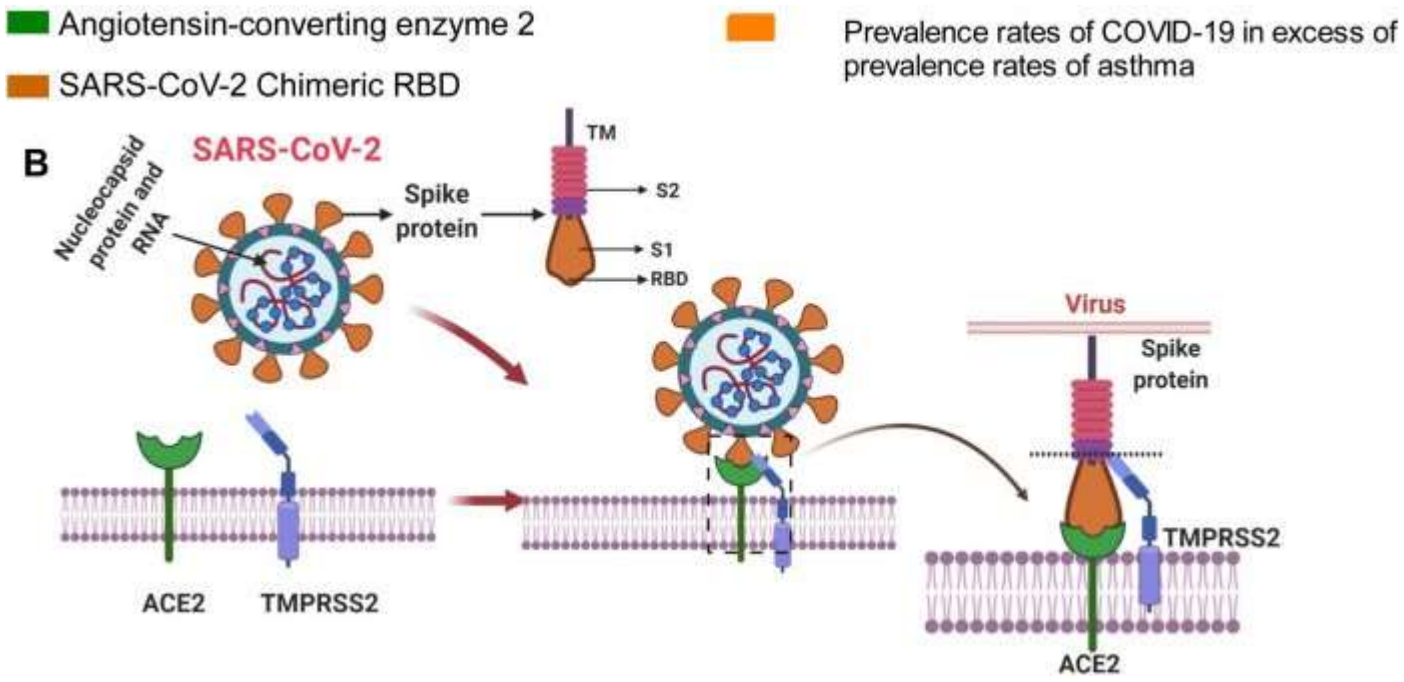
Zoom Corona Round Table: SARS-CoV-2 and COVID-19: science in the spotlight
October 6, 2020

SARS-CoV-2: natural origin or laboratory creation? Does it matter?

Michael Antoniou

Mechanism of coronavirus (CoV) infection



- CoV binds to ACE2 receptor on cell surface via the spike protein S1 region reception binding domain
- Protein cleaving enzyme (TMPRSS2 in illustration) cuts between the spike protein S1 and S2 regions
- S2 region facilitates entry of CoV into cells

Nature Medicine **26**: 450-455, 2020

The proximal origin of SARS-CoV-2

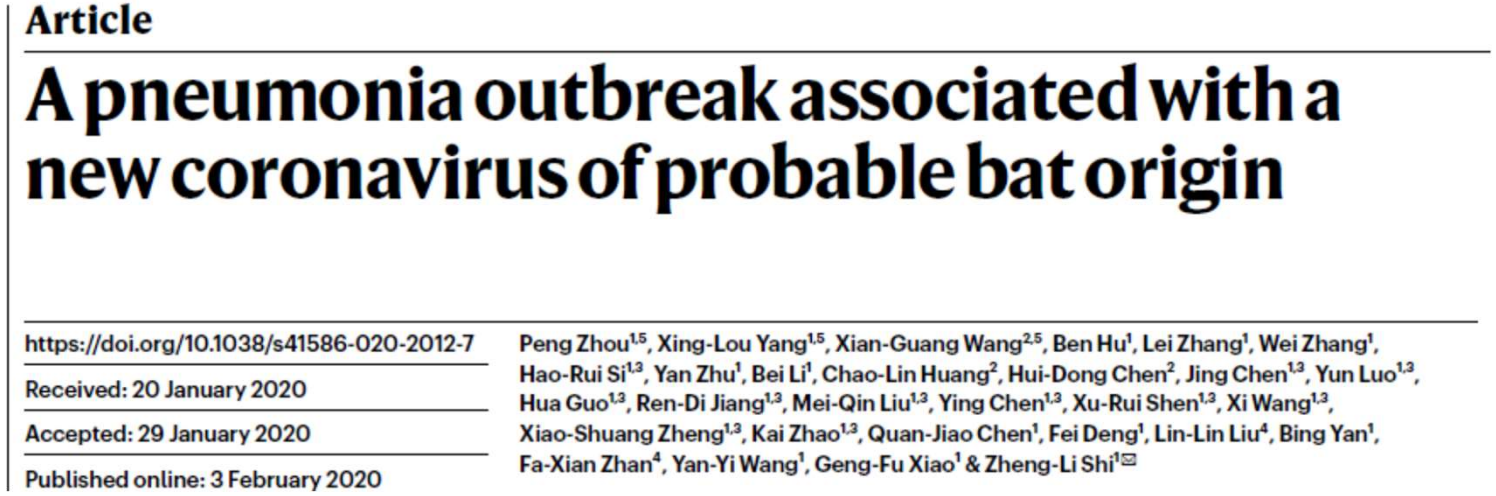
Andersen KG, Rambaut A, Lipkin WI, Holmes EC and Garry RF

- Sequence analysis of RNA genomes of CoVs
- Computer to determine “ideal” CoV sequence for human infectivity
- SARS-CoV-2 does not fit computer model
- SARS-CoV-2 cannot be lab creation

BUT ….

Puts blind faith in computer predictions
Ignores lab methods for creating and selecting CoVs for human infectivity (eg iterative evolutionary selection)
[see https://www.gmwatch.org/en/news/latest-news/19383-where-did-the-covid-19-virus-come-from]

Nature, **579**: 270



Article

A pneumonia outbreak associated with a new coronavirus of probable bat origin

https://doi.org/10.1038/s41586-020-2012-7

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Peng Zhou[1,5], Xing-Lou Yang[1,5], Xian-Guang Wang[2,5], Ben Hu[1], Lei Zhang[1], Wei Zhang[1], Hao-Rui Si[1,3], Yan Zhu[1], Bei Li[1], Chao-Lin Huang[2], Hui-Dong Chen[2], Jing Chen[1,3], Yun Luo[1,3], Hua Guo[1,3], Ren-Di Jiang[1,3], Mei-Qin Liu[1,3], Ying Chen[1,3], Xu-Rui Shen[1,3], Xi Wang[1,3], Xiao-Shuang Zheng[1,3], Kai Zhao[1,3], Quan-Jiao Chen[1], Fei Deng[1], Lin-Lin Liu[4], Bing Yan[1], Fa-Xian Zhan[4], Yan-Yi Wang[1], Geng-Fu Xiao[1] & Zheng-Li Shi[1]✉

Bat CoV strain RaTG13 proposed as “proximal origin” of SARS-CoV-2 (overall 96% same sequence

Anomalies of RaTG13:

Originally isolated from bats in Yunan province and partial sequence posted on 2013; why wait so long to report on a bat CoV with potential to cross to humans?

Divergence in genome sequence between RaTG13 and SARS-CoV-2 does not follow recognised principles of evolutionary genetics, especially in spike protein gene region

SARS-CoV-2 has identical E protein gene sequence to two other bat CoVs (ZC45 and ZXC21) published in 2018; mutations in E protein well tolerated and so accumulate rapidly so why identical?

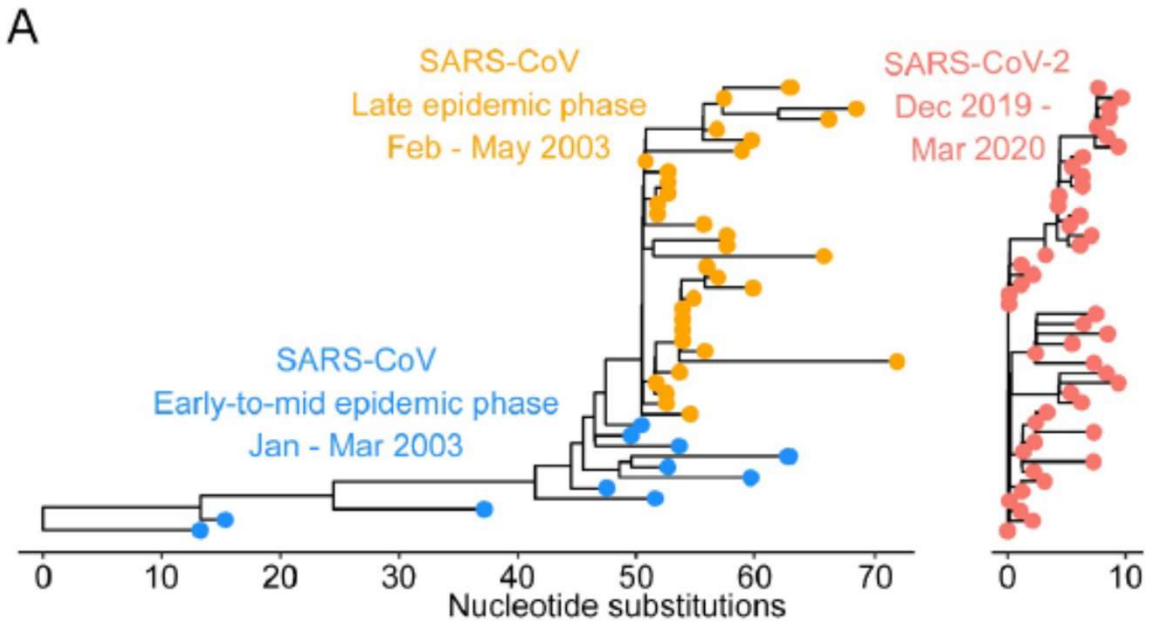
Does RaTG13 actually exist?

https://nerdhaspower.weebly.com/ratg13-is-fake.html#

SARS-CoV-2 is well adapted for humans.

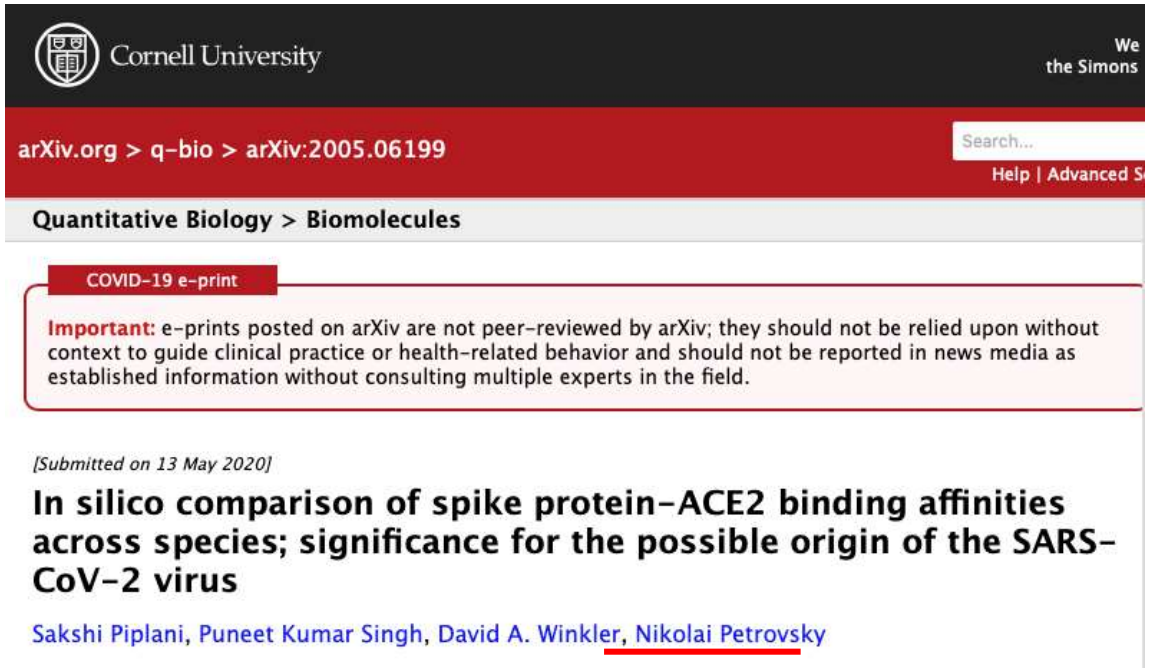
What does this mean for re-emergence?

Shing Hei Zhan[1,2*], Benjamin E. Deverman[3], Yujia Alina Chan[3*]



Comparison of the genetic progression of SARS-CoV and SARS-CoV-2

"*The sudden appearance of a highly infectious SARS-CoV-2 presents a major cause for concern that should motivate stronger international efforts to identify the source and prevent near future re-emergence*." In this context they conclude that the possibility of a lab escape "*should be considered regardless of how likely or unlikely*".
https://gmwatch.org/en/news/latest-news/19412-lab-escape-theory-of-sars-cov-2-origin-gaining-scientific-support



Cornell University

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arXiv.org > q-bio > arXiv:2005.06199

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Quantitative Biology > Biomolecules

COVID-19 e-print

Important: e-prints posted on arXiv are not peer-reviewed by arXiv; they should not be relied upon without context to guide clinical practice or health-related behavior and should not be reported in news media as established information without consulting multiple experts in the field.

[Submitted on 13 May 2020]

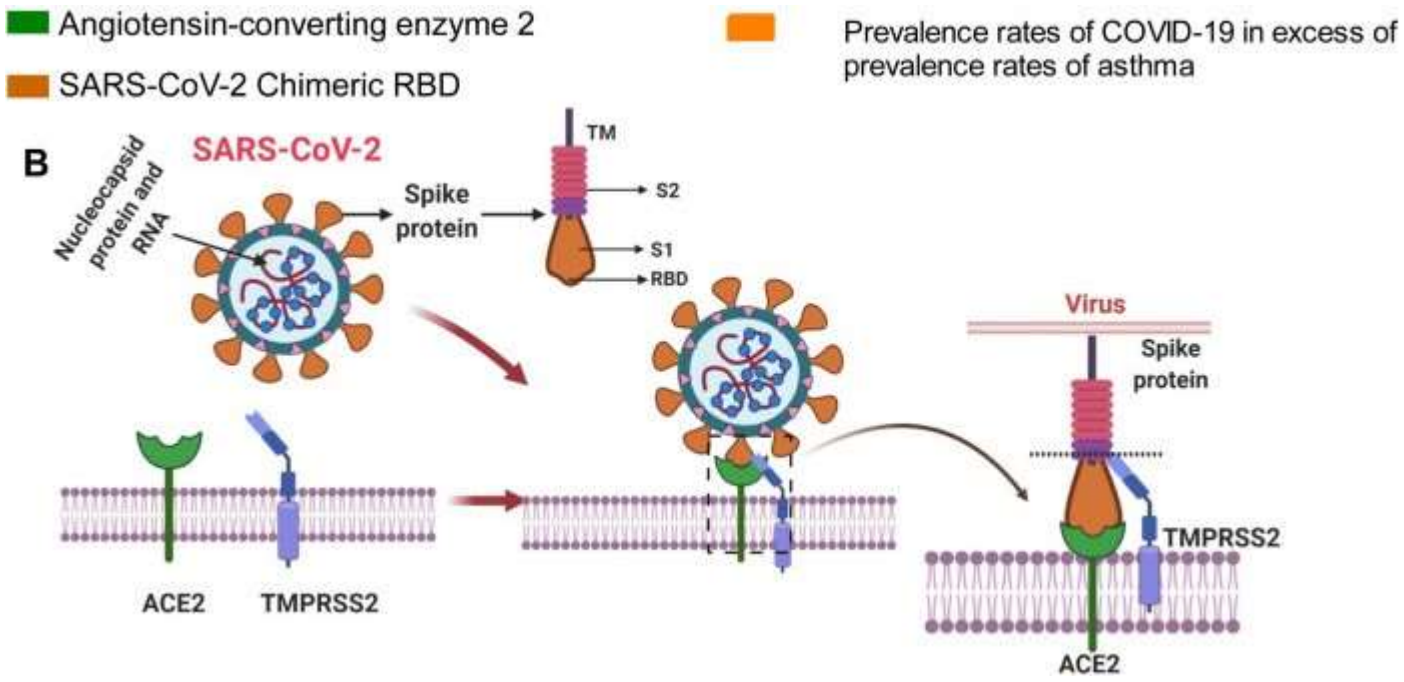
In silico comparison of spike protein-ACE2 binding affinities across species; significance for the possible origin of the SARS-CoV-2 virus

Sakshi Piplani, Puneet Kumar Singh, David A. Winkler, Nikolai Petrovsky

"Notably, SARS-CoV-2 spike protein had the highest overall binding energy for human ACE2, greater than all the other tested species including bat, the postulated source of the virus. This indicates that SARS-CoV-2 is a highly adapted human pathogen."

The virus's ability to bind to human cells "*far exceeds*" its ability to infect other animals, he said. He added, "*This, plus the fact that no corresponding virus has been found to exist in nature, leads to the possibility that COVID-19 is a human-created virus. It is therefore entirely plausible that the virus was created in the biosecurity facility in Wuhan [WIV] by selection on cells expressing human ACE2 [receptor], a laboratory that was known to be cultivating exotic bat coronaviruses at the time.*"
https://www.washingtontimes.com/news/2020/may/21/australian-researchers-see-virus-design-manipulati/

Mechanism of coronavirus (CoV) infection



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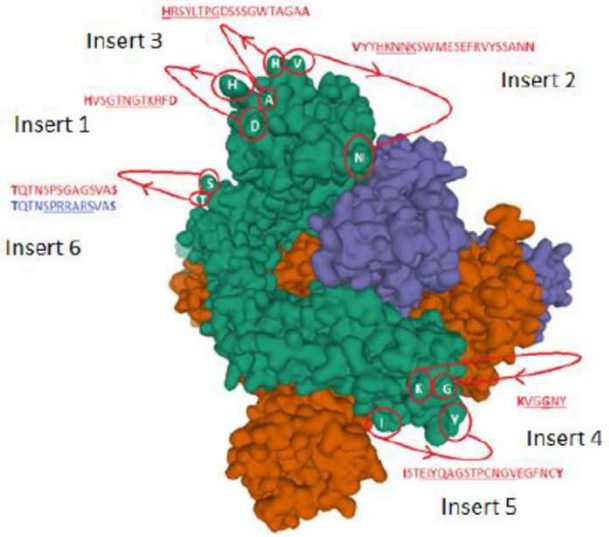
ACE-2 receptor independent infection of SARS-CoV-2?

The Evidence which Suggests that This Is No Naturally Evolved Virus

A Reconstructed Historical Aetiology of the SARS-CoV-2 Spike

Birger Sørensen, Angus Dalgleish & Andres Susrud
Immunor & St Georges University of London

https://www.minervanett.no/files/2020/07/13/TheEvidenceNoNaturalEvol.pdf



- Insertions of clusters of amino acids around receptor binding domain of SARS-CoV-2 spike protein
- Gives positive charge to region
- Allows binding to, and infection of cells that do not possess the ACE2 receptor (cf CoV causing Swine Acute Diarrhoea Syndrome)
- Major contributing factor to body-wide infectivity of SARS-CoV-2
- Extremely unlikely to have occurred by natural selection

Furin cleavage site unique to SARS-CoV-2 within its class

DOI: 10.13140/RG.2.2.31358.13129/1

Is considering a genetic-manipulation origin for SARS-CoV-2 a conspiracy theory that must be censored?

Rossana Segreto[1#] and Yuri Deigin[2]

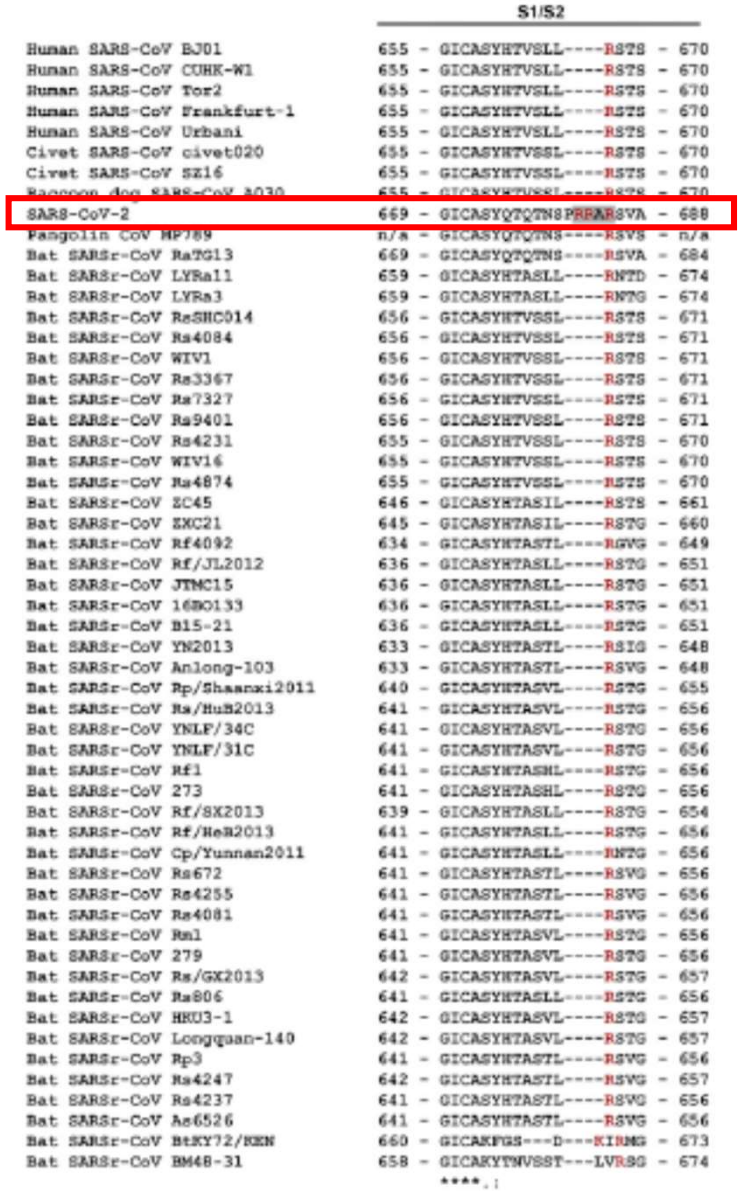
Unusual Features of the SARS-CoV-2 Genome Suggesting Sophisticated Laboratory Modification Rather Than Natural Evolution and Delineation of Its Probable Synthetic Route

Li-Meng Yan (MD, PhD)[1], Shu Kang (PhD)[1], Jie Guan (PhD)[1], Shanchang Hu (PhD)[1]

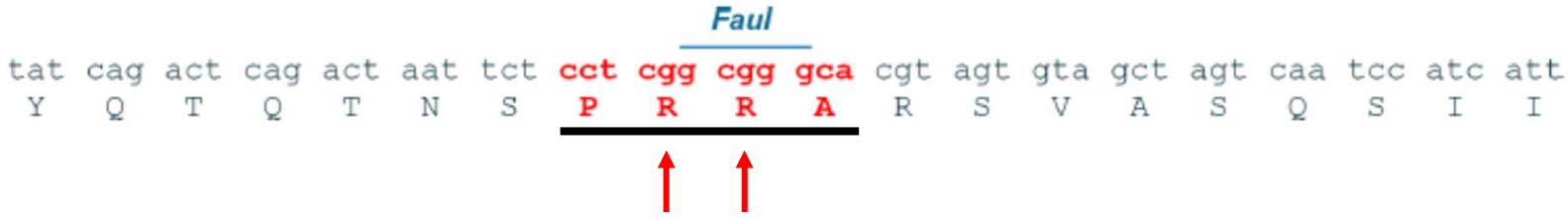
What is furin and why its presence between S1 and S2 domains of spike protein enhance wide-spread infectivity?

- Protein cleaving enzyme
- Widely distributed around the body
- Furin cleavage site between S1 and S2 domains of CoV spike protein would result in wide-spread infectivity after ACE2 receptor dependent or independent cell association

- SARS-CoV-2 is unique in its class of CoVs in having a perfect furin cleavage site between S1 and S1 spike domains
- Deletion of furin cleavage site from SARS-CoV-2 abrogates its infectivity (Hoffmann M et al., 2020, *Molecular Cell* 78, 779–784



Furin cleavage site encoded by rare codons



furin cleavage recognition site

Summary:

- Perfect furin cleavage site
- Perfect location between S1 and S2 spike protein domains
- Highly unusual codon usage; could allow its easy detection
- Suggests intentional manipulation?

CoV Gain-of-Function Research

Intentional creation of human infectious CoV

- Scientists in China and USA independently and in collaboration have been working on CoV gain-of-function research for over 10 years
- Attempts to convert a bat CoV into a human pathogen

A SARS-like cluster of circulating bat coronaviruses shows potential for human emergence

Vineet D Menachery[1], Boyd L Yount Jr[1], Kari Debbink[1,2], Sudhakar Agnihothram[3], Lisa E Gralinski[1], Jessica A Plante[1], Rachel L Graham[1], Trevor Scobey[1], Xing-Yi Ge[4], Eric F Donaldson[1], Scott H Randell[5,6], Antonio Lanzavecchia[7], Wayne A Marasco[8,9], Zhengli-Li Shi[4] & Ralph S Baric[1,2]

Nature Medicine, **21**: 1508, 2015

Fusion of bat and mouse CoV unexpectedly resulted in high human cell infectivity

Furin cleavage of the SARS coronavirus spike glycoprotein enhances cell–cell fusion but does not affect virion entry

Kathryn E. Follis, Joanne York, Jack H. Nunberg *

Virology, **350:** 358–369, 2006

Insertion of furin cleavage site between S1 and S2 spike protein domains of CoV markedly enhanced first stages of infectivity

Conclusions

Is there definitive evidence of a zoonotic, natural mutation and selection origin of SARS-CoV-2?
NO!

Is there definitive evidence that SARS-CoV-2 was either propagated and/or genetically manipulated in a lab and accidently escaped?
NO!

What we do know is:

Arguments as to how SARS-CoV-2 arose (natural mutation selection or laboratory creation) offer alternatives and do not exclude the other

SARS-CoV-2 possesses several unique genetic and structural features, with the balance of evidence in favour of a laboratory creation

CoV gain-of-function research has been going on for years

Combining knowledge of CoV infectivity and genetic technology, it is easy to conceive how SARS-CoV-2 could have been a laboratory creation

science in the spotlight

Why has gain-of-function research of CoV and other pathogenic viruses ever been allowed?

Why are mainstream journals refusing to publish evidence by scientists providing for a laboratory propagation / manipulation and escape?
https://www.gmwatch.org/en/news/latest-news/19475-journals-censor-lab-origin-theory-for-sars-cov-2

SARS-CoV-2 causes COVID-19, but it is the cause of the pandemic?