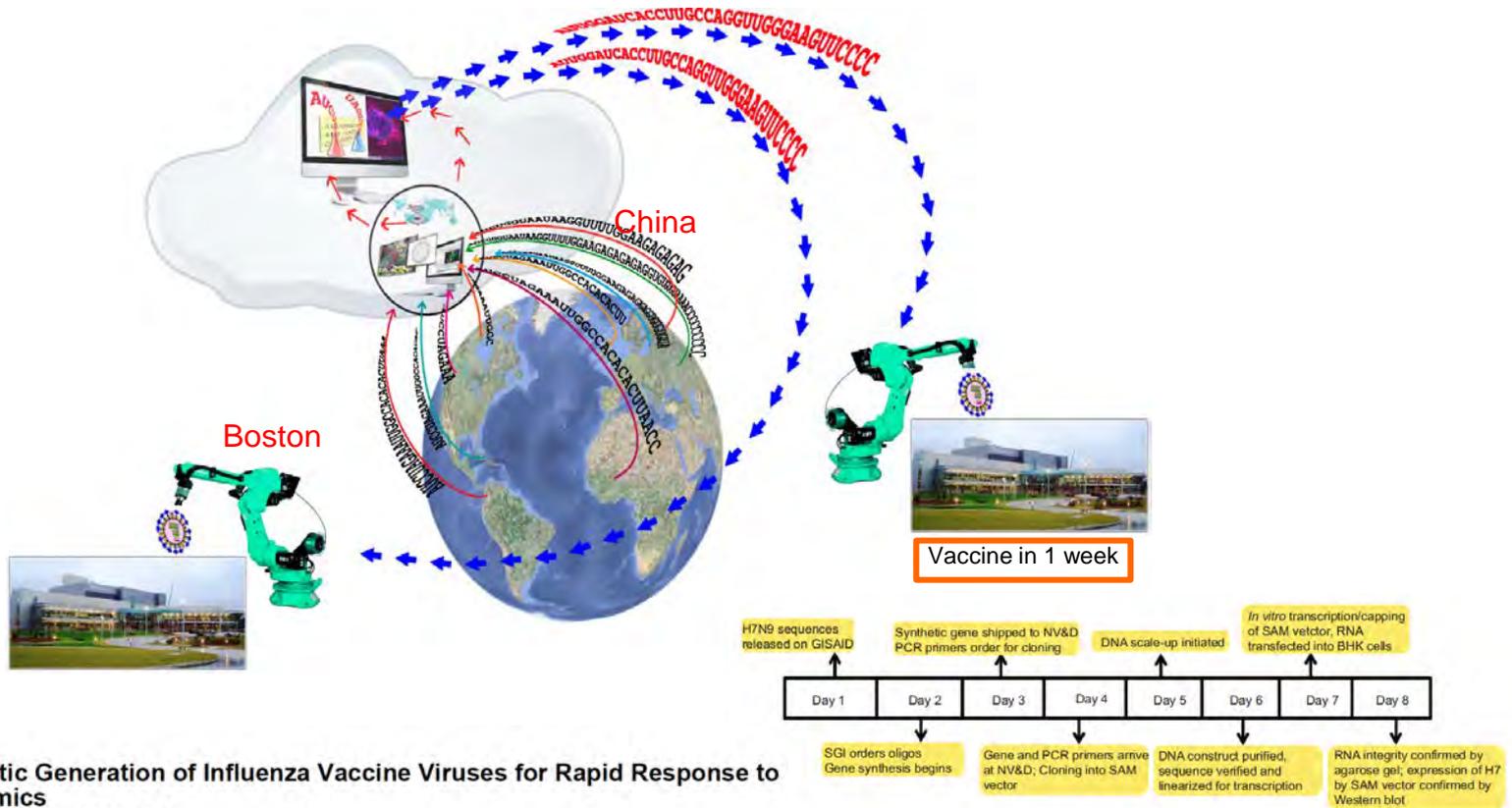


mRNA vaccines

- 1993 First demonstration of immune responses induced by mRNA
- 2000 Curevac incorporated
- 2005 RNA vaccine described for cancer
- 2008 BioNTec incorporated
- 2008 Novartis RNA program for infectious diseases vaccines
- 2009 first clinical trial (cancer)
- 2010 Moderna incorporated
- 2012 lipid nanoparticles for RNA delivery
- 2013 influenza mRNA vaccine in one week
- 2015 first Moderna clinical trial
- 2020 COVID-19 vaccines

Internet-based vaccines in one week

In 2013 an RNA vaccine and a virus seed in one week using information teleported by internet



Synthetic Generation of Influenza Vaccine Viruses for Rapid Response to Pandemics

Philip R. Dormitzer *et al.*

Sci Transl Med 5, 185ra68 (2013);

DOI: 10.1126/scitranslmed.3006368

selfie from electronic gene sequence posting to production of RNA prior to formulation with the LNP delivery system. GISAID, Global Initiative for Sharing Data; PCR, polymerase chain reaction.

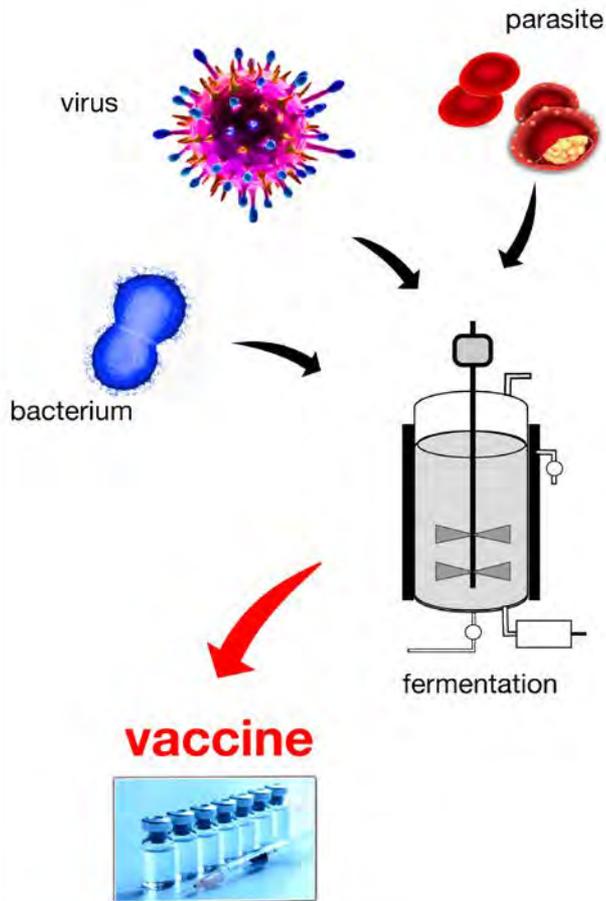
Emerging Microbes and Infections (2013) 2, e52; doi:10.1038/emi.2013.54

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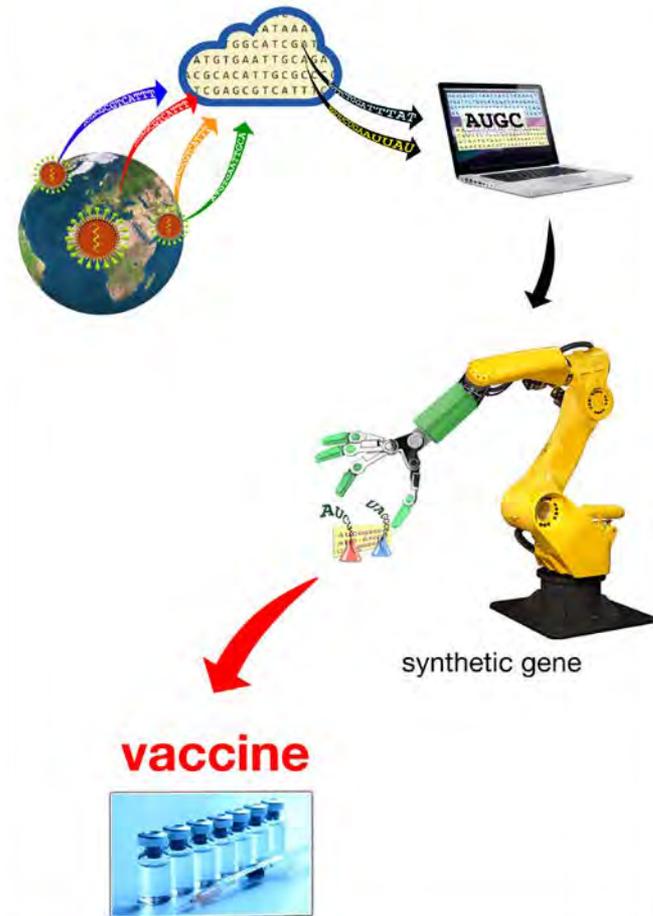
www.nature.com/emi



Analogic vaccines



Digital vaccines RNA



Three main vaccine types for Covid-19

Immunogenicity

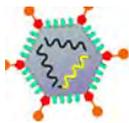


Novavax, Sanofi/GSK, Clover/Dynavax,
Medicago/GSK, SK/GSK



Moderna, BionTech/Pfizer, Curevac

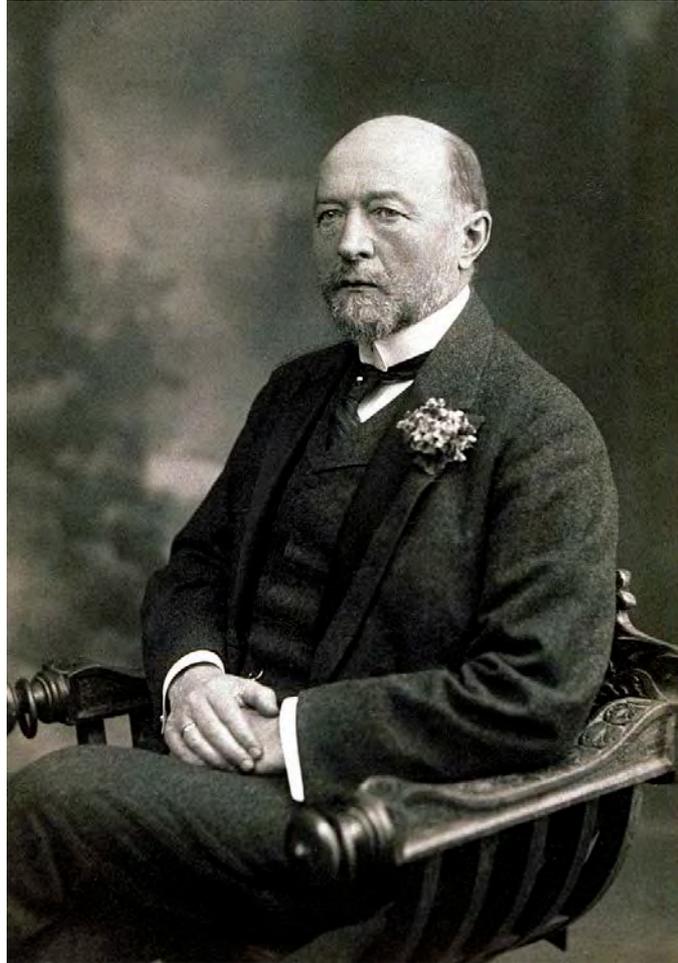
Viral vectors



Oxford/Astra Zeneca, J&J, Reithera
Russian Vaccine, Chinese vaccines

Passive immunization

Serum therapy has been a life-saving tool since 1890



Emil von Behring
First Nobel prize for Medicine

Human monoclonal antibodies 50 billion sales

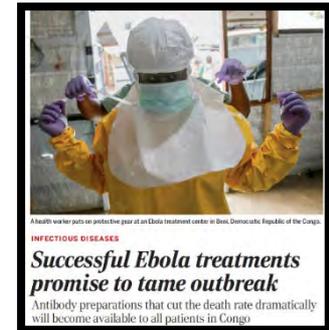
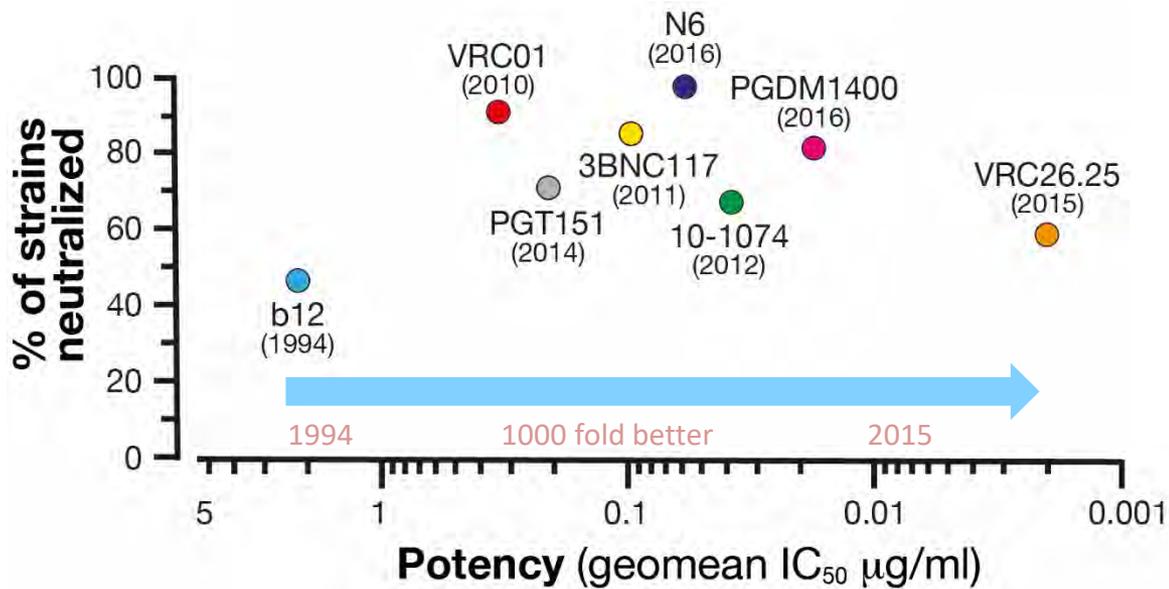
Figure 4: Top 10 drugs by sales, in 2018



Source: Urquhart L. (2019) Nat Rev Drug Discov.

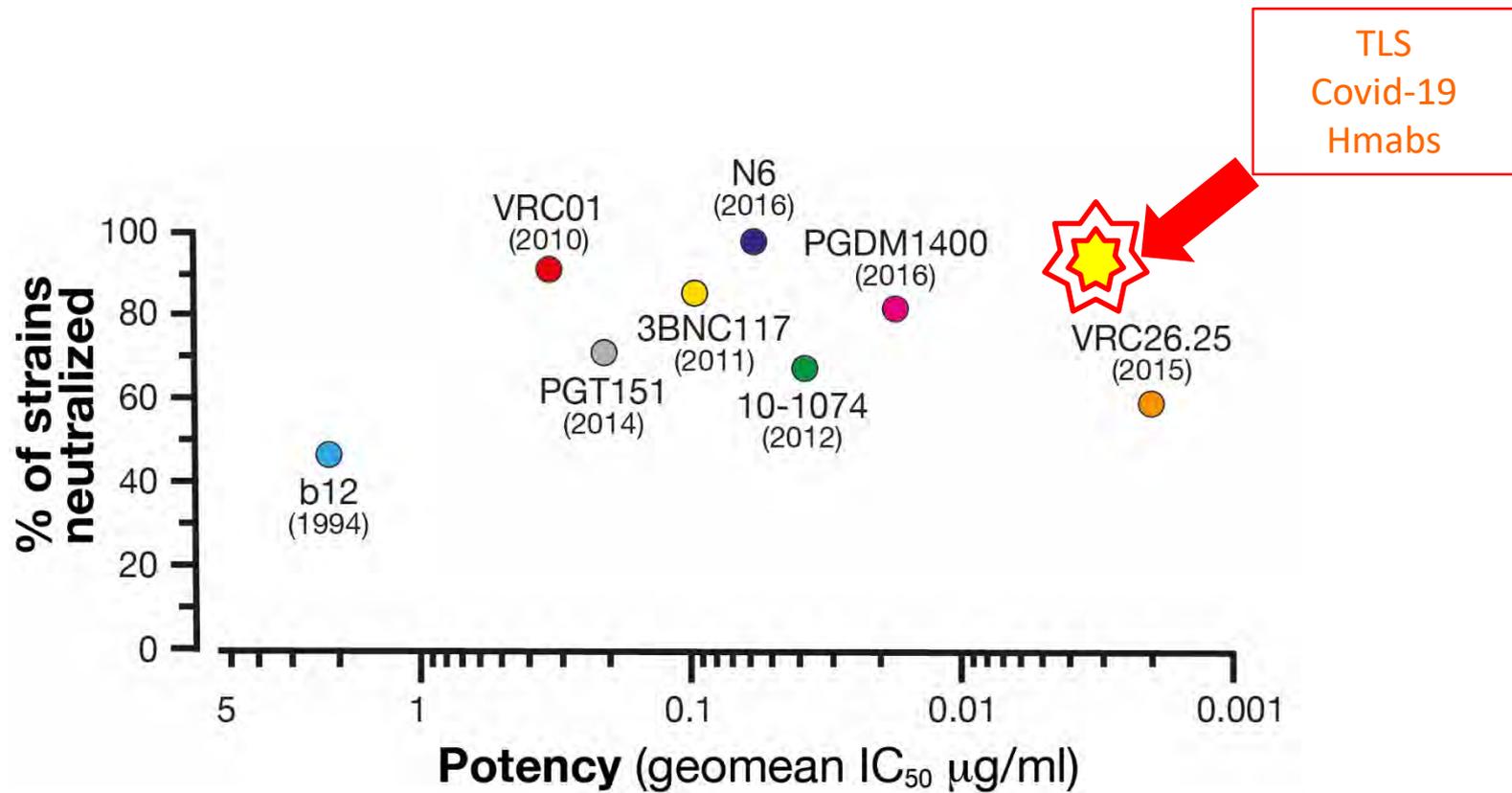
Technology for human monoclonal antibodies has improved more than 1000 times

The case of HIV



First Ebola drug approved by FDA

Extremely potent TLS Hmabs were isolated in less than 3 months



The importance of second generation human monoclonal antibodies

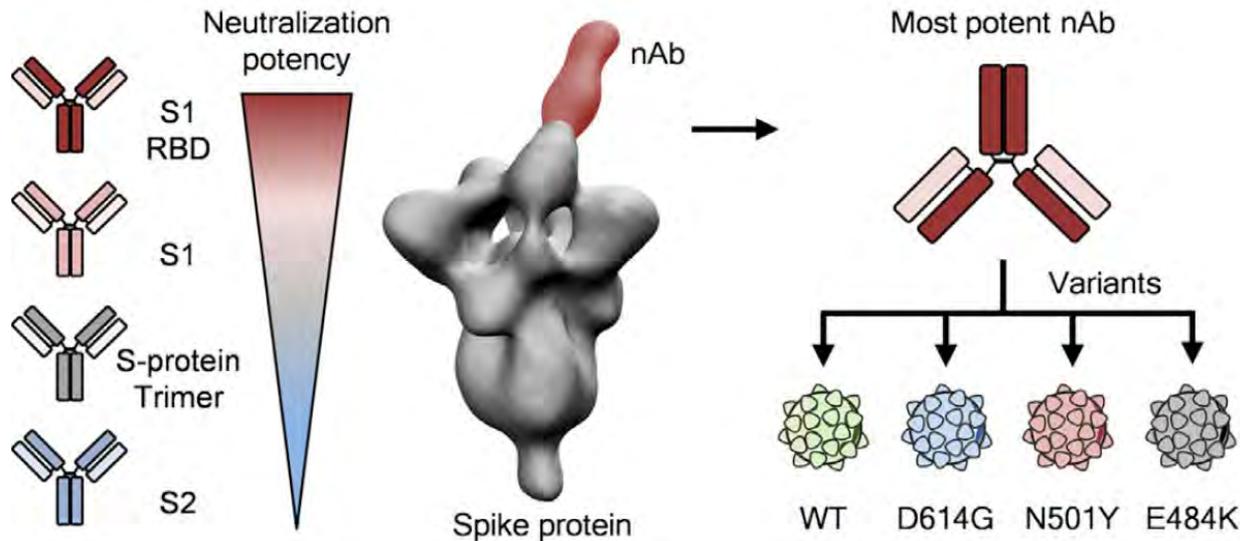
Human monoclonals used for therapy usually have low neutralizing potency (ranging from 100 ng/ml to 500 ng/ml or more). The TLS antibodies are very potent and neutralize the virus at less than 10 ng/ml. This allows to use a low therapeutic dose which can be administered also outside of the hospital environment

	Neutralizing potency (ng/ml)		Therapeutic dose	Administration
1 st gen	500		5 g	Intravenous infusion (hospital)
	100		1 g	Intravenous infusion (hospital)
2 nd gen	10	TLS Hmabs	0.1 g	im or sc (doctor office)

Extremely potent human monoclonal antibodies from COVID-19 convalescent patients

Emanuele Andreano,^{1,17} Emanuele Nicastri,^{4,17} Ida Paciello,¹ Piero Pileri,¹ Noemi Manganaro,¹ Giulia Piccini,² Alessandro Manenti,^{2,3} Elisa Pantano,¹ Anna Kabanova,^{1,11} Marco Troisi,^{1,9} Fabiola Vacca,^{1,9} Dario Cardamone,^{1,10} Concetta De Santi,¹ Jonathan L. Torres,¹⁶ Gabriel Ozorowski,¹⁶ Linda Benincasa,³ Hyesun Jang,¹³ Cecilia Di Genova,¹⁵ Lorenzo Depau,¹² Jlenia Brunetti,¹² Chiara Agrati,⁴ Maria Rosaria Capobianchi,⁴ Concetta Castilletti,⁴ Arianna Emiliozzi,^{5,6} Massimiliano Fabbiani,⁶ Francesca Montagnani,^{5,6} Luisa Bracci,¹² Giuseppe Sautto,¹³ Ted M. Ross,^{13,14} Emanuele Montomoli,^{2,3,7} Nigel Temperton,¹⁵ Andrew B. Ward,¹⁶ Claudia Sala,¹ Giuseppe Ippolito,⁴ and Rino Rappuoli^{1,8,18,*}

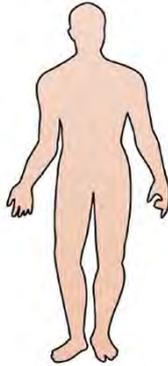
¹Monoclonal Antibody Discovery (MAD) Lab, Fondazione Toscana Life Sciences, Siena, Italy



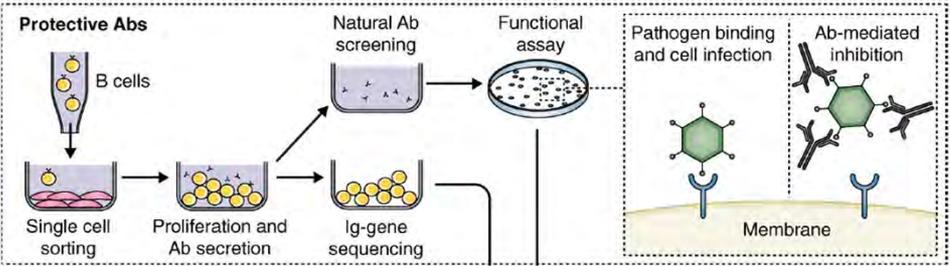
Isolating Covid-19 human monoclonal antibodies

Istituto
Spallanzani

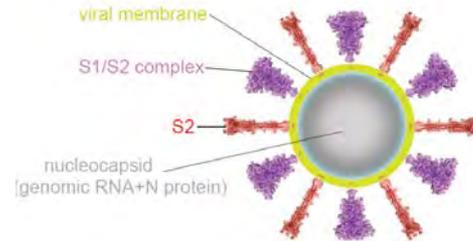
COVID-19
Convalescent
Patients



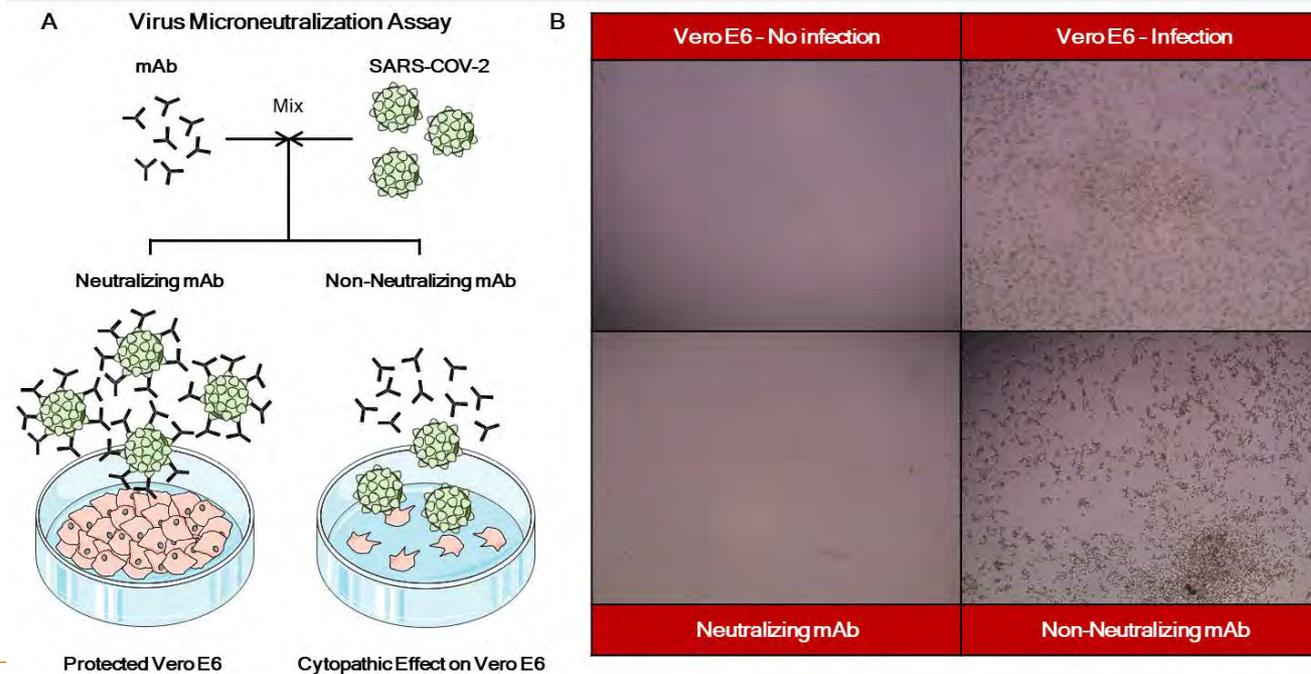
University of Siena
Hospital



Virus

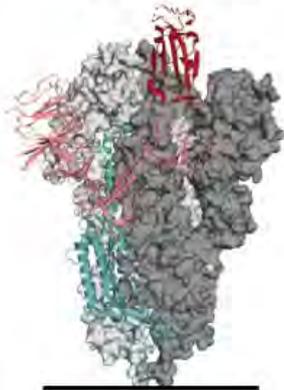


Cai *et al.*, *Science* **369**, 1586–1592 (2020) 25 September 2020



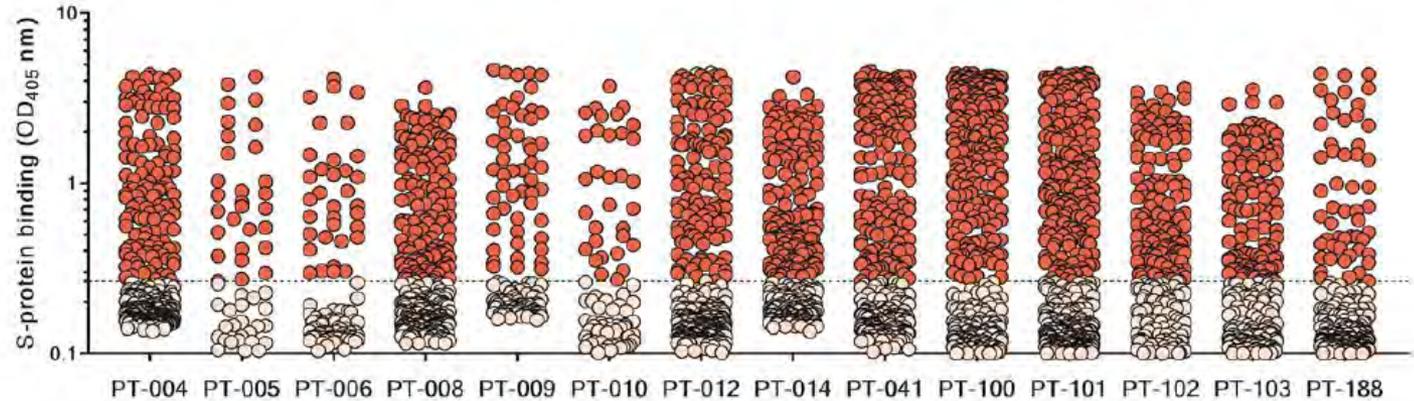
4277 B cells specific for SARS-Cov-2 spike

S-protein Trimer

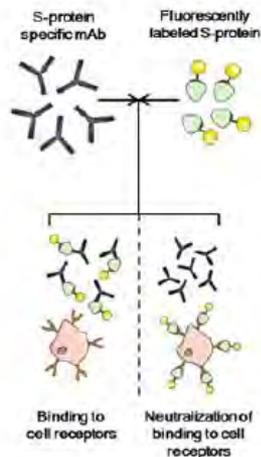


Viral Membrane

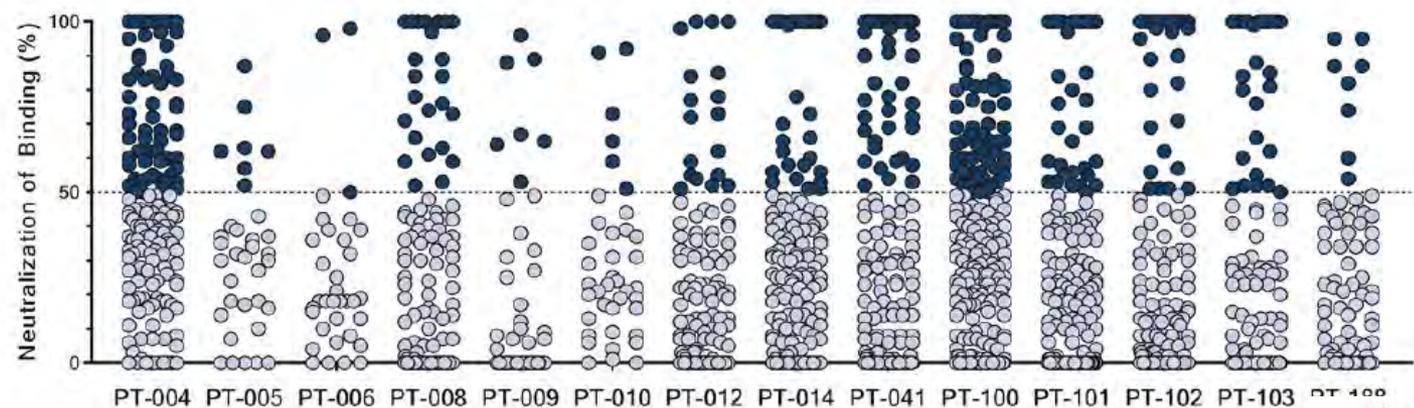
Monoclonal Antibodies Binding to SARS-CoV-2 S-protein prefusion trimer



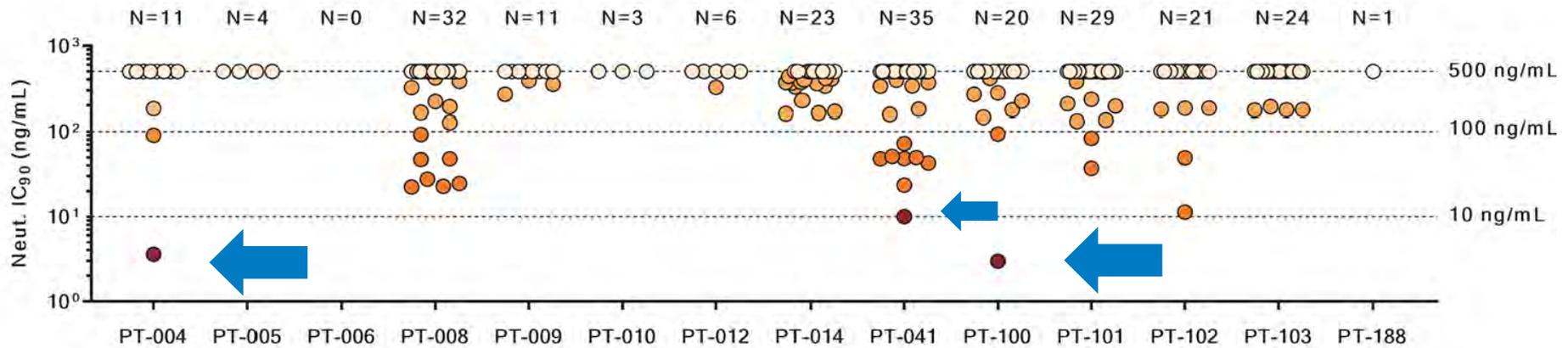
C



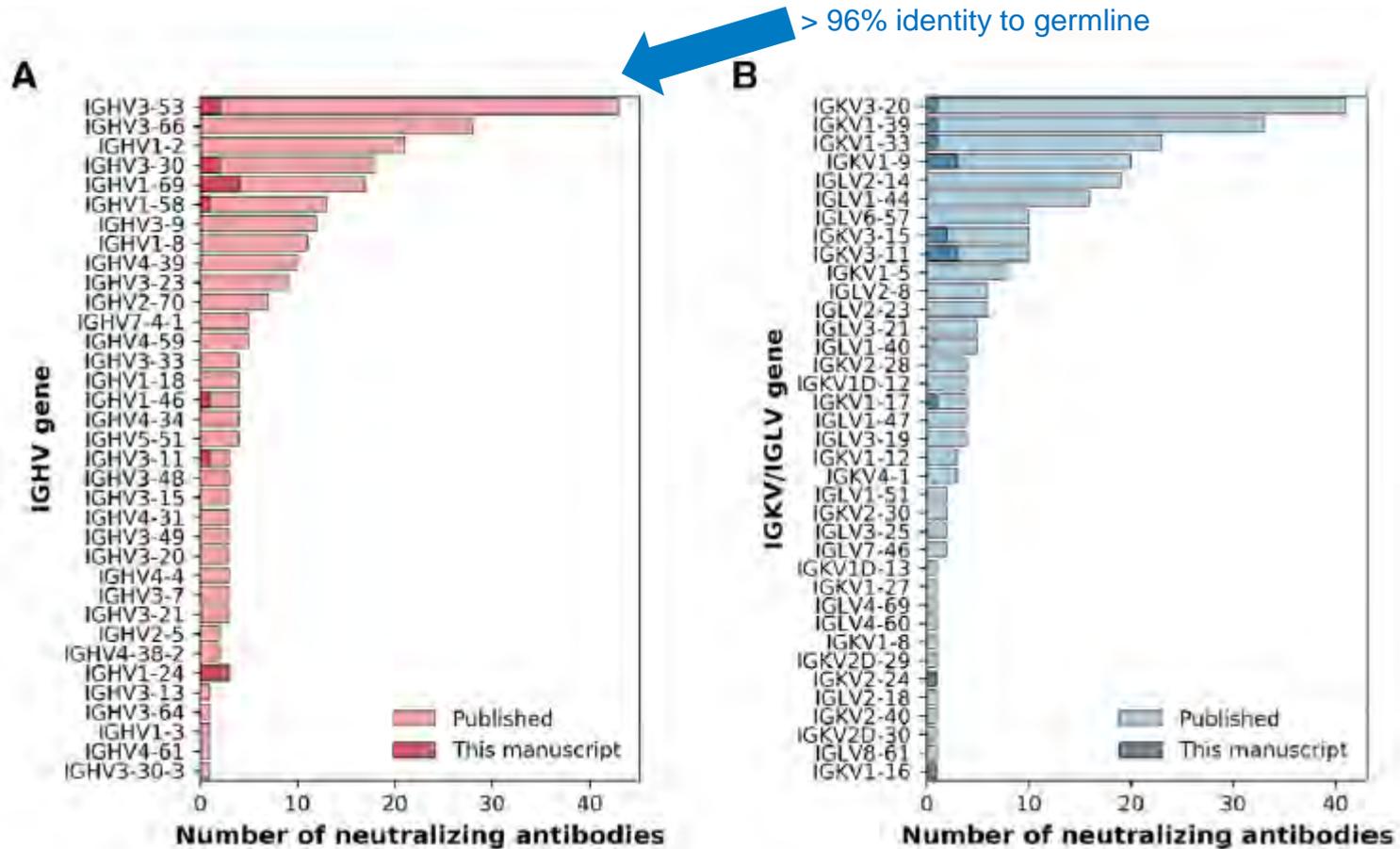
Monoclonal Antibodies Neutralization of S-protein Binding to Vero E6



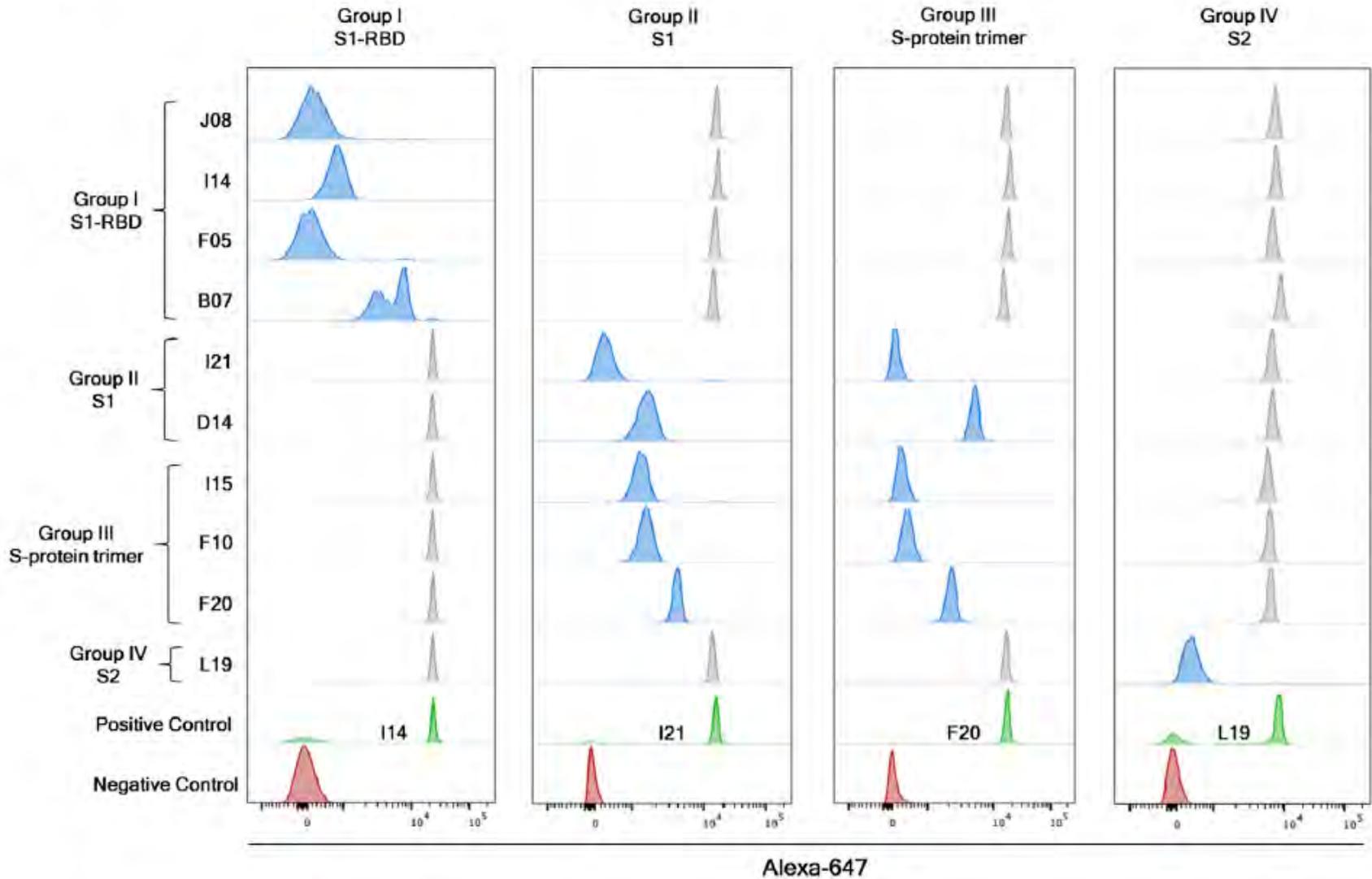
4277 B cells specific for Spike 453 produced neutralizing antibodies for SARS-Cov-2



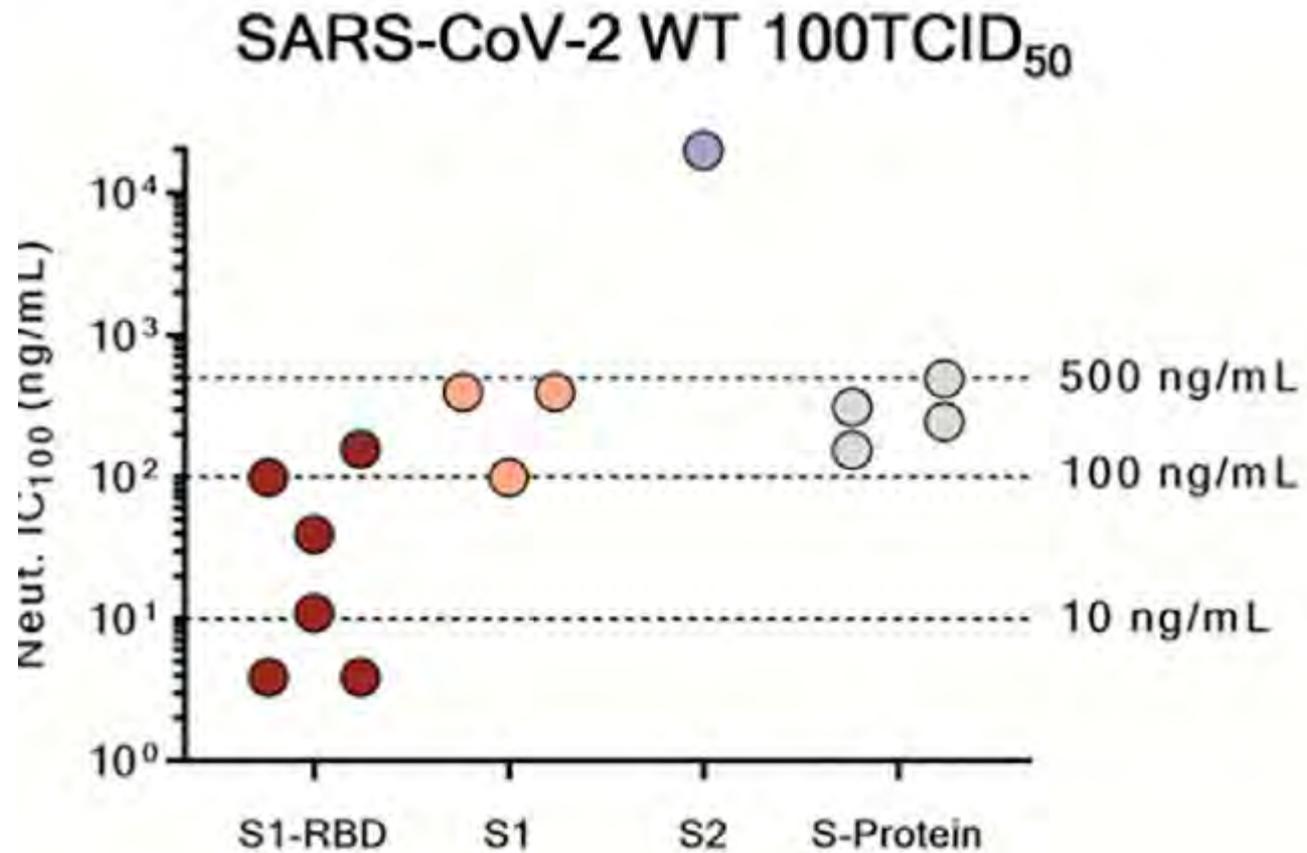
Neutralizing antibodies derive mostly from germline IGHV3-53 With very few somatic mutations



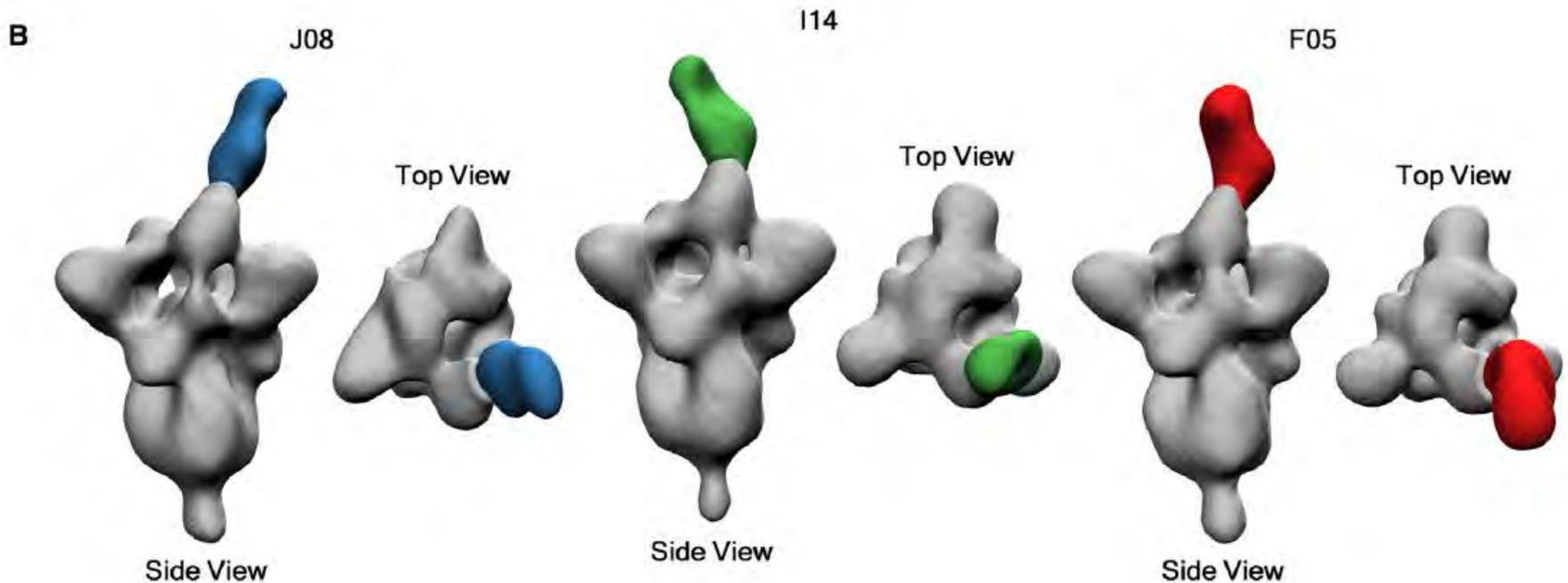
Neutralizing antibodies can be divided into four non competing groups



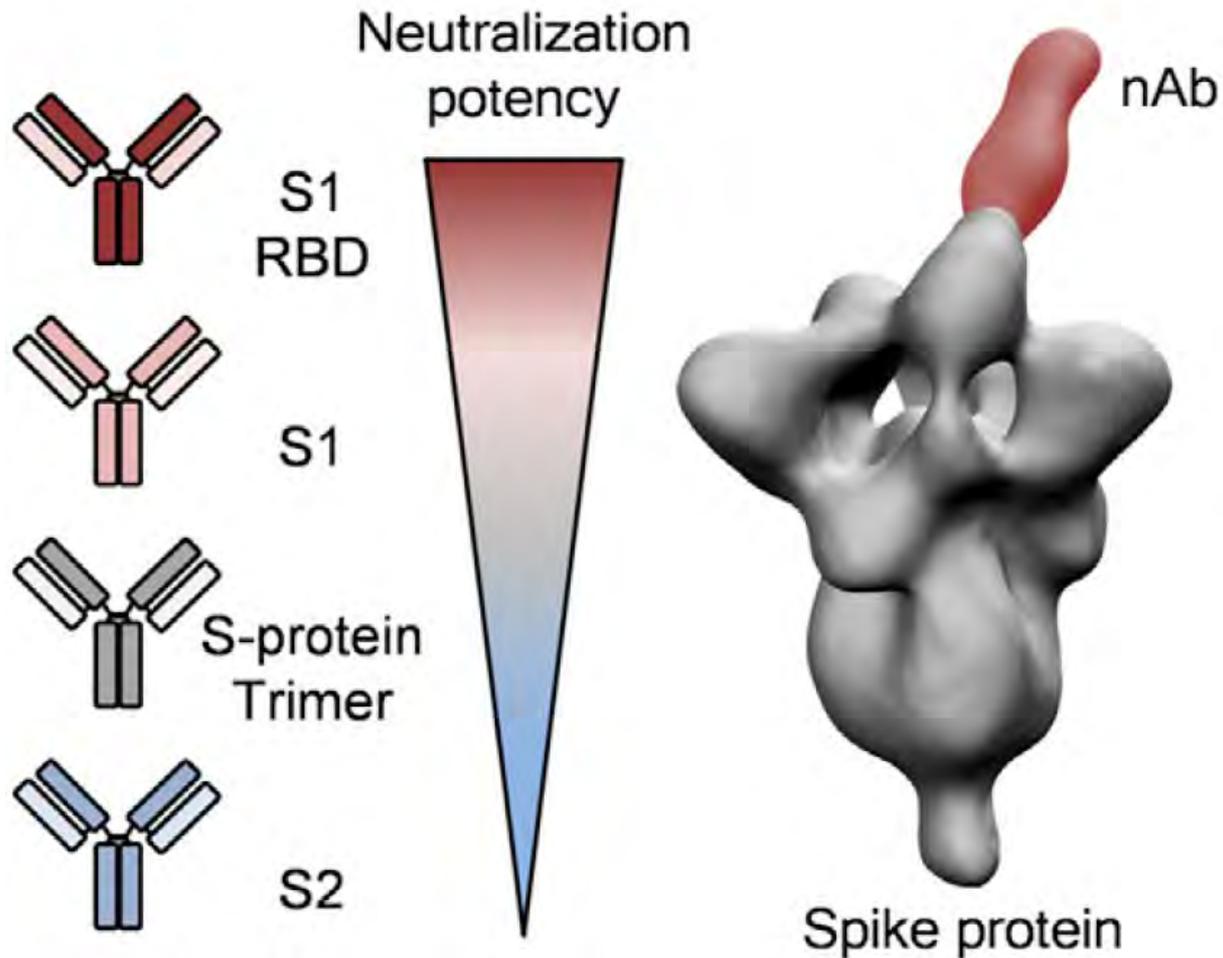
Most potent neutralizing antibodies bind RBD



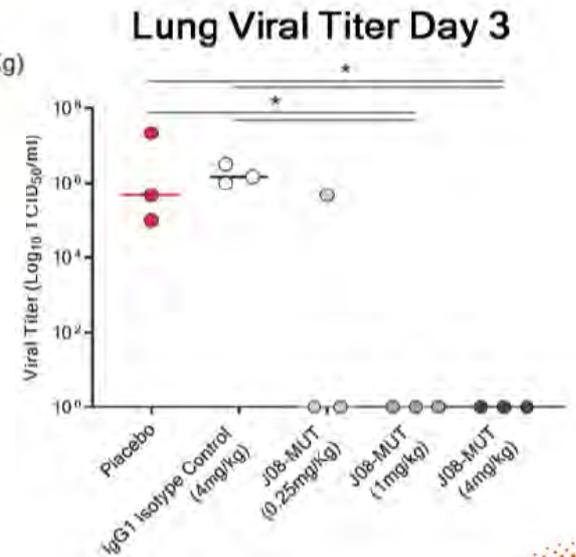
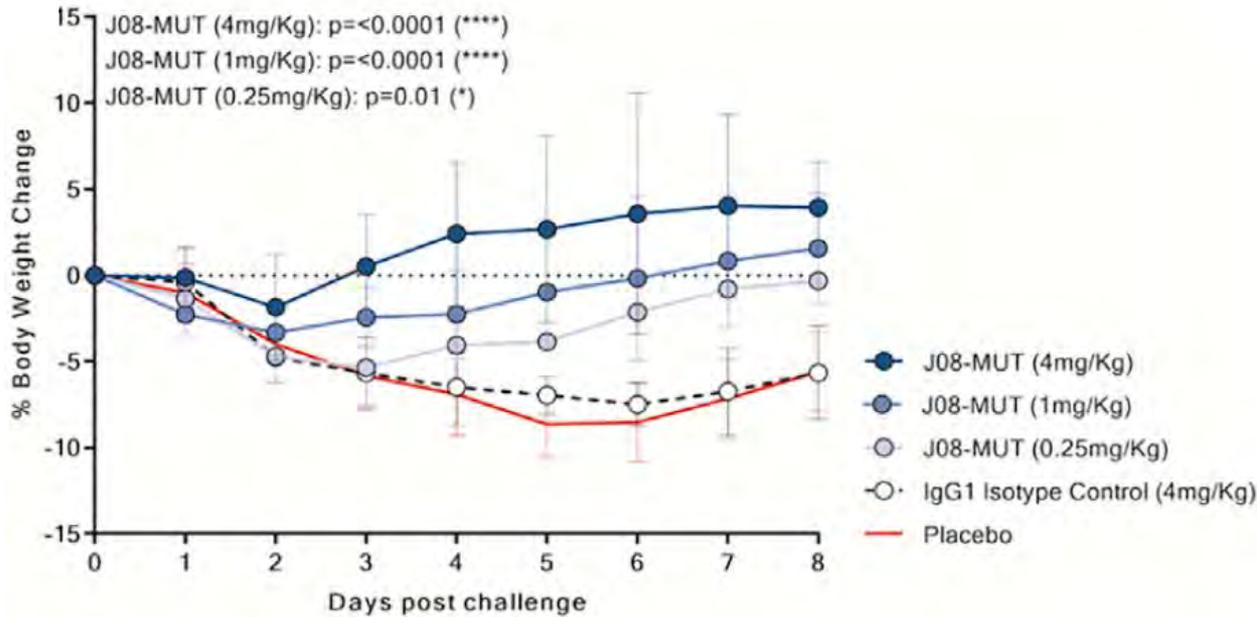
Most potent neutralizing antibodies bind RBD



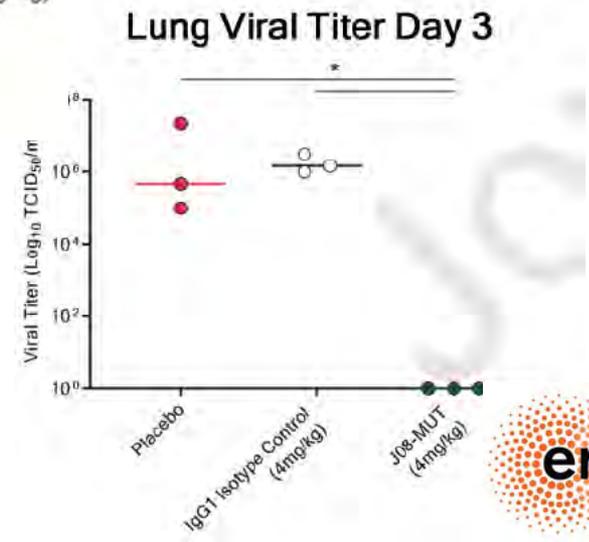
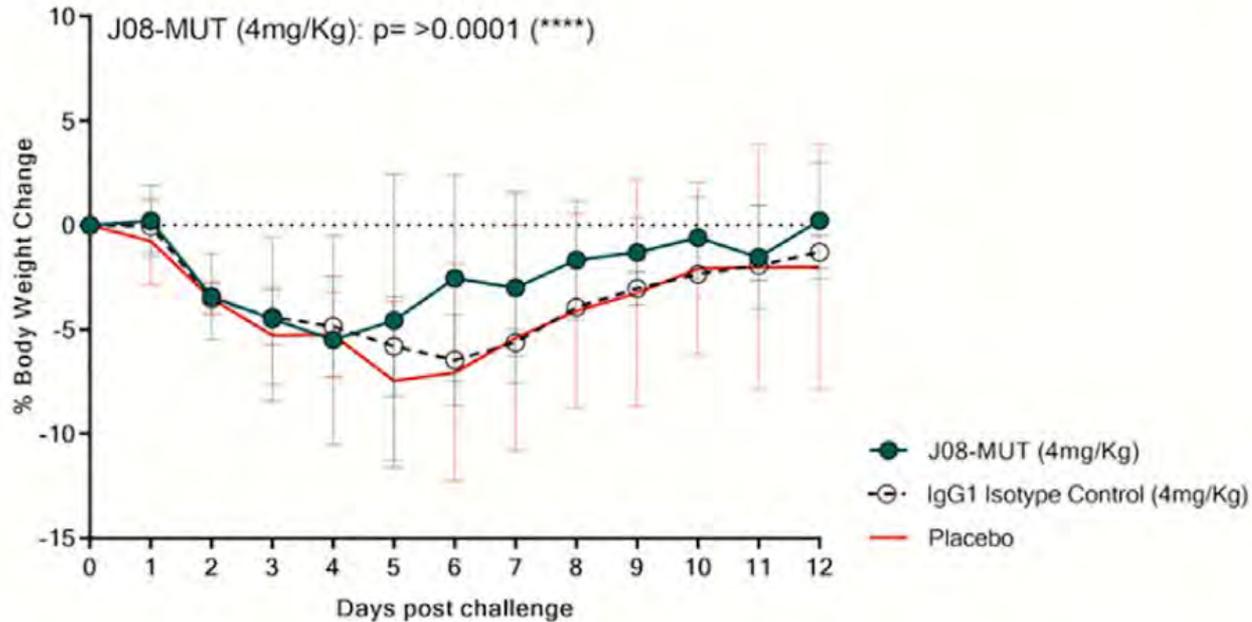
Most potent neutralizing antibodies bind RBD



J08 Prevention in hamsters with 0.25 mg/Kg

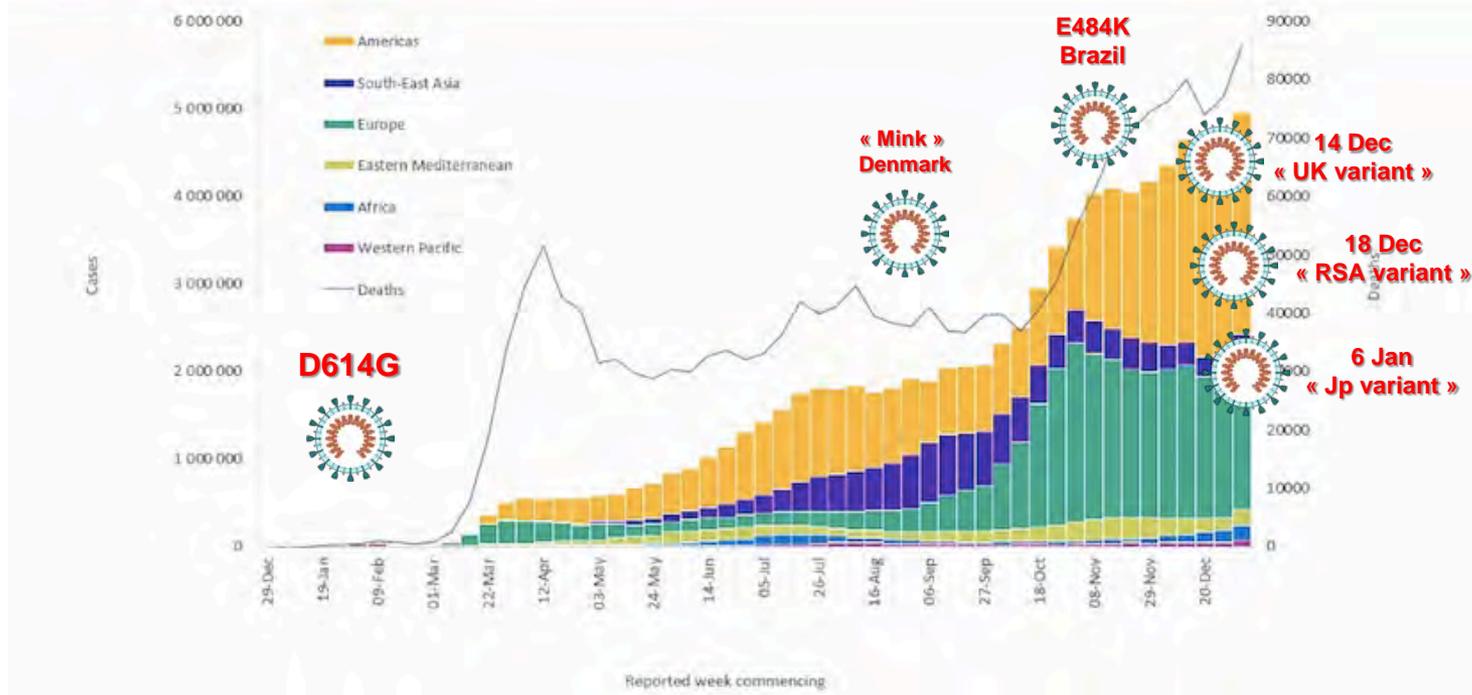


J08 Therapy in hamsters 4 mg/Kg

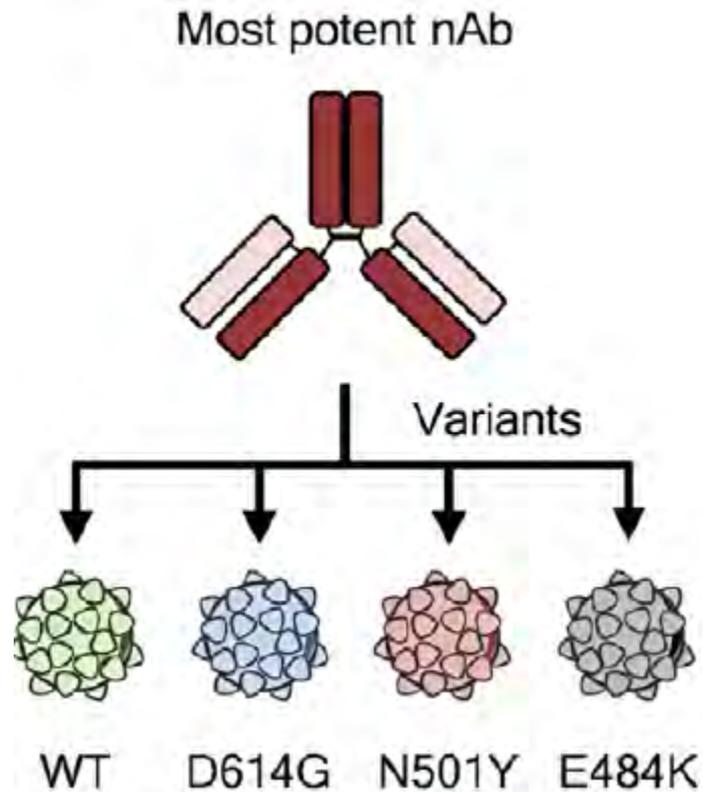


Historical emergence of SARS-CoV-2 variants

Global Situation: Weekly Overview (as of 10 January 10H CET)



J08 Neutralizes UK variant and E484K mutation of Brazilian and South African Variants



March 10th

press releases report efficacy in clinical trials

Eli Lilly 87% efficacy against hospitalization and death

March 10, 2021

- New data show therapy reduced risk of hospitalizations and death by 87 percent
- Second positive Phase 3 trial readout for bamlanivimab and etesevimab together
- Results support use of bamlanivimab 700 mg and etesevimab 1400 mg, the dose authorized in U.S. and several countries around the world

Vir/GSK 85% efficacy against hospitalization and death

The IDMC recommendation was based on an interim analysis of data from 583 patients enrolled in the COMET-ICE trial, which demonstrated an 85% ($p=0.002$) reduction in hospitalization or death in patients receiving VIR-7831 as monotherapy compared to placebo, the primary endpoint of the trial. VIR-7831 was well tolerated. As the trial remains ongoing and blinded with patients continuing to be followed for 24 weeks, additional results, including epidemiology and virology data, will be forthcoming once the trial is completed.



In 2021 Vaccines and Passive Immunization are going to give us back our Liberty



Vaccines and passive immunization are needed for our Liberty

Infectious Diseases take away our freedom

During the recent lockdown, Covid-19 took away our freedom to:

- go out
- walk
- work
- travel
- meet friends
- visit relatives
- Still we cannot travel freely, we need to wear masks, undergo swabs and quarantine

Vaccination freed mankind from the slavery of most infectious diseases of the past

The concept that infectious disease take away our freedom was suggested by Luca Carra during a recent discussion about the effects of Covid-19



MAD Lab Team



- Claudia Sala
- Emanuele Andreano
- Ida Paciello
- Piero Pileri
- Noemi Manganaro
- Elisa Pantano
- Marco Troisi
- Fabiola Vacca
- Dario Cardamone
- Anna Kabanova
- Concetta De Santi

Collaborators

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- Andrew Ward
- Jonathan Torres

University of Austin

- Jeson McLellan

University of Kent & University of Greenwich

- Nigel Temperton
- Cecilia Di Genova

University of Georgia

- Ted Ross
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