

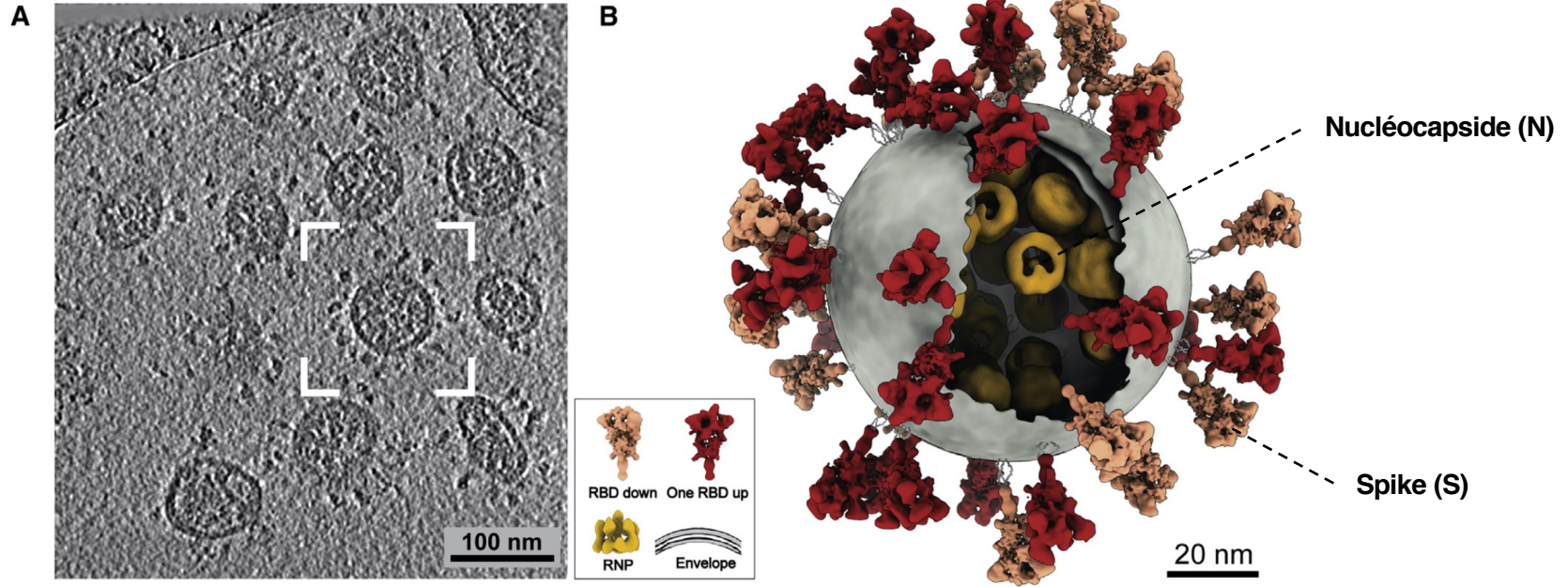
Exploration des mécanismes de mutation virale : clés pour anticiper les nouveaux variants et prédire le risque infectieux

Timothée Bruel, PhD, HDR

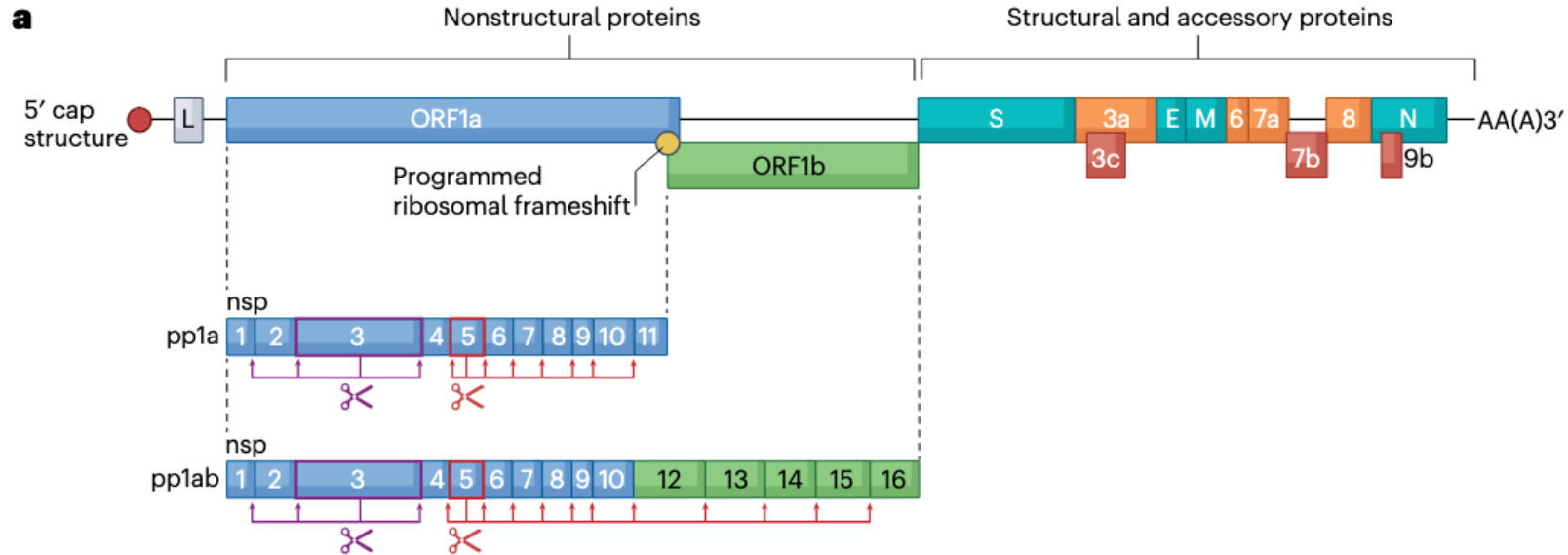
Déclaration d'intérêt de 2014 à 2023

Co-inventeur d'anticorps anti-RBD (PCT/FR2021/070522).

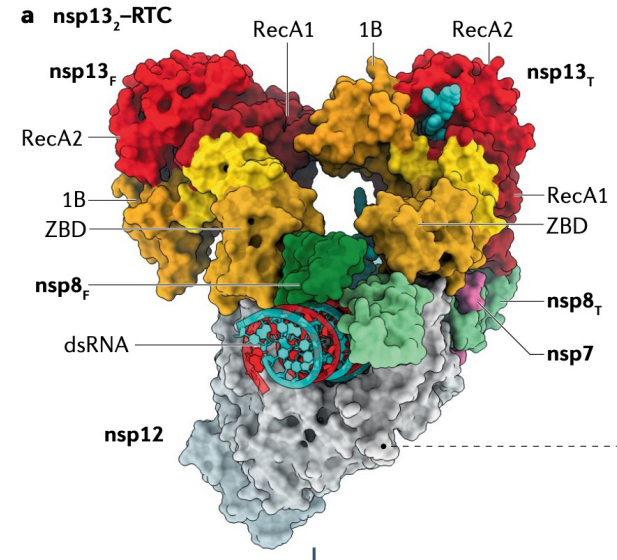
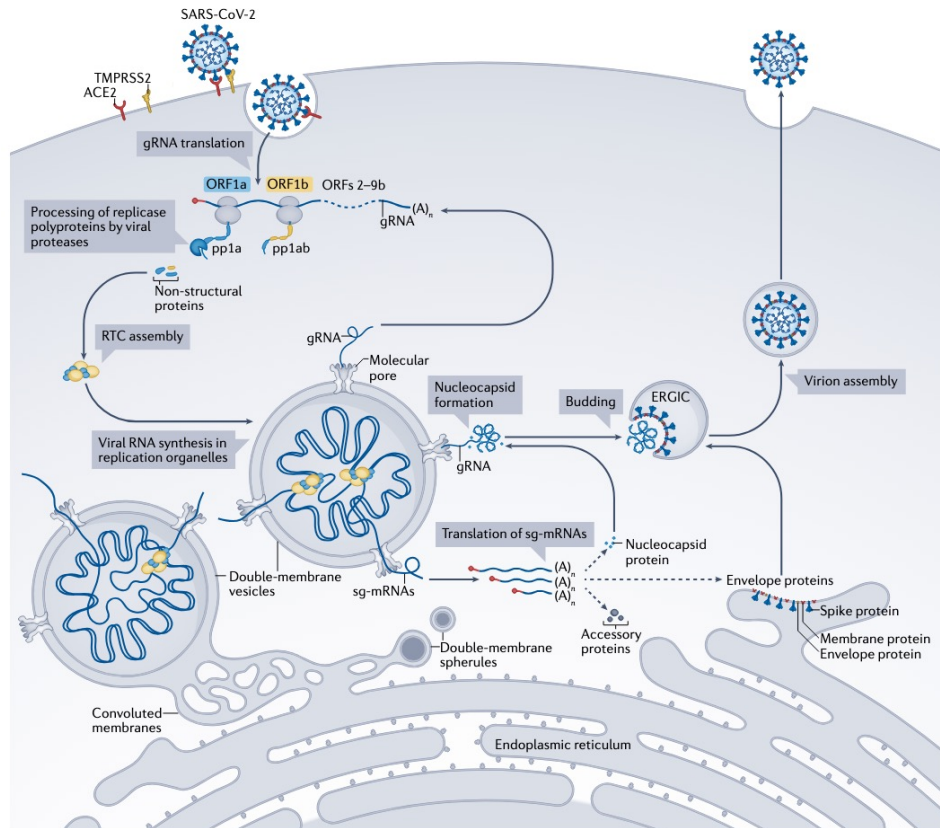
SARS-CoV-2 : vue d'ensemble



Le genome de SARS-CoV-2

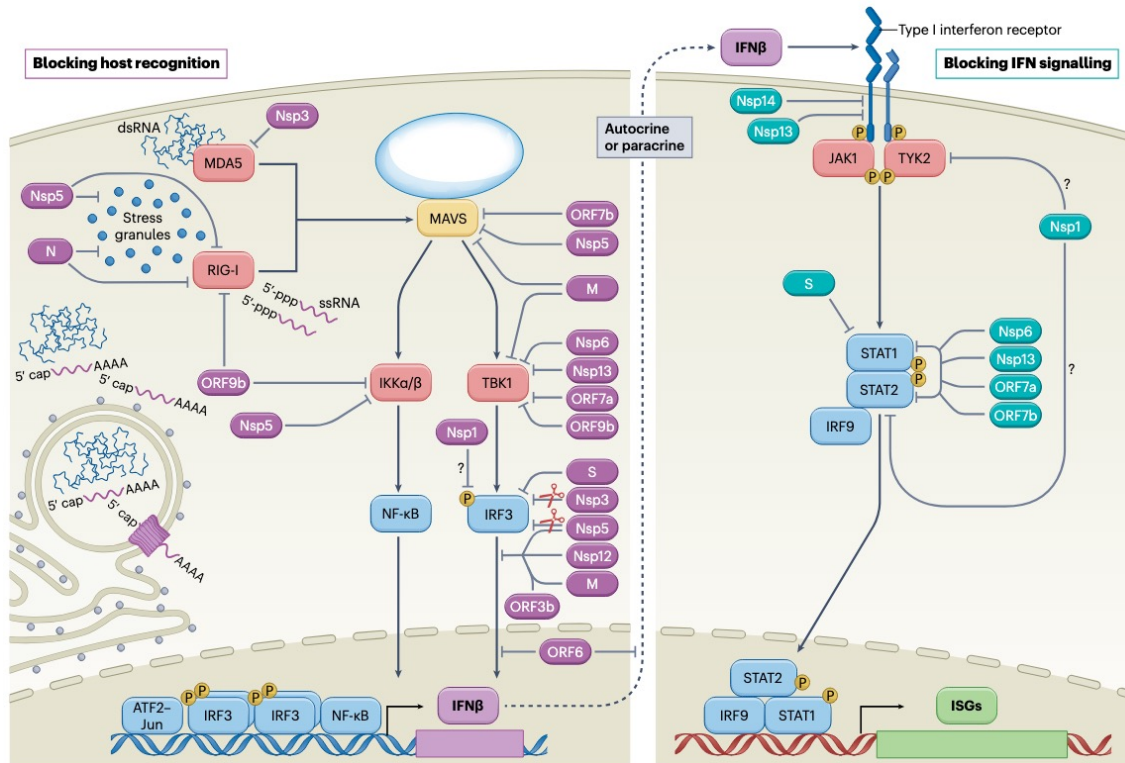


Les protéines non-structurales répliquent le génome



Nsp14 : proof-reading
1 mutation / 20 cycles

Les protéines accessoires contournent l'immunité



Adapted from Minkoff et al., Nat Rev NCB 2023

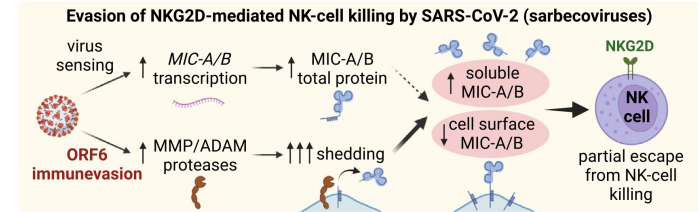
Cell

CellPress

Article

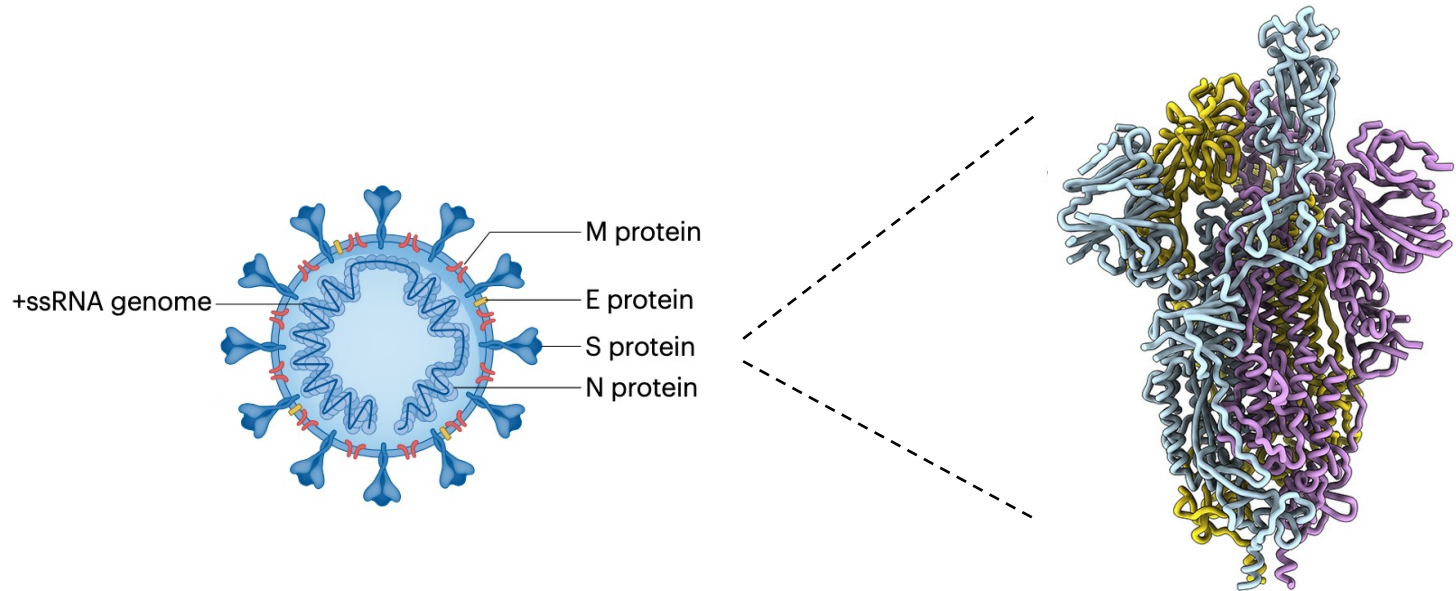
Evasion of NKG2D-mediated cytotoxic immunity by sarbecoviruses

Jordan A. Hartmann,^{1,2,17} Marcella R. Cardoso,^{1,17} Maria Cecilia Ramiro Talarico,¹ Devin J. Kenney,^{3,4} Madison R. Leone,¹ Dagny C. Reese,^{1,2} Jacquelyn Turcinovic,¹ Aoife K. O'Connell,¹ Hans P. Gerjts,⁴ Caitlin Marino,¹ Pedro E. Ojeda,¹ Erich V. De Paula,^{5,6} Fernanda A. Orsi,⁵ Licio Augusto Velloso,^{5,6} Thomas R. Caferio,¹ John H. Connor,⁴ Alexander Ploss,⁸ Angelique Hoelzemer,^{9,10,11} Mary Carrington,^{12,13} Amy K. Barczak,^{1,2,14} Nicholas A. Crossland,^{3,4,15} Florian Douam,^{3,4} Julie Boucay,^{1,*} and Wilfredo F. Garcia-Beltran^{1,16,18,*}

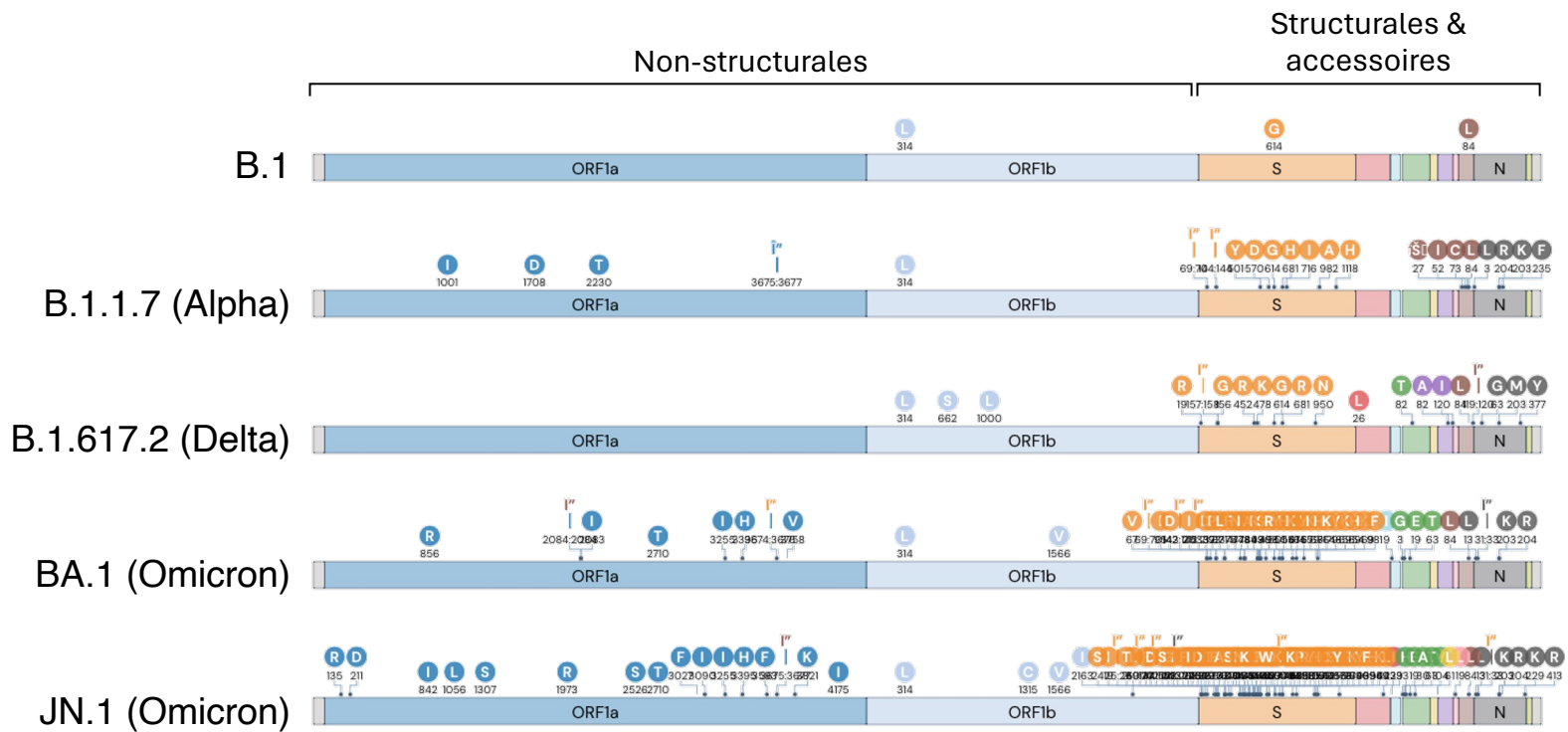


May 2024

Les protéines structurales



Les variants de SARS-CoV-2 accumulent des mutations



nomenclature

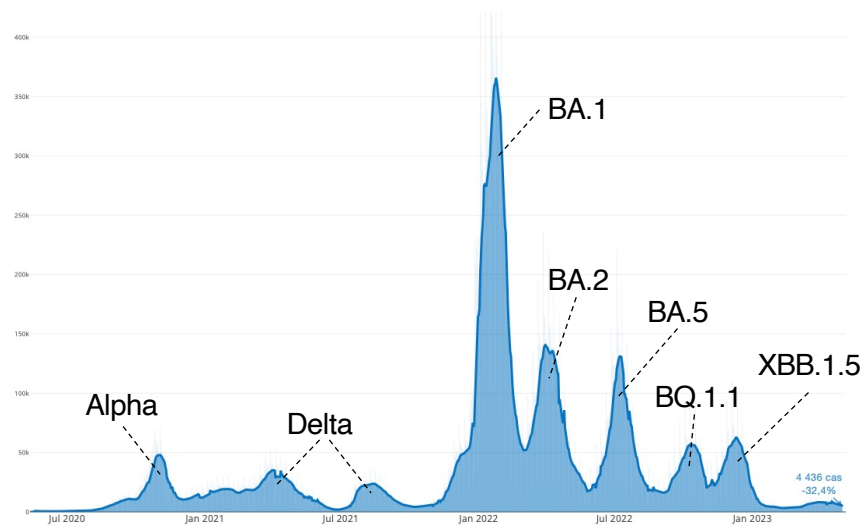
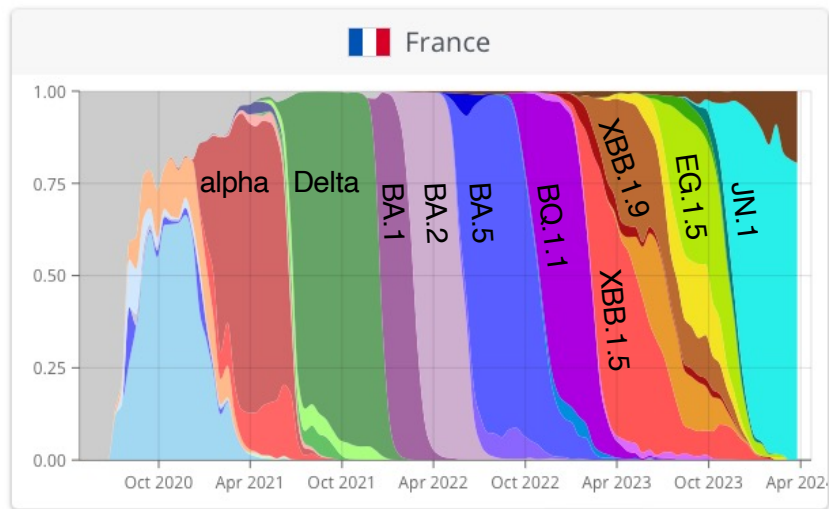
B.1.1.521.1

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BA.1

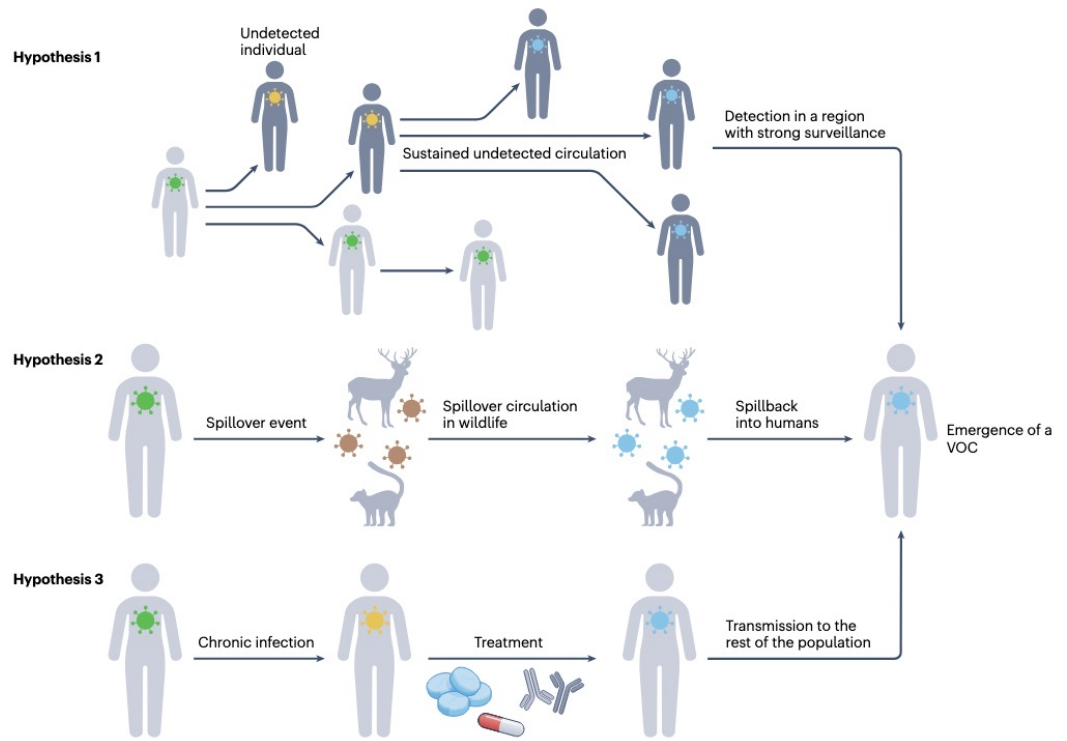
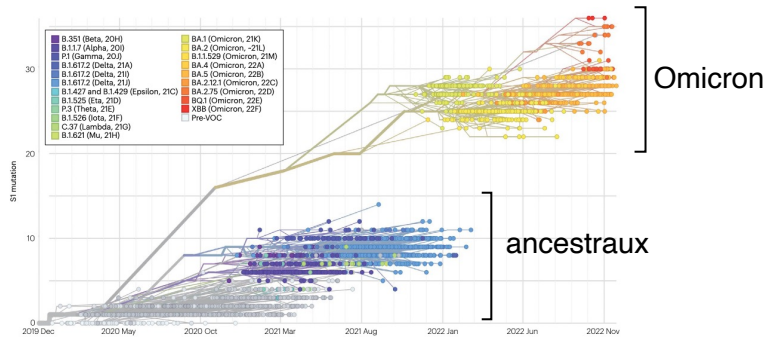
Jamais >3 chiffres
Jamais >2 lettres
X = recombinants

Les variants causent de nouvelles vagues épidémiques

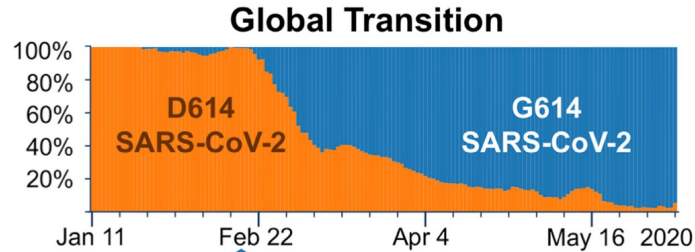


L'origine des variants?

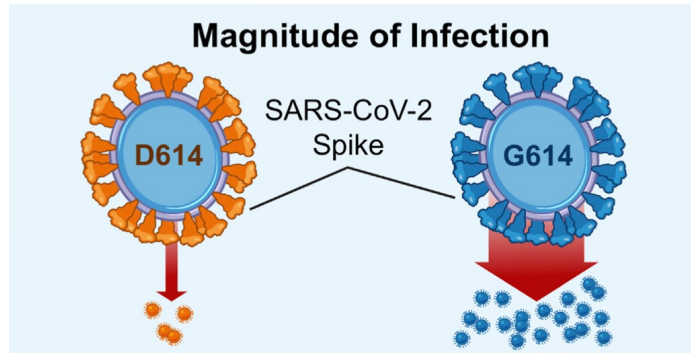
Sauts évolutifs



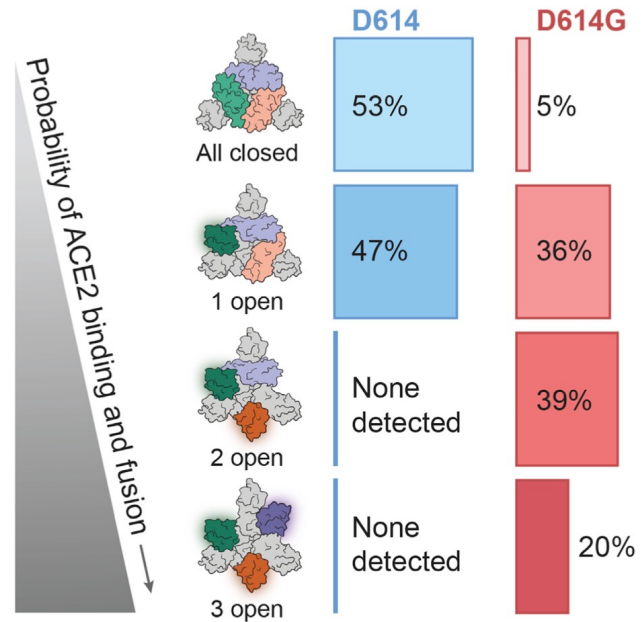
Comment expliquer le succès de certains variants?



G614 emerges in Europe

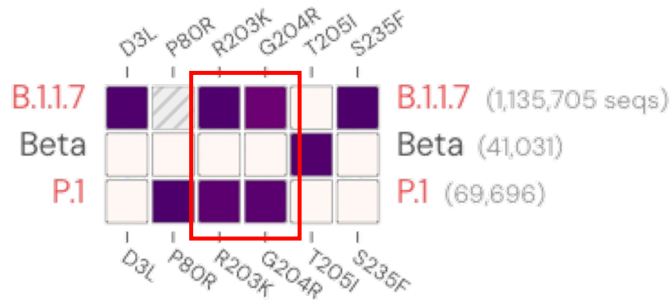


Receptor binding domain conformation

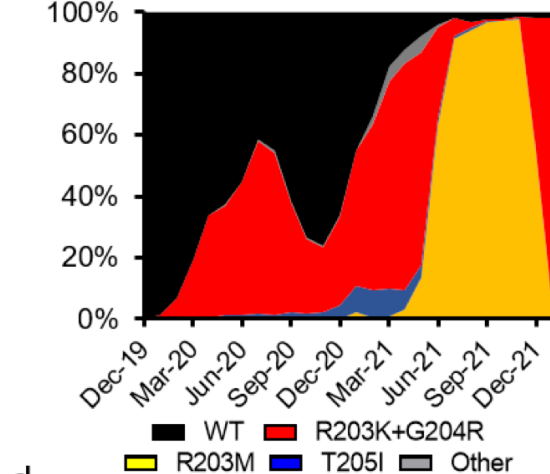


Les mutations **N501Y** (ACE2) et **P681H/R** (clivage furine) sont elles aussi responsable de gains d'infectivité

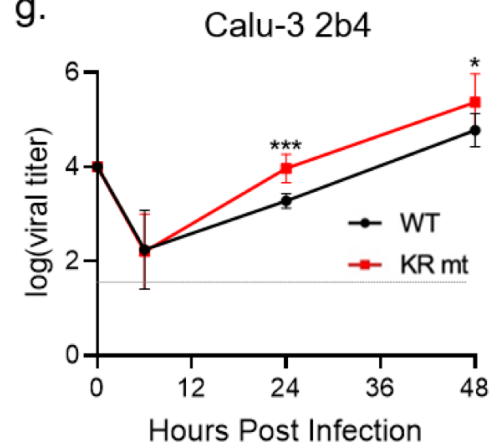
La spike mute, mais pas que !



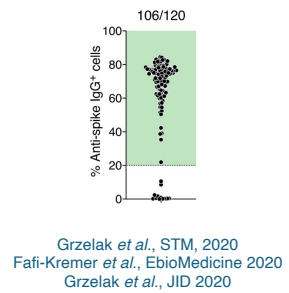
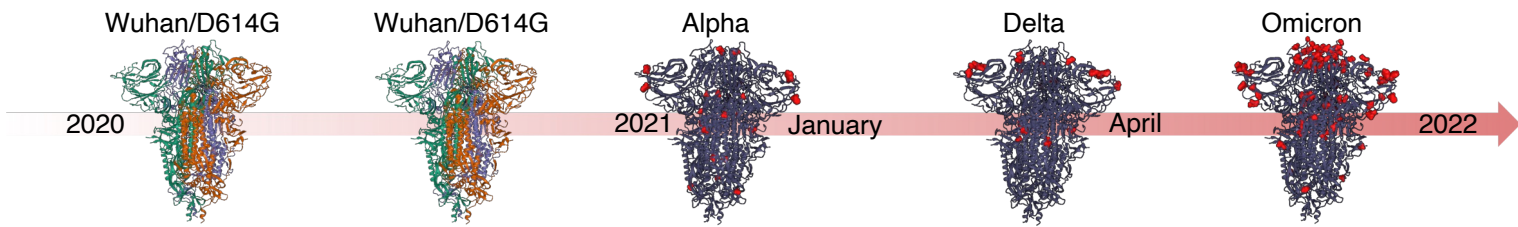
a. Variation in N residues 203-205



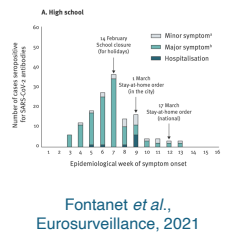
g.



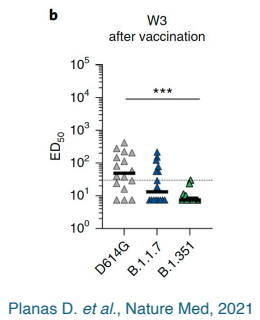
Les variants de SARS-CoV-2 échappent aux anticorps



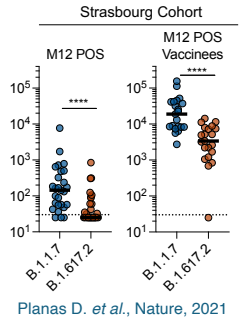
Seroconversion
neutralization



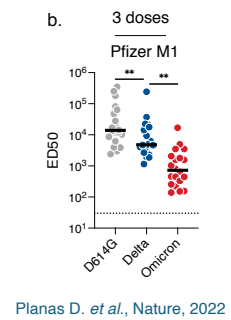
Seroepidemiology



Need of 2 doses

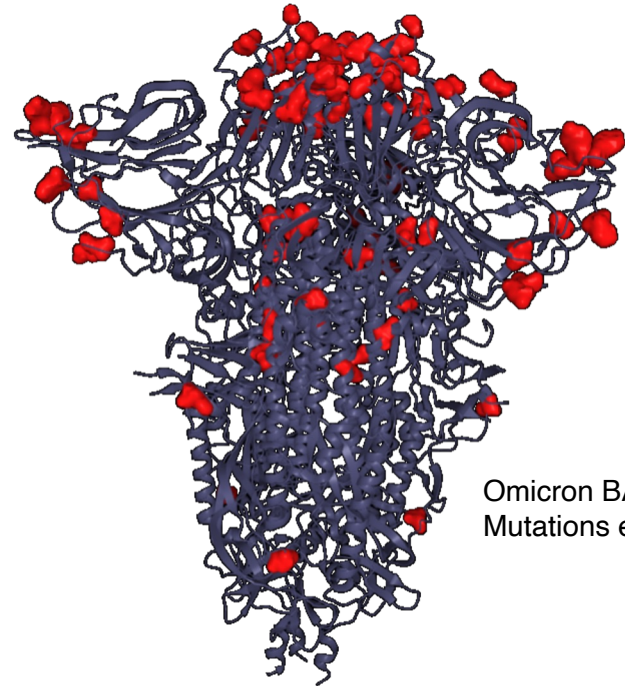
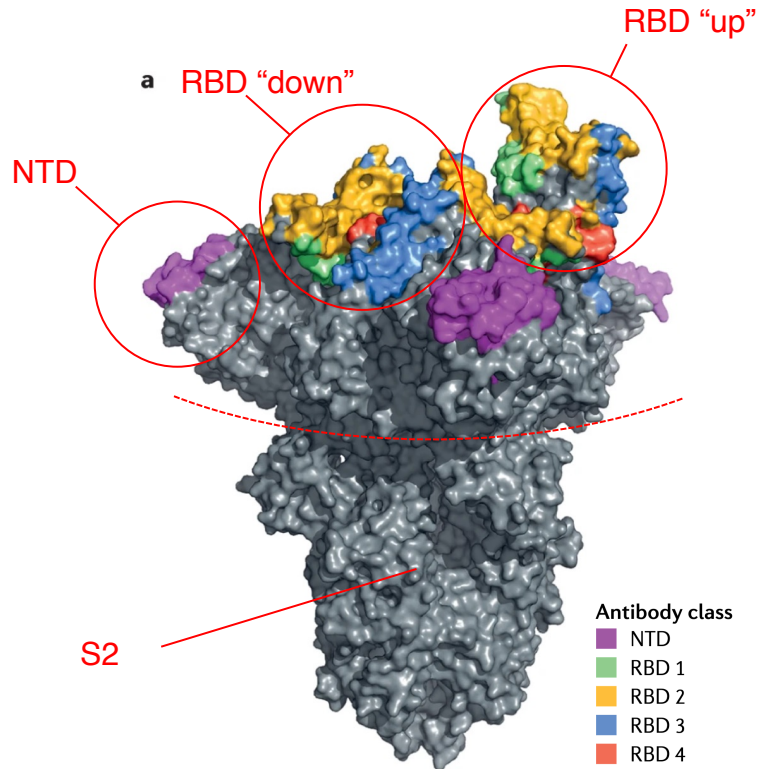


Convalescents
need a dose



Booster dose

Les épitopes des anticorps neutralisants sont hypermutés



SARS-CoV-2 échappe aux anticorps, mais pas que !

Article

Evolution of enhanced innate immune evasion by SARS-CoV-2

<https://doi.org/10.1038/s41586-021-04352-y>

Received: 31 May 2021

Accepted: 14 December 2021

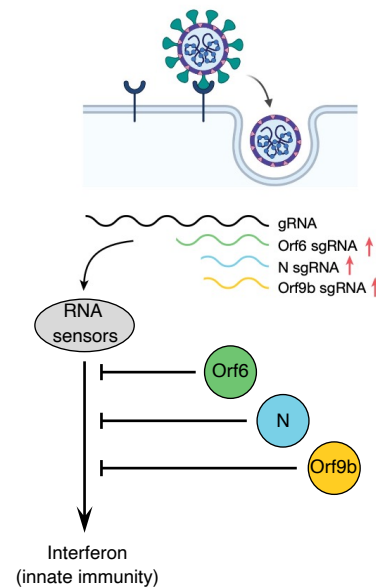
Published online: 23 December 2021

Open access

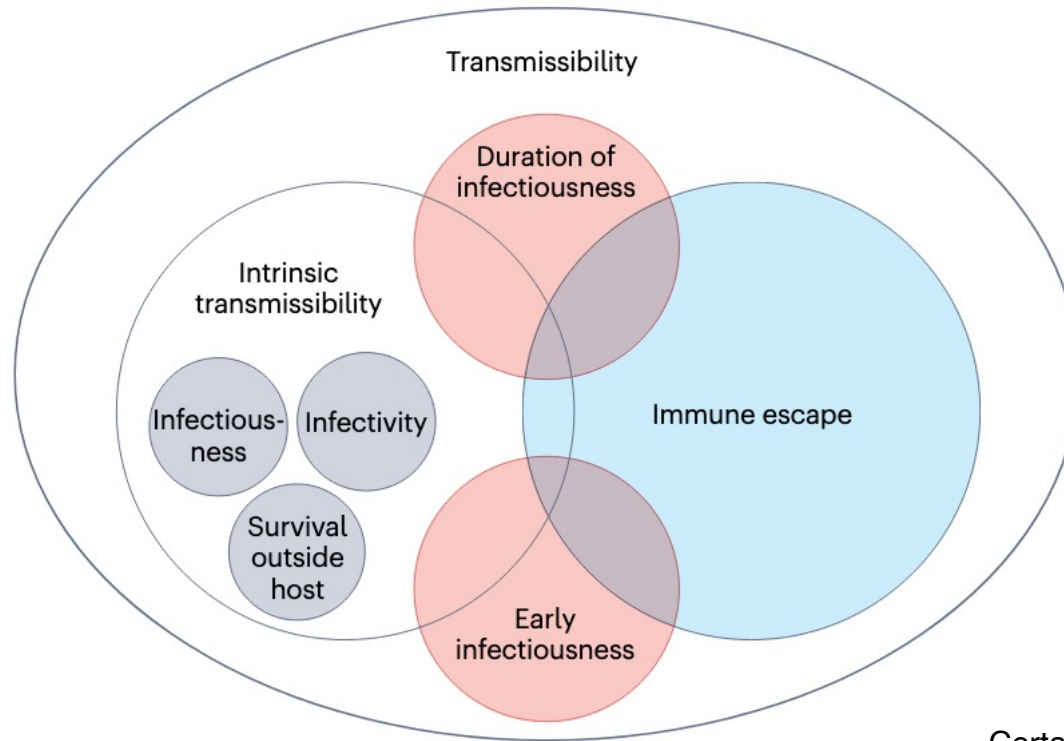
 Check for updates

Lucy G. Thorne^{1,19}, Mehdi Bouhaddou^{2,3,4,5,19}, Ann-Kathrin Reuschl^{1,19}, Lorena Zuliani-Alvar ez^{2,3,4,5,19}, Ben Polacco^{2,3,4,5}, Adrian Petin^{2,3,4,5}, Jyoti Batra^{2,3,4,5}, Matthew V. X. Whelan¹, Myra Hosmillo⁶, Andrea Fossati^{2,3,4,5}, Roberta Ragazzini⁷, Irwin Jungreis^{8,9}, Manisha Ummadi^{2,3,4,5}, Ajda Rojc^{2,3,4,5}, Jane Turner¹, Marie L. Bischof¹, Kirsten Obernier^{2,3,4,5}, Hannes Braberg^{2,3,4,5}, Margaret Soucheray^{2,3,4,5}, Alicia Richards^{2,3,4,5}, Kuei-Ho Chen^{2,3,4,5}, Bhavya Harjai^{2,3,4,5}, Danish Memon¹⁰, Joseph Hiatt^{2,3,4,5}, Romel Rosales^{11,12}, Briana L. McGovern^{11,12}, Aminu Jahun⁶, Jacqueline M. Fabius^{2,3,4,5}, Kris White^{11,12}, Ian G. Goodfellow⁶, Yasu Takeuchi¹, Paola Bonfanti⁷, Kevan Shokat^{2,3,4,5,13}, Natalia Jura^{2,3,5,14,15}, Klim Verba^{2,3,5}, Mahdad Noursadeghi¹, Pedro Beltrao^{2,10}, Manolis Kellis^{8,9}, Danielle L. Swaney^{2,3,4,5}, Adolfo Garcia-Sastre^{11,12,16,17,18}, Clare Jolly¹⁵, Greg J. Towers¹⁵ & Nevan J. Krogan^{2,3,4,5,52}

Nature

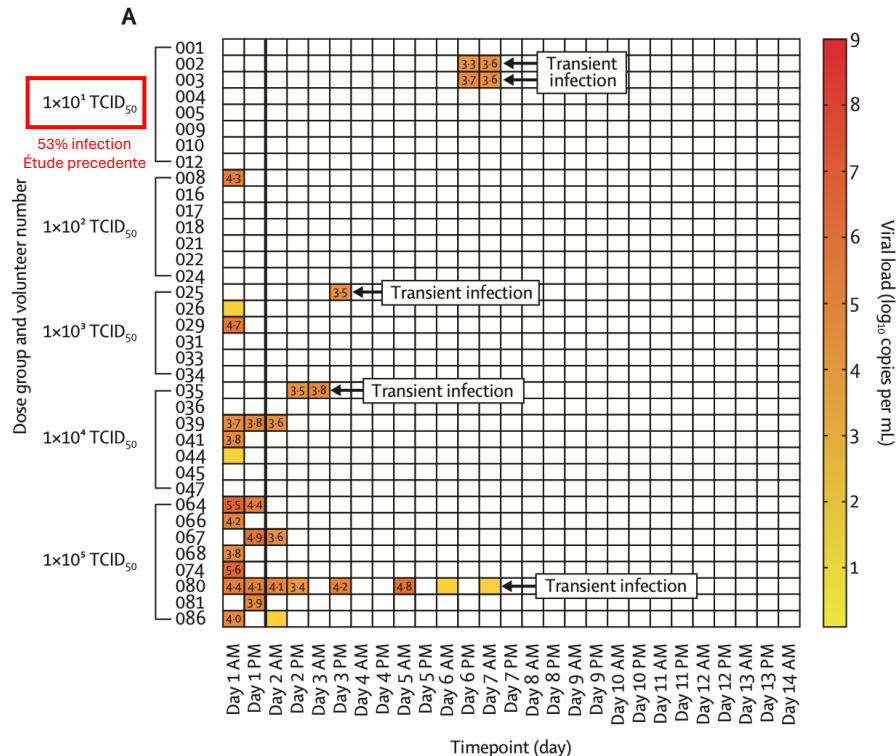
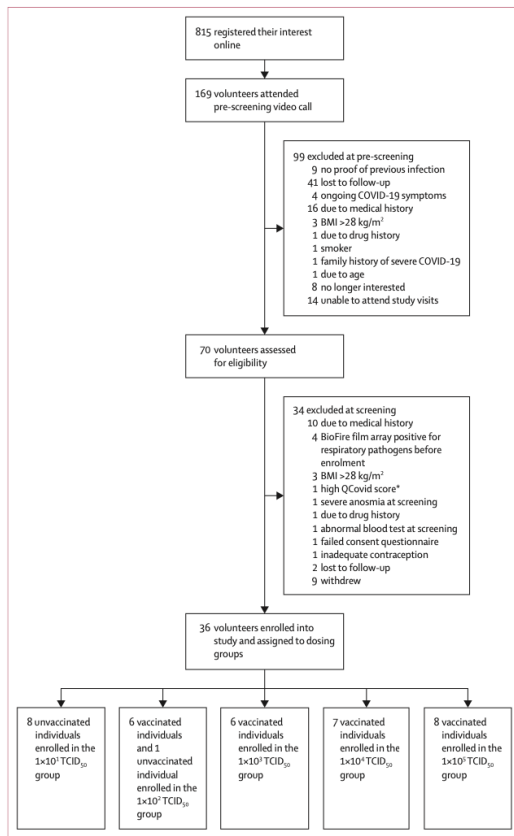


Mécanismes de sélection des variants



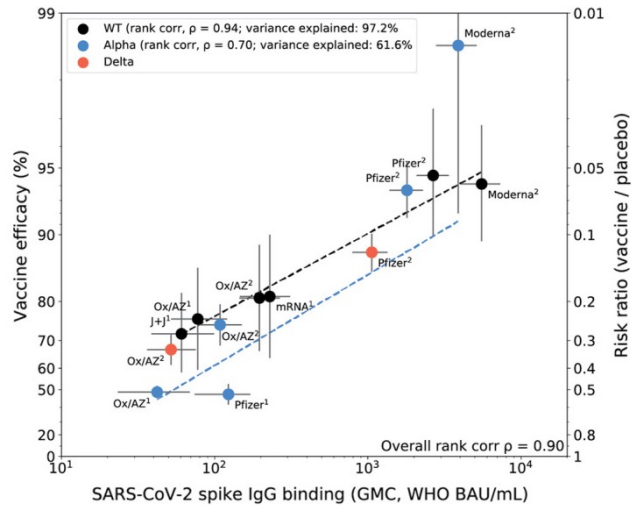
Certaines mutations se fixent par
dérive génétique i.e hasard

Muter est une question de survie pour SARS-CoV-2

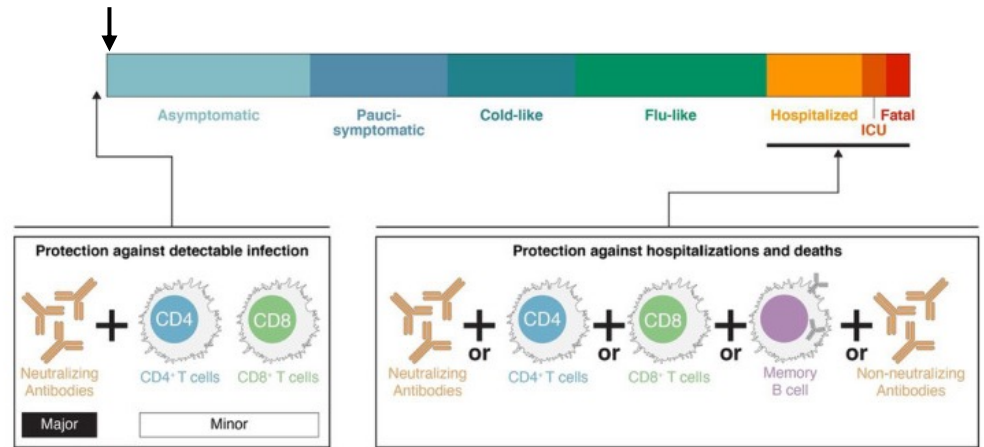


14 des 36 (39%)
volontaires vont
faire une
breakthrough
infection après
l'essai!

Les anticorps sont un corrélat de protection

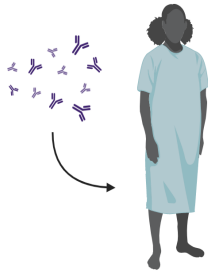


Infection



Anticorps thérapeutiques contre SARS-CoV-2

Thérapeutique



Patients with co-morbidities

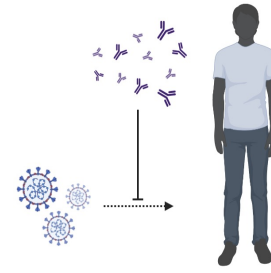
Casirivimab + Imdevimab

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

Sotrovimab

Gupta et al., NEJM 2021
(relative risk reduction: 85% (44-96); $P = 0.002$)

Prophylactique



Mostly
Immunocompromised
(lack of vaccine
immunogenicity)

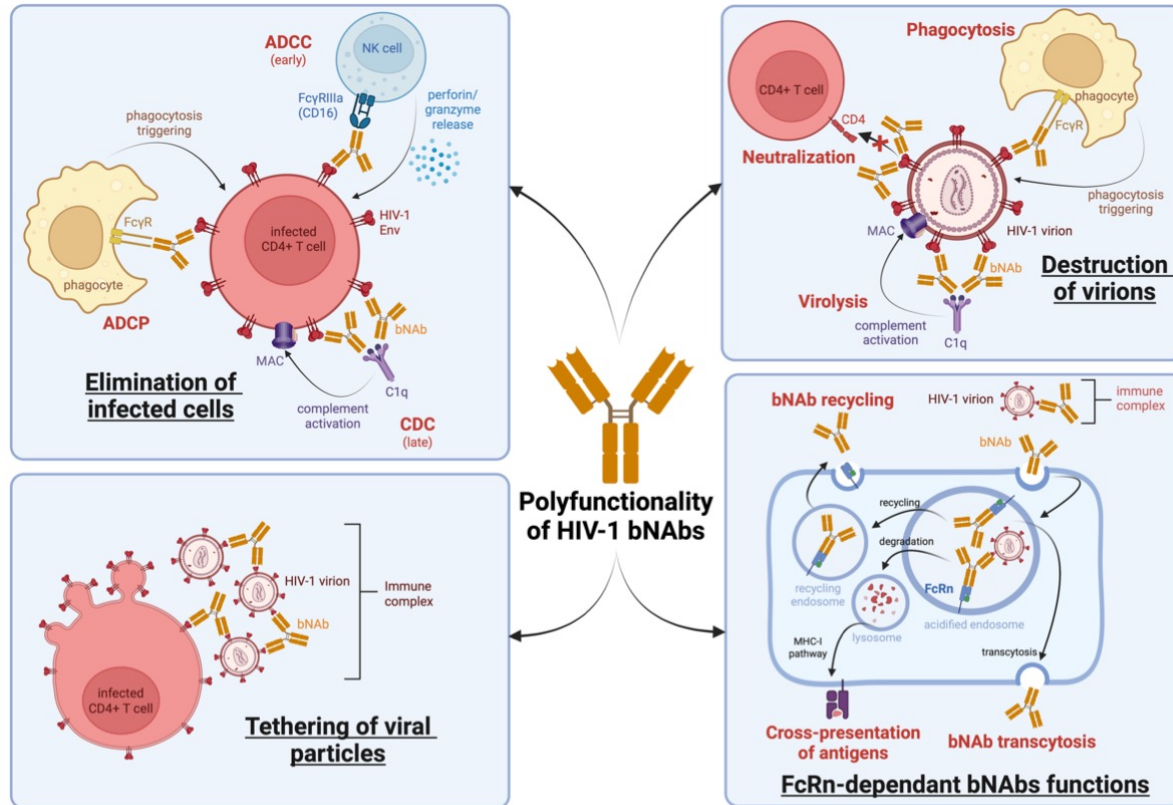
Casirivimab + Imdevimab

O'bien et al., NEJM 2021
(relative risk reduction: 81.4%; $P < 0.001$)

Cilgavimab + Tixagevimab

Levin et al. NEJM 2022
(relative risk reduction: 76.7%; $P < 0.001$)

Les anticorps sont polyfonctionnels

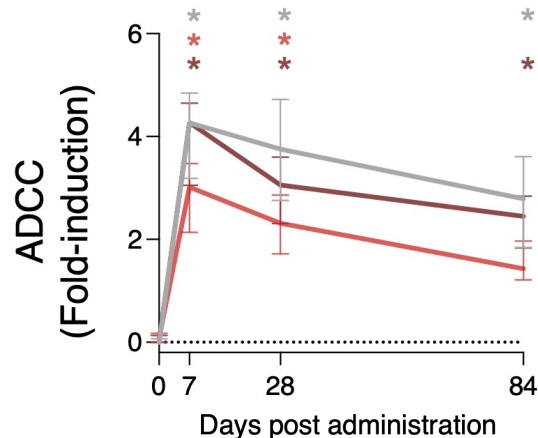
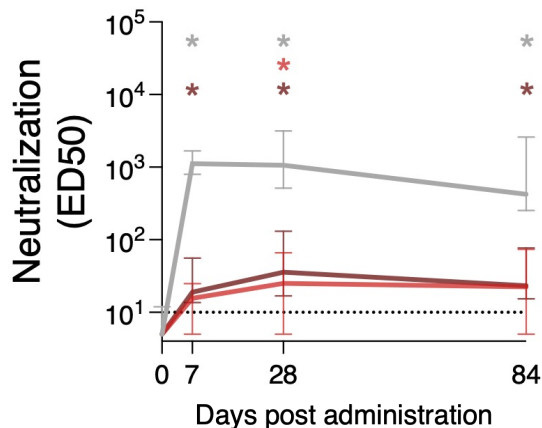


Polyfonctionnalité, variants et efficacité thérapeutique

Cohorte
CoCoPrev

anrs
MALADIES INFECTIEUSES
ÉMERGENTES Inserm

Sotrovimab



- D614G
- BQ.1.1
- XBB.1.5

Bruel et al., Med 2023

↓

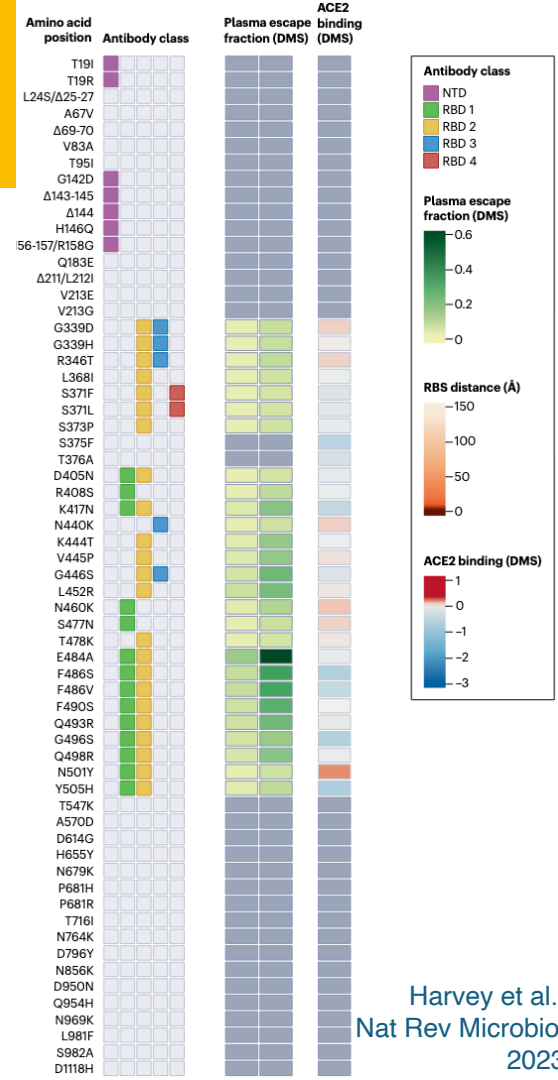
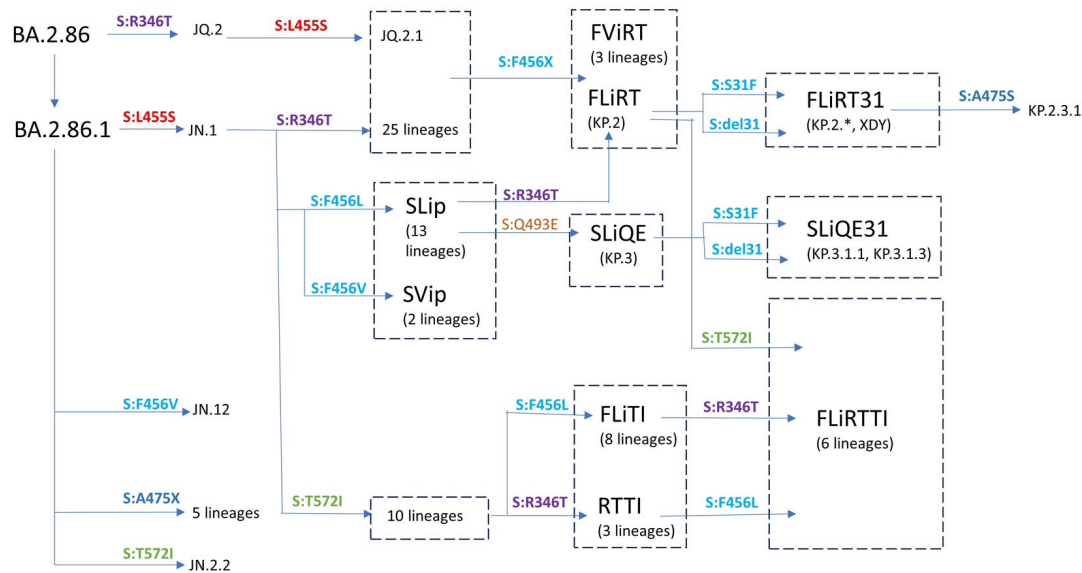
Y-a-t'il un seuil de neutralisation qui indique une efficacité clinique?

↓

Est-ce que l'ADCC contribue à l'efficacité clinique?

mécanismes d'action = meilleur sélection des leads et meilleure prédiction avec l'in vitro

Comment prédire le prochain variant ?



From X, @dfocosi
June 5, 2024

Harvey et al.,
Nat Rev Microbiol
2023

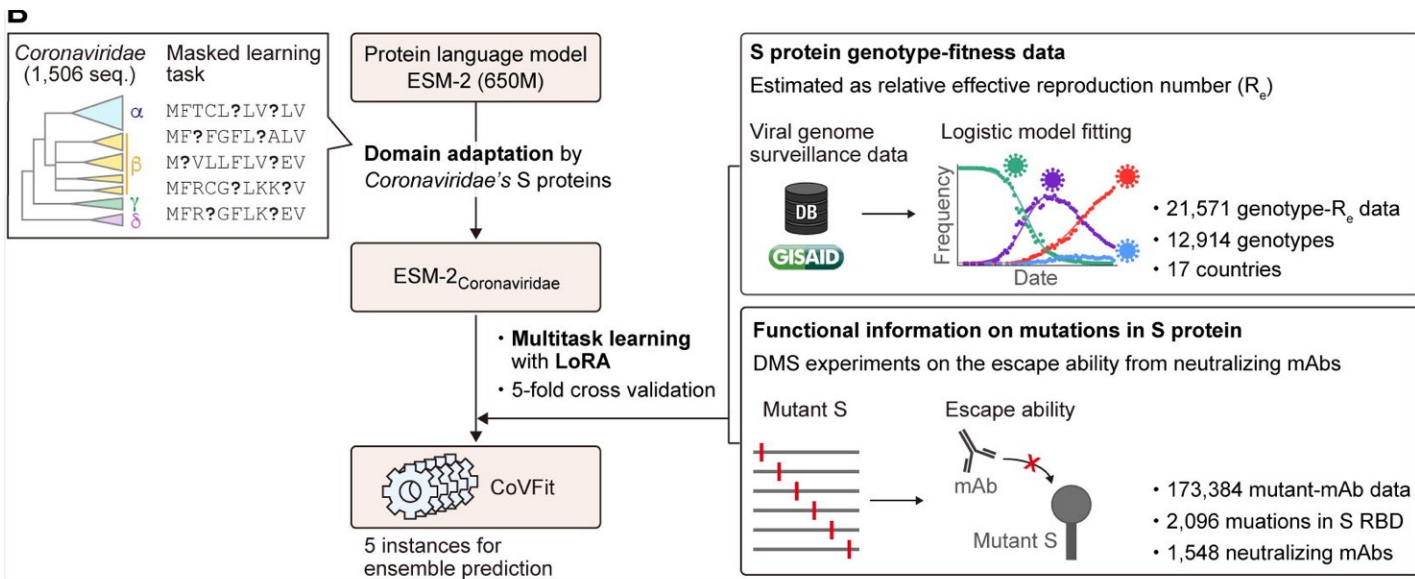
Comment prédire le prochain variant ?

New Results

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A Protein Language Model for Exploring Viral Fitness Landscapes

Junpei Ito, Adam Strange, Wei Liu, Gustav Joas, Spyros Lytras,
The Genotype to Phenotype Japan (G2P-Japan) Consortium, Kei Sato
doi: <https://doi.org/10.1101/2024.03.15.584819>

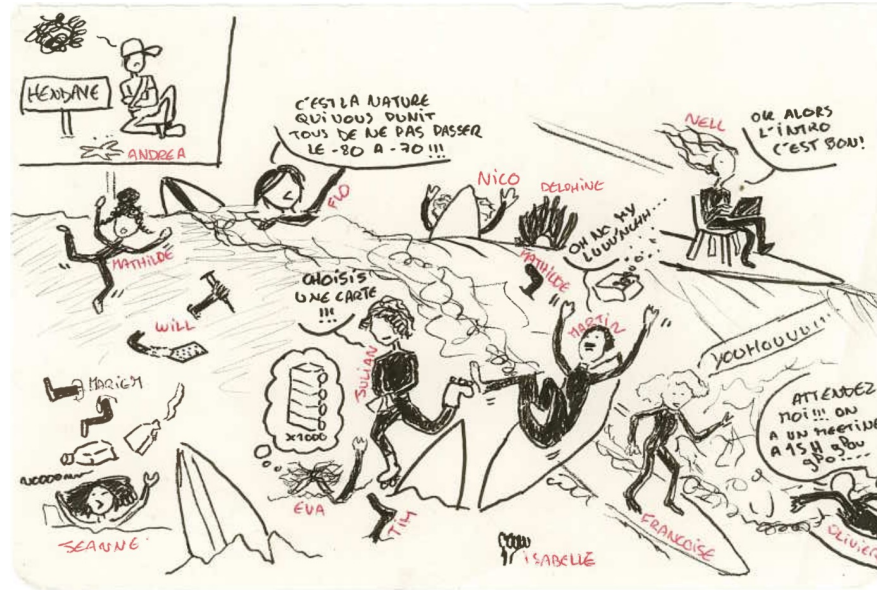


Conclusion

- ➔ L'ensemble du génome de SARS-CoV-2 mute pour augmenter la réplication virale et échapper à l'immunité.
- ➔ La spike est un hotspot de mutation car la réponse humorale (anticorps) est très efficace contre SARS-CoV-2.
- ➔ L'échappement à la réponse humorale entraîne un échappement aux anticorps monoclonaux qui en sont dérivés.
- ➔ Les fonctions non-neutralisantes des anticorps peuvent avoir un intérêt thérapeutique.
- ➔ L'infection chronique de patients immunodéprimés explique sûrement les “sauts évolutifs” de SARS-CoV-2, mais d'autres hypothèses existent

Remerciements

Virus et Immunité – Schwartz Lab – Institut Pasteur



Amélie Wileveau ©

Dérive génétique : le rôle important du hasard

