Institut Pasteur

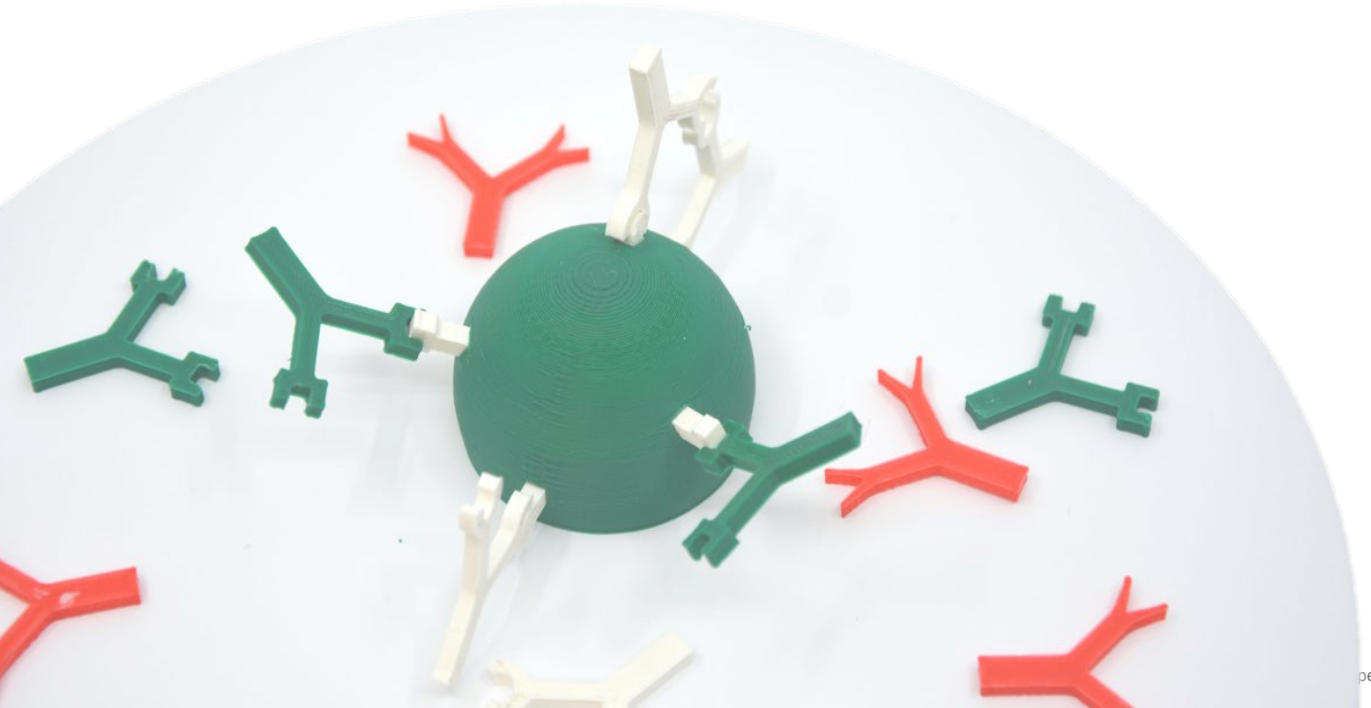
Virology

Evidence in support of the use of serum neutralisation data to justify a dose increase of monoclonal antibodies to tackle new variants

Timothée Bruel

December 15, 2022 @ EMA/FDA joint meeting

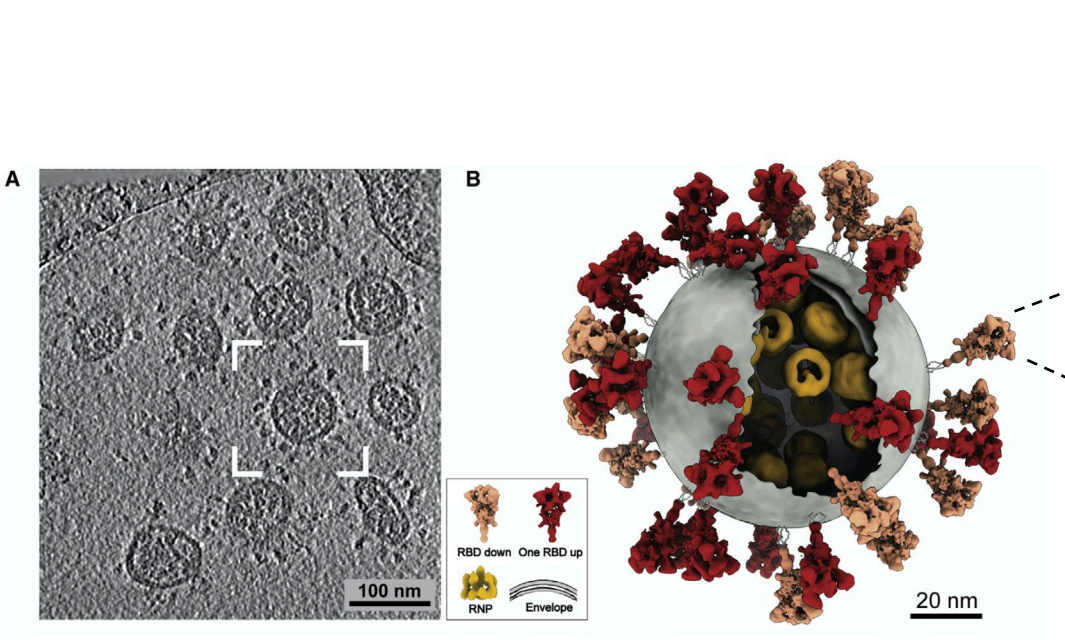
Virus and Immunity Unit
Olivier Schwartz's Lab

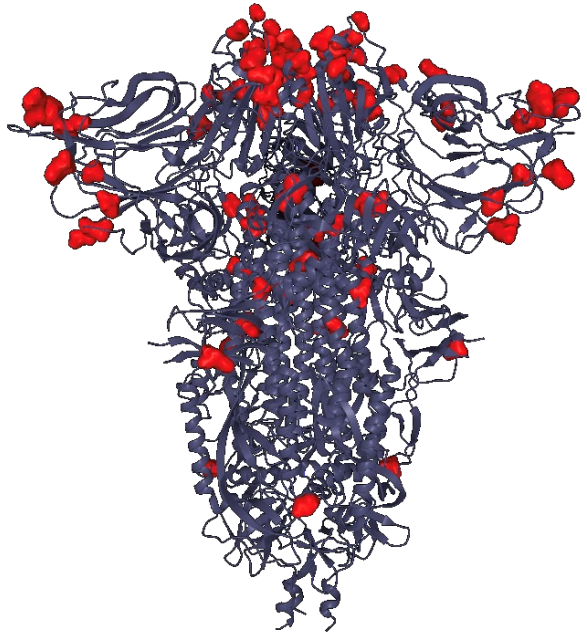


pean Medicines Agency${lf.End}

Credit: Albane Imbert, FabLab of the institute Pasteur

Neutralizing antibodies target SARS-CoV-2 spike





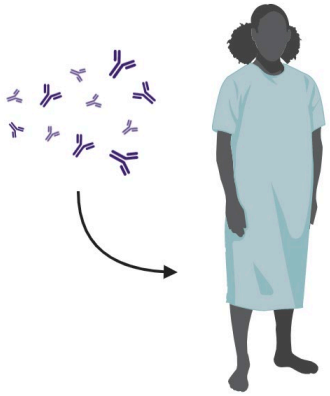
SARS-CoV-2 Omicron BA.1 spike

- Spike is the target of all known neutralizing antibodies
- Mutations promote immune evasion, infectivity and change tropism

Adapted from Yao et al., Cell 2020 and Harvey et al., Nat Rev Microbiol 2021

Therapeutic and prophylactic use of mAbs

Therapeutic



Patients with co-morbities

Casirivimab + Imdevimab (REGN-CoV-2)

Weinreich et al., NEJM 2021a
Weinreich et al., NEJM 2021b (relative risk reduction: 71.3%; P<0.001)
RECOVERY Collaborative Group., Lancet 2022

Sotrovimab (Xevudy™)

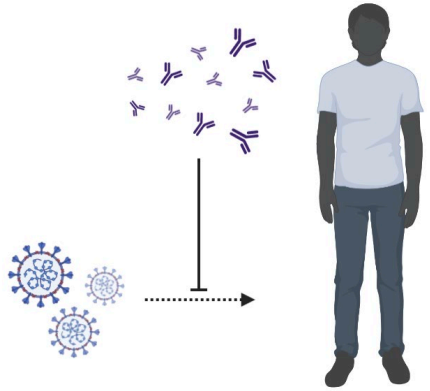
Gupta et al., NEJM 2021

(relative risk reduction: 85% (44-96); P=0.002)

Bebtelovimab

EUA by the FDA in February 2022

Prophylactic



Mostly Immunocompromised
(lack of vaccine immunogenicity)

Casirivimab + Imdevimab (Ronapreve™)

O'bien et al., NEJM 2021

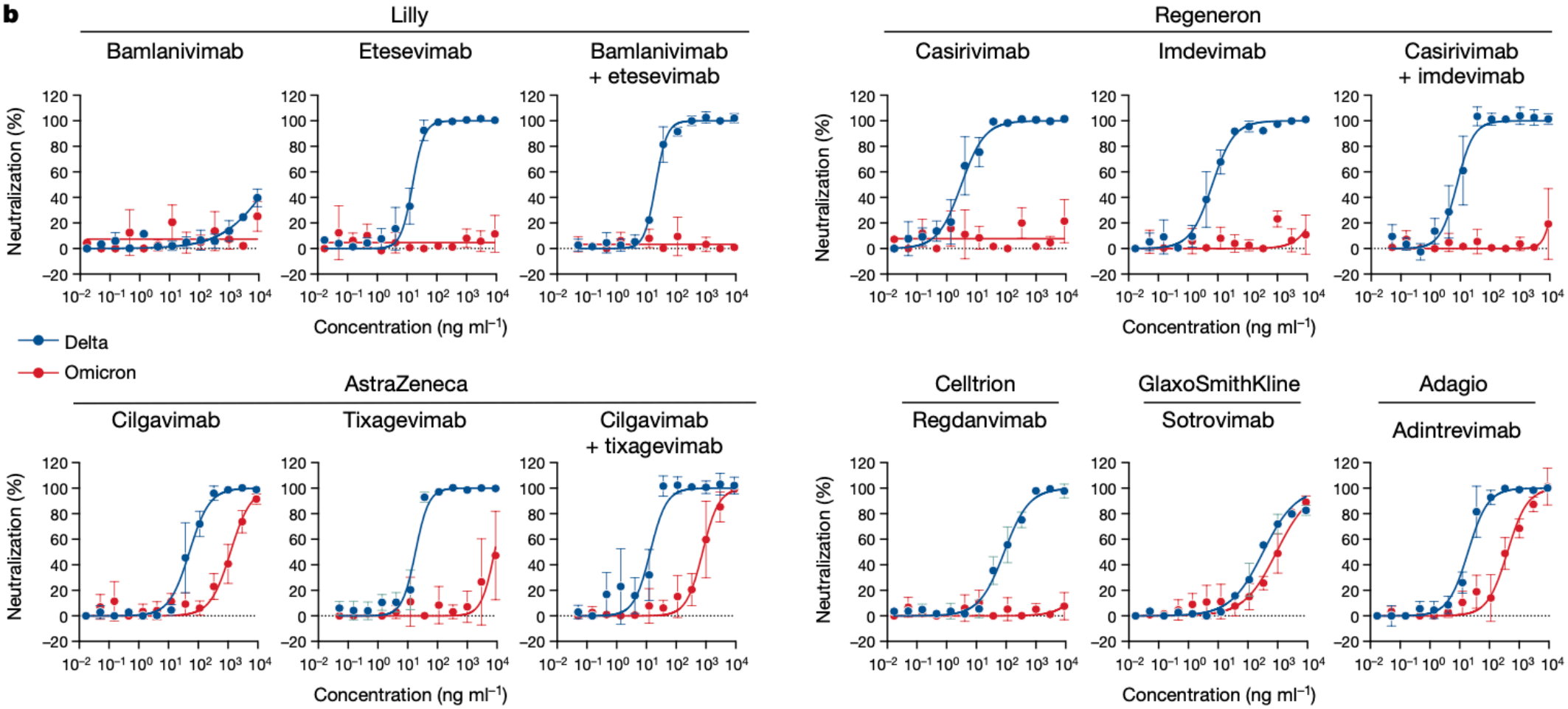
(relative risk reduction: 81.4%; P<0.001)

Cilgavimab + Tixagevimab (Evusheld™)

Levin et al. NEJM 2022

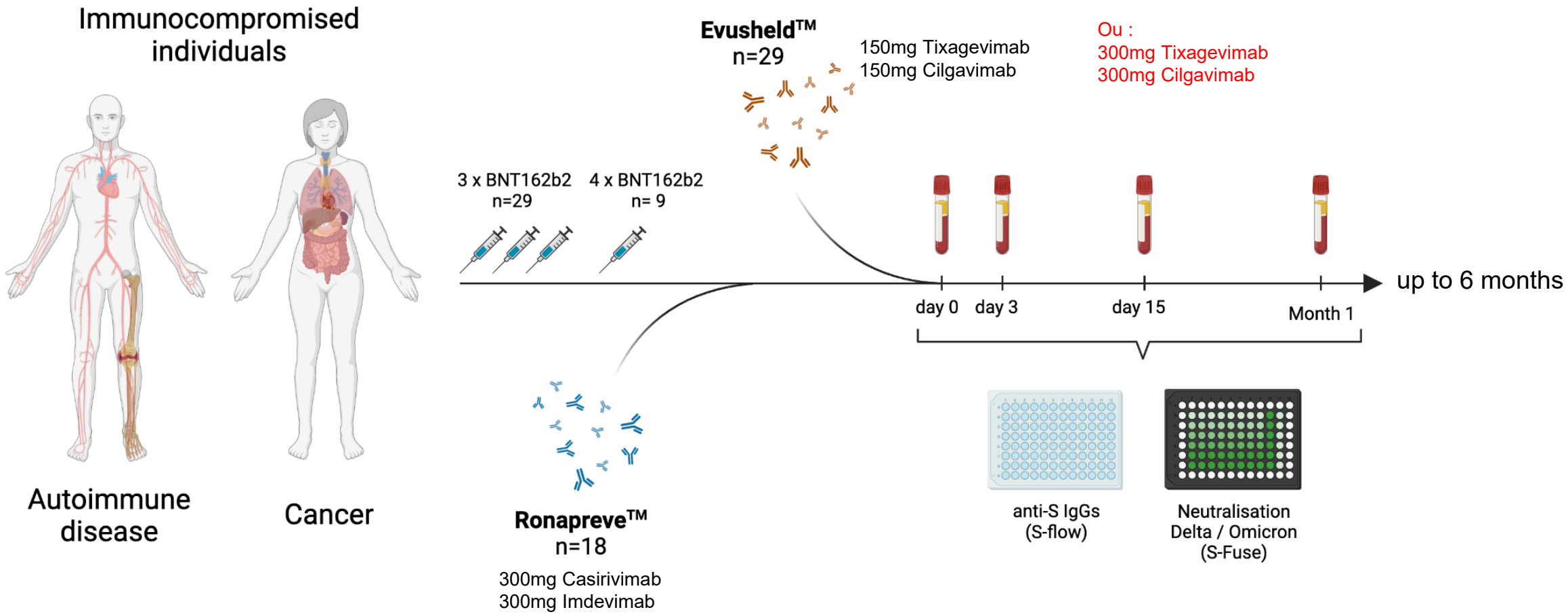
(relative risk reduction: 76.7%; P<0.001)

Neutralization activity of therapeutic mAbs



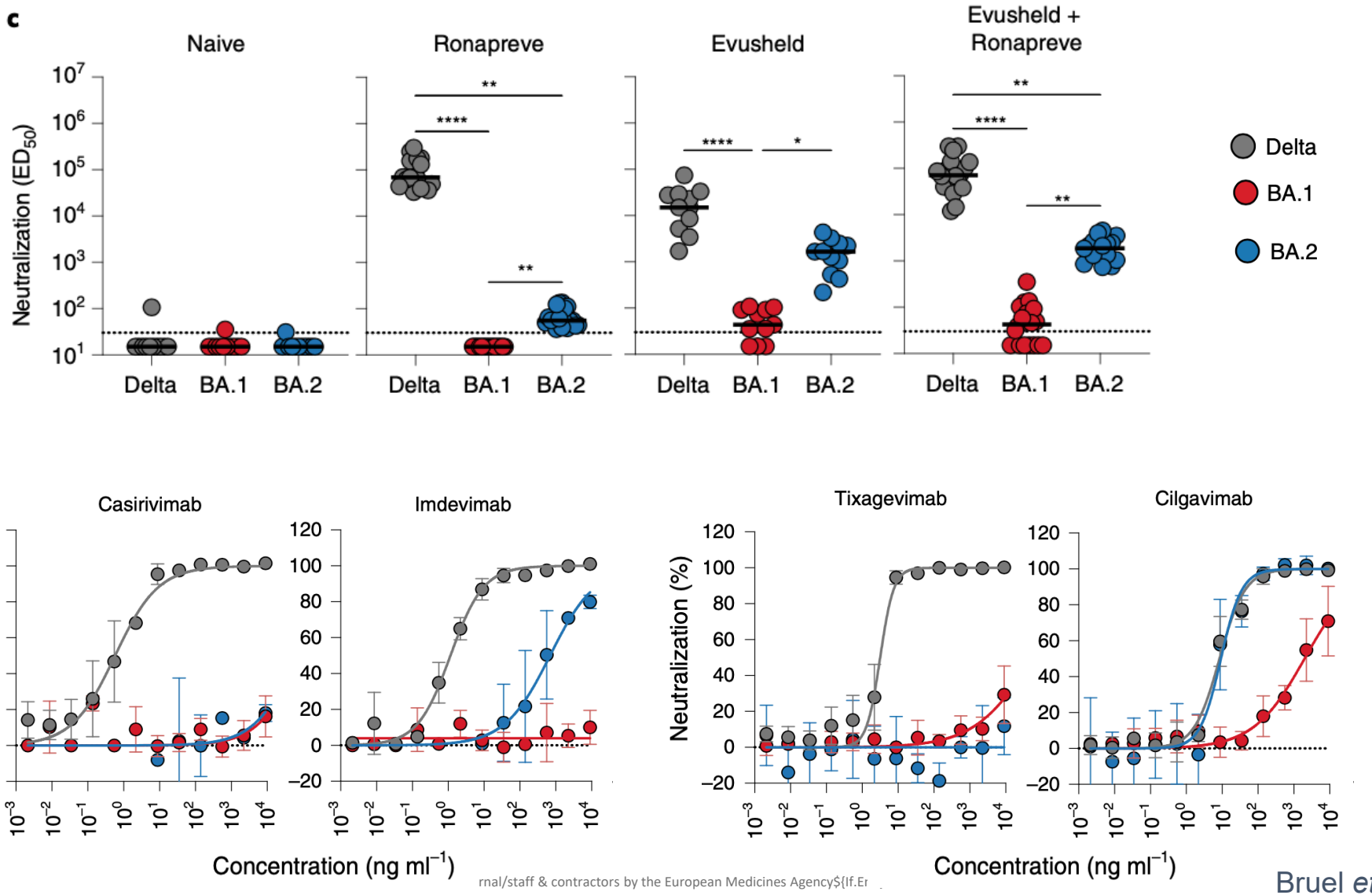
Planas *et al*, Nature 2022

Which levels of neutralization is provided by mAbs in vivo?



Cohorts : PNAS (CHR Orléans – **Thierry Prazuck**) and COVADIS (Hôpital Cochin – **Benjamin Terrier**)

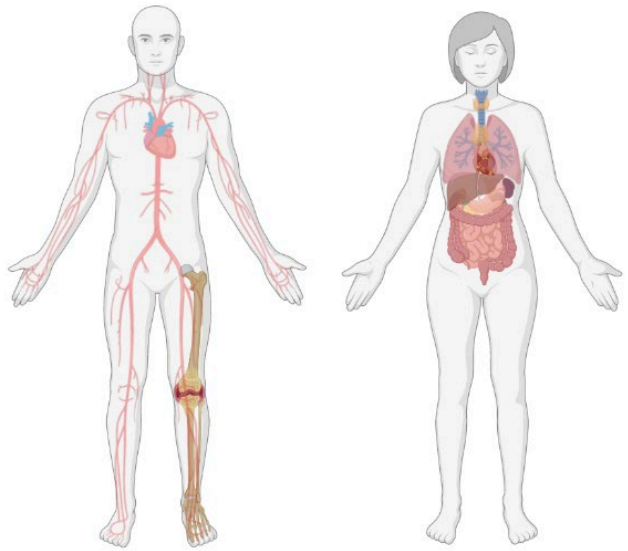
Limited neutralization of BA.1 in sera of Evusheld recipients.



Bruel *et al*, Nat Med. 2022

Antibody levels in sera after mAbs administration

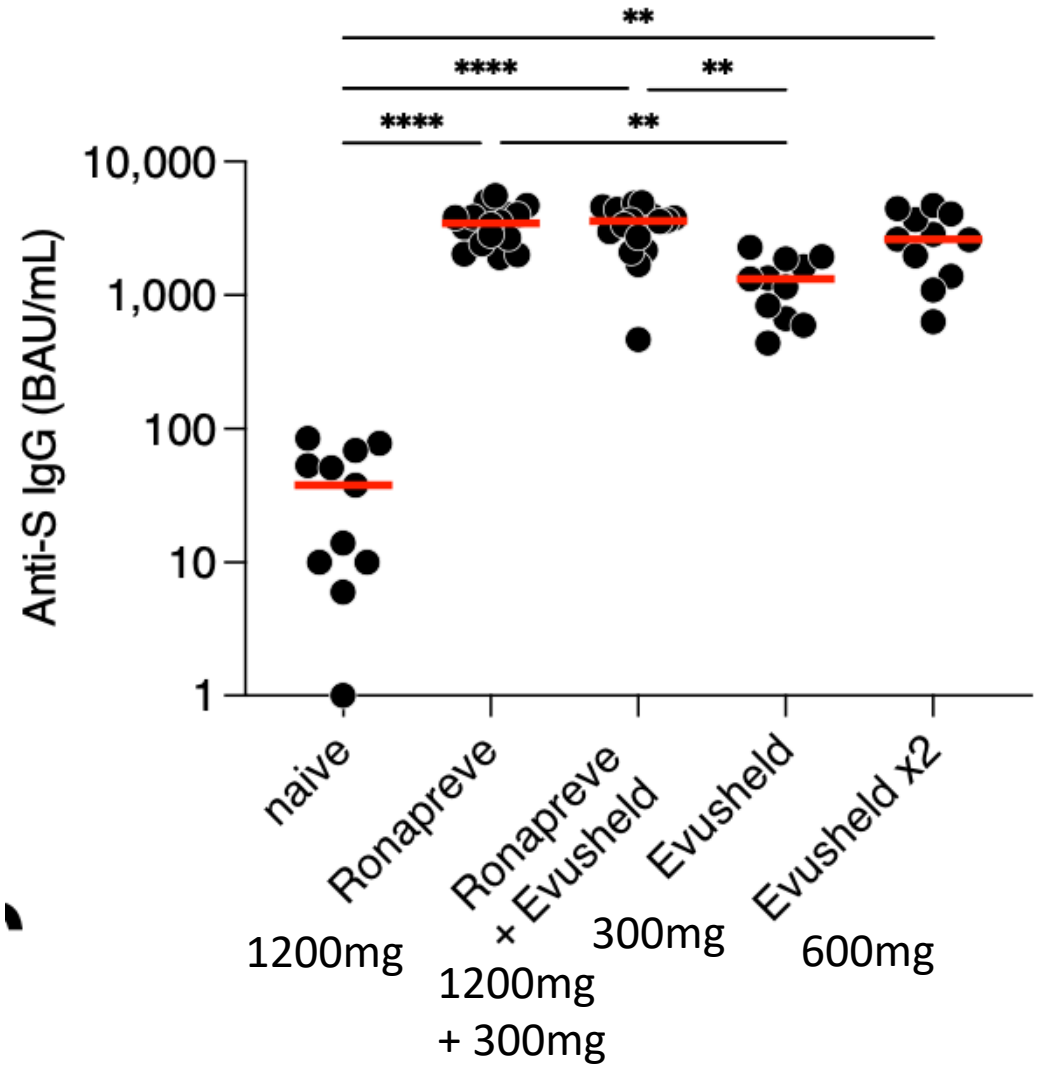
Immunocompromised individuals



Autoimmune disease

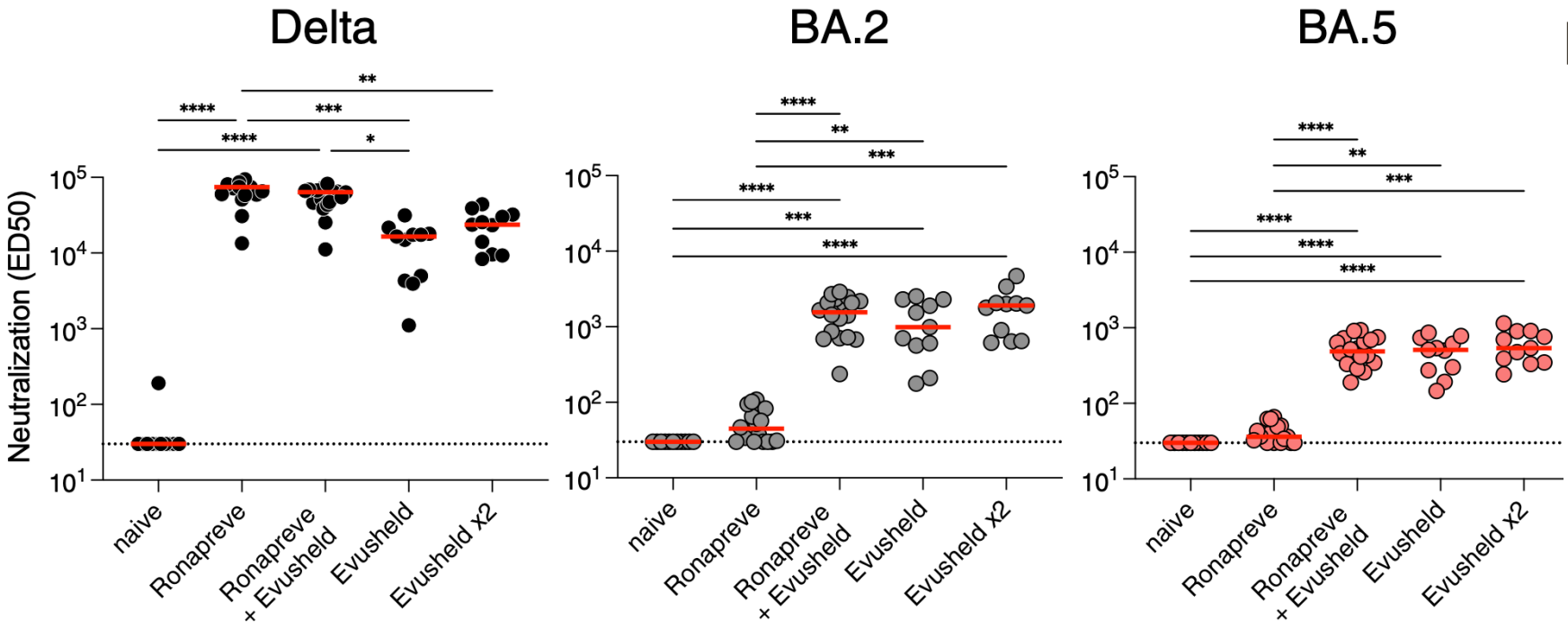
Cancer

n = 40

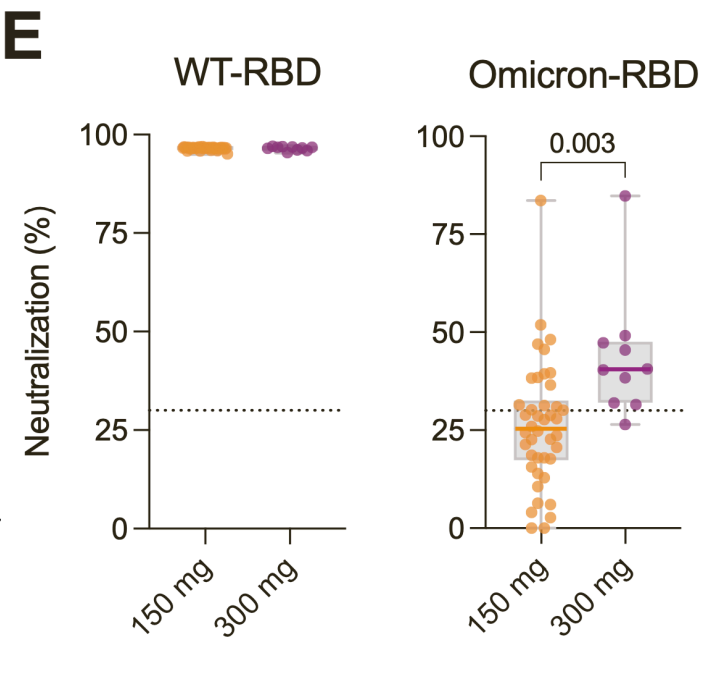


Bruel *et al*, Cell Rep Med. 2022

Serum neutralization in sera after mAbs administration

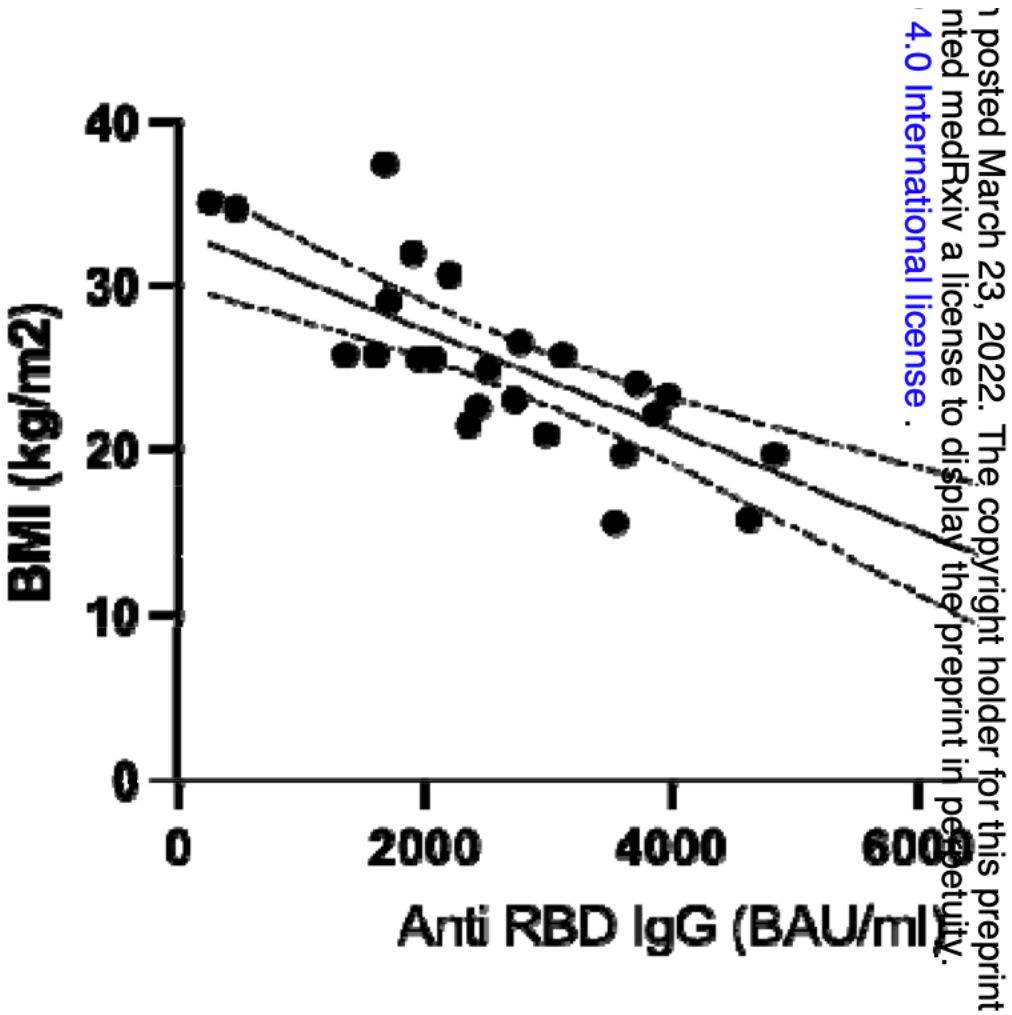


Bruel *et al*, Cell Rep Med. 2022



Stuver *et al*, Cancer Cell. 2022

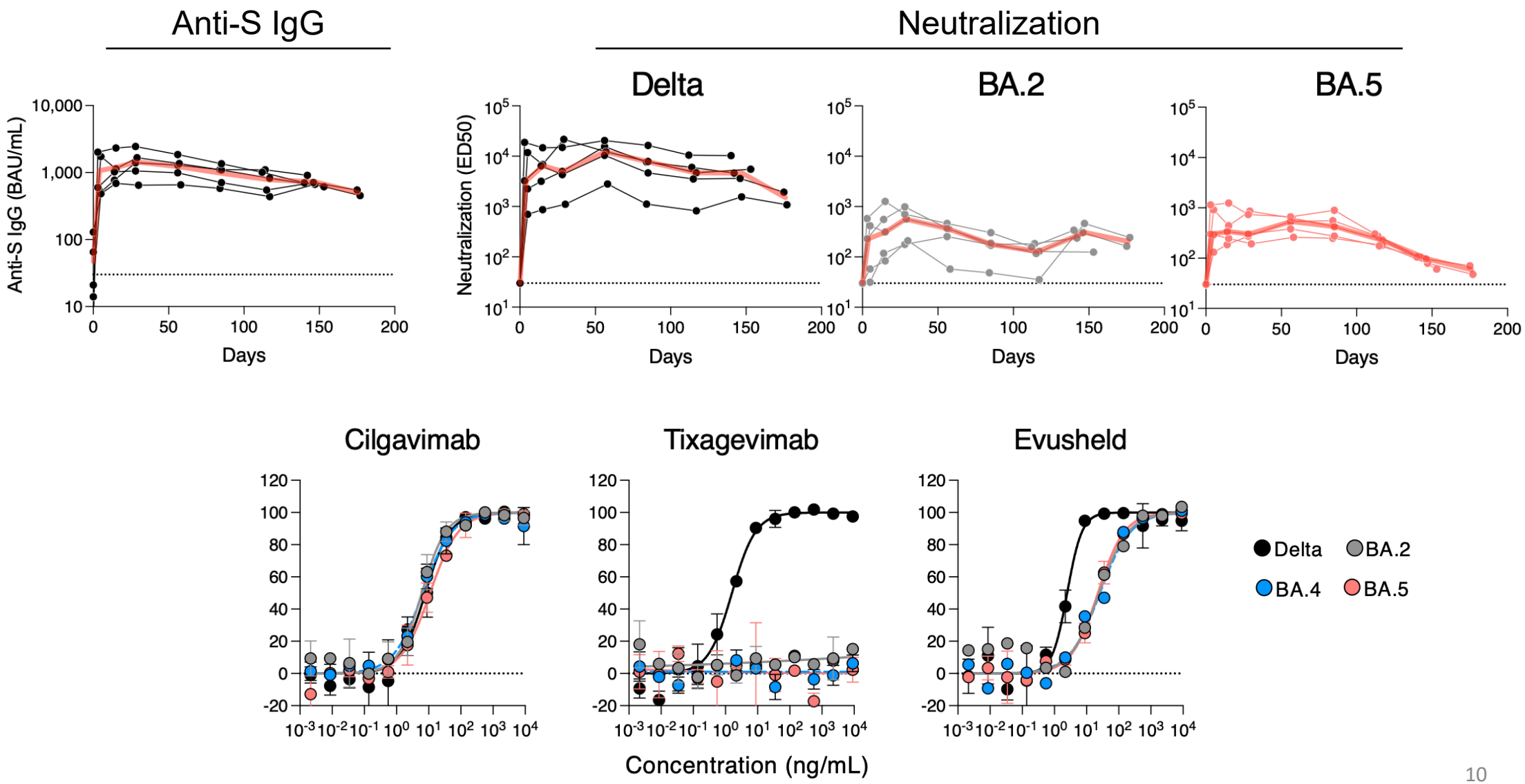
Body mass index influences antibody levels



Benotmane *et al*, MedrXiv. 2022

Adapting the dose to BMI?

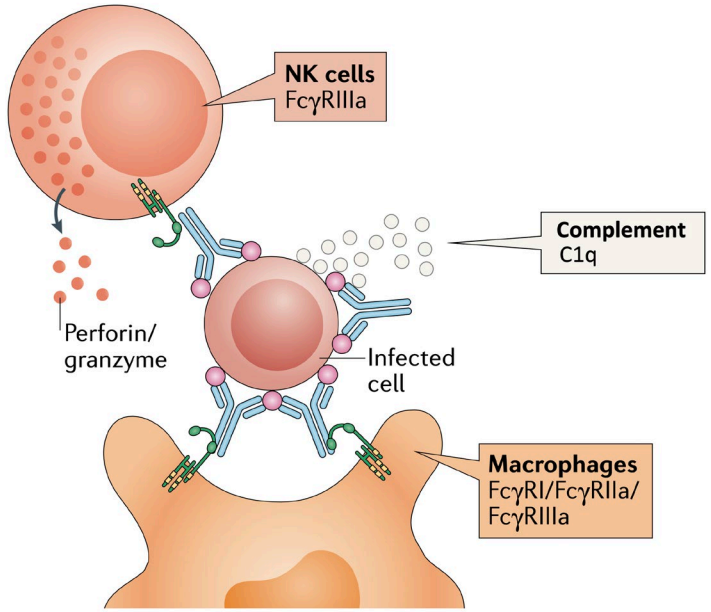
Longitudinal analysis of mAbs support the use of booster doses



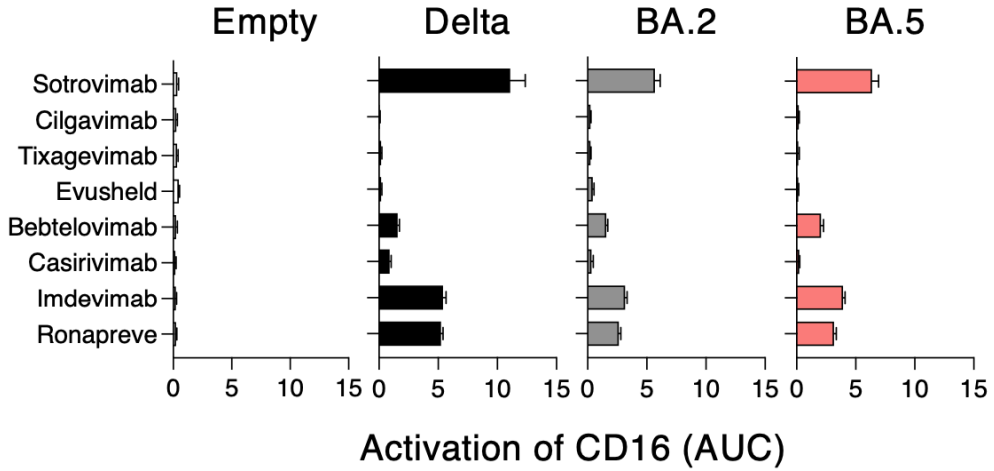
Bruel *et al*, Cell Rep Med. 2022

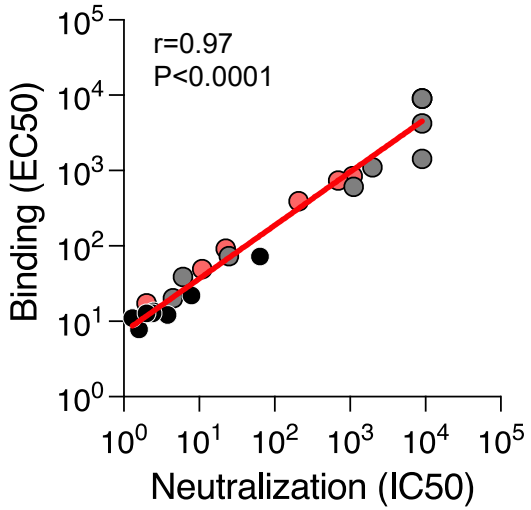
Fc-effector functions of therapeutic mAbs

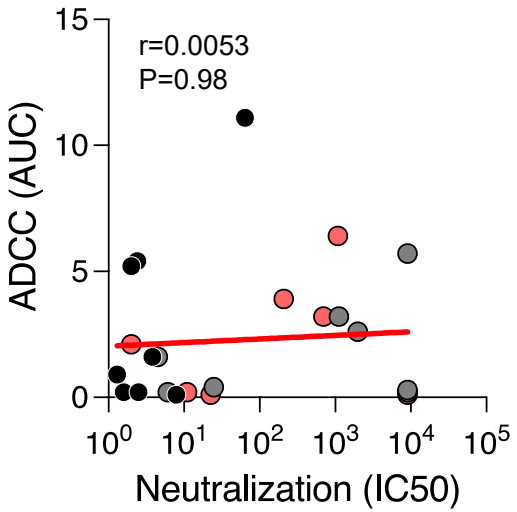
Fc-effector functions

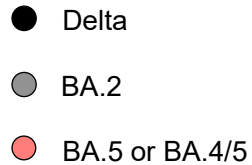


Adapted from Bournazos et al., Nature 2020



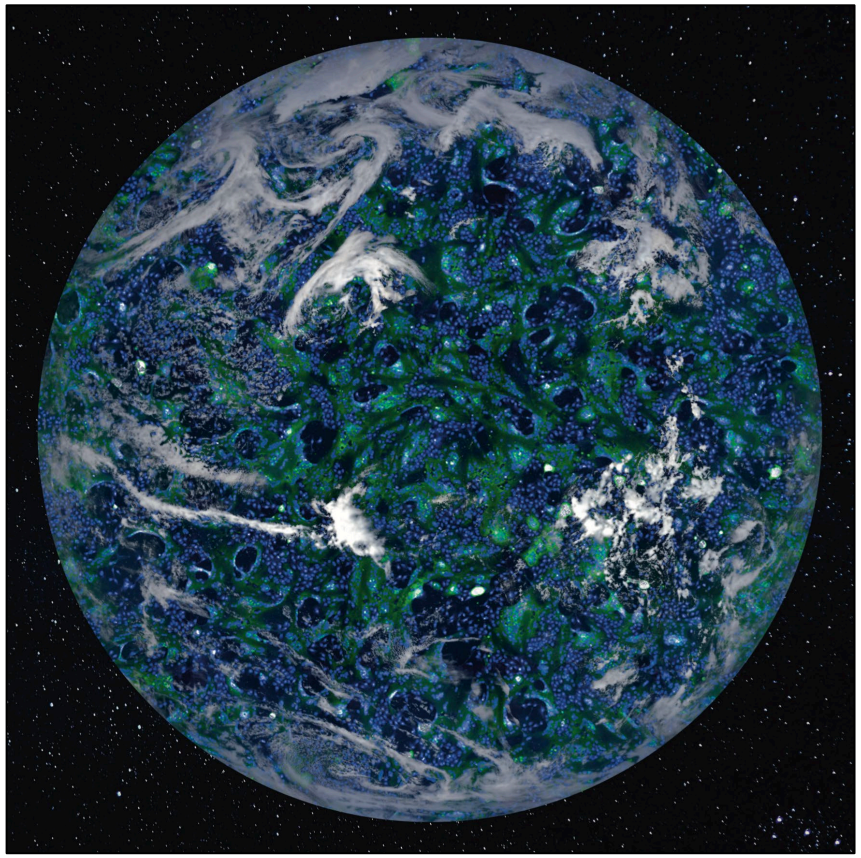






Bruel *et al*, Cell Rep Med. 2022

Conclusions



Credit: Nell Saunders, Delphine Planas, Timothée Bruel and Olivier Schwartz

- Serum neutralization revealed a lack of BA.1 neutralization on Evusheld.
- Doubling Evusheld dose increased antibody levels and neutralization.
- **Serum neutralization consider *in vitro* potency, dose and half-life.**
- Sotrovimab is the best ADCC inducer, despite limited binding.

A comprehensive evaluation of mAbs functions and bio-disponibility (dose and half-life) is required.

Acknowledgements

Virus and Immunity

Olivier Schwartz
Nico Casartelli
Françoise Porrot
Florence Guivel-Benhassine
Isabelle Staropoli
Delphine Planas
Mathieu Hubert
Julian Buchrieser
Nell Saunders
William-Henri Bolland
Mariem Znaidia
Lou-Léna Vrignaud
Augustin Martin
Lisa Chakrabarti
Raphael Jeger-Madiot
Martin Groznica
Isma Ziani
Jocelyne Creff

Jérémy Dufloo
Ludivine Grzelak
Donatella Tonuitti
Jérome Kervevan
Stacy Gellenoncourt

Spring 2022

Acknowledgements

Humoral Response to Pathogen

Hugo Mouquet
Cyril Planchais
Valérie Iorin

Dartmouth University

Margaret Ackerman
Benjamin Goldberg

Oregon National Primate Research Center

Ann Hessell
David Spencer

Center for translationnal Research

Bruno Hoen
Camille Besombes
Marie-Noëlle Ungeheur
Guillaume Melon
Pascal Morel
Simon Rolland
Sandrine Fernandes-Pellerin
Nathalie Jolly
Charlotte Renaudat

Pasteur-Theravectys

Pierre Charneau
Francois Anna
Philippe Souque

UPV-CNR

Sylvie Van der Werf
Sylvie Behillil
Vincent Enouf
Caroline Demeret
Mélanie Albert
Kuang-Yu Chen
Bernadette Crescenzo
Flora Doanti

Emerging Diseases Epidemiology

Arnaud Fontanet
Laura Tondeur
Yoan Madec
Rebecca Grant

Institut Pasteur (various units)

Arnaud Echard
Stéphane Frémont
Etienne Simon-Lorrière
Mathieu Prot
Félix Rey
Jim Di Santo
Darragh Duffy
Philippe Bousso
Maxime Chazal
Christele Huon
Marion Gransagne
Jacques Bellalou
Mireille Nowakowski
Stéphane Petres
Marija Bakovic
Audrey Lemaitre
Marie-Aude Creach
Nicolas Escriou
Ferdinand Roesch
Marc Eloit
Sarah Temmam

AP-HP

HEGP
Hélène Péré
David Veyer

Cochin
Jérome Hadjadj
Yan Nguyen
Benjamin Terrier

Bichat
Quentin le Hingrat
Diane Descamps
Yazdan Yasdanpanah

Hopital du Kremlin-Bicêtre - APHP

Olivier Lambotte
Katia Bourdic

Hopitaux Universitaire de Strasbourg

Samira Fafi-Kremer

CHR d'Orléans

Thierry Prazuck
Laurent Hocqueloux
Aymeric Sève

UZ/KU Leuven

Emmanuel André
Piet Maes

CHU de Tours

Karl Stéfic

All Patients and cohort participants

Thank you !

pean Medicines Agency${lf.End}

Credit: Albane Imbert, FabLab of the institute Pasteur

More 3D-printed things:
https://3dpasteur.wordpress.com