Structural Biology Response to Biomedical Threats

Wladek Minor
University of Virginia

Instruct-ERIC Events
ReNaFoBiS/FRISBI Webinar
December, 2021, France

Disclosure

WM notes that he has been involved in the development of state-of-the-art software, data management and mining tools; some of them were commercialized by HKL Research and are mentioned in this presentation. WM is the co-founder of HKL Research and a member of the board. The author(s) have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

American Journal of Pharmaceutical Education 2010; 74 (2) Article 19.

VIEWPOINTS

A Crisis Is a Really Terrible Thing to Waste

Marie A. Chisholm-Burns, PharmD, MPH

The University of Arizona College of Pharmacy

In times of prosperity, it is more difficult to engage interest in change and progress since prosperity is generally equated with stability, affluence, and thriving. There is no need to change or rock the boat.

Challenge to 'business as usual'

A crisis forces a shift in mindset: to retain or regain prosperity, change, progress, and identification of new opportunities become a necessity.

Masterpieces

Black Death, Florence, 1348

Giovanni Boccaccio: Decameron

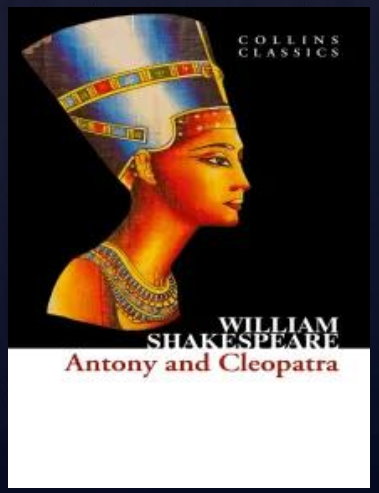
Boccaccio and others fleeing the plague; illumination of a French edition of the Decamerone (c. 1485)

Bubonic Plague 1605-1606

William Shakespeare: ???

Macbeth ? King Lear ?

Antony and Cleopatra



Great Plague (Black Death) of London in 1665

Ancient version of social distancing

Cambridge -> Woolsthorpe Manor

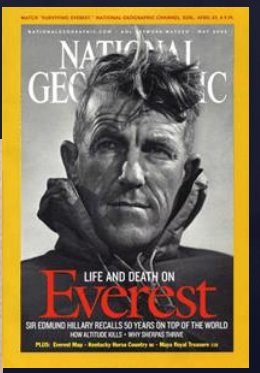
The years of wonders

Early calculus, optics, apple tree ?

Publications/PDB/Google

PubMed title with	
SARS-COV-2	> 27,000
COVID-19	> 125,000
SARS-COV-2 OR COVID-19	> 150,000
Structures in PDB	> 1000
Google COVID-19	> 4,000,000,000
Google SARS-COV-2	> 290,000,000

Little over 68 years ago



Newcastle Journal
North Mail
No. 33,336 TUESDAY JUNE 2 1953 A KEMSLEY NEWSPAPER 2d
6 AM

Britain on top of the world on this Elizabeth II day

EVEREST IS CONQUERED

Queen awakened to hear of climbers' triumph

4-PAGE TV AND RADIO GUIDE INSIDE

COMMENTARY

Queen of all hearts

THIS is a great day. Once more we British make plain to the world that we hold firmly to our way of life.

And, most appropriately, last night brought great news to back the claim that our way usually takes us, in the end, to the top.

At the third attempt, the sixth British expedition, under Col. John Hunt, has conquered Everest. It is the happiest of omens.

Skill, tenacity, courage, and great endurance have overcome the terribly powerful defences of the mightiest mountain on earth.

Right instinct

THE significance of Everest may be clearer to the mass of our people than is the symbolism of the Coronation ceremony.

But they know instinctively that the underlying concern is always for them; for their welfare, their protection, their rights and liberties.

They know, too, something which baffles other peoples; that the Crown has gained in influence far more than has been surrendered in direct power.

Yet, ordinarily, they make no parade whatever of their

2 REACH SUMMIT 11th EXPEDITION

THE QUEEN WAS WAKENED AT BUCKINGH LATE LAST NIGHT TO BE TOLD THAT T EXPEDITION HAS CONQUERED MOUNT EV

This great news, on the eve of the Coronation, reac night in a message to "The Times" from Col. John H the expedition.

The climb was made on F Hunt has reported that "all is

The successful assault was m Hillary, a New Zealander, and th named Tensing Bhutia.

This great feat of the new Elizabethans flashed round the world adding still further joy to the heightening Coronation fever.

Mr. Hillary, aged 34, is a beekeeper in New Zealand. His climbing experience was gained in the Southern Alps in the South Island, a range that has attracted mountaineers from all over the world because of the difficulty of the climbs.

MR. E. P. HILLARY
He reached the summit.

New route

He was an originator of winter ski mountaineering in New Zealand. During the war he served in the Royal New Zealand Air Force.

He had experience in the Himalayas two years ago, when he was a member of the expedition which, led by Eric Shipton, found a way into the Western Cwm.

This discovery opened up a new route for attacks on Everest, and it has been by following up the pioneering work done by Shipton's and other expeditions of the last two years that success has been achieved this time.

Tensing, the "King" of the Sherpa porters of Mount Everest is renowned as one of

DN GOWAY

1 a. R ROUTE BARRIERS ARE CLOSED

CROWD barriers were closed hours before schedule early this morning as tens of thousands of sightseers camped along the Coronation route.

Fifty thousand people jammed in Trafalgar

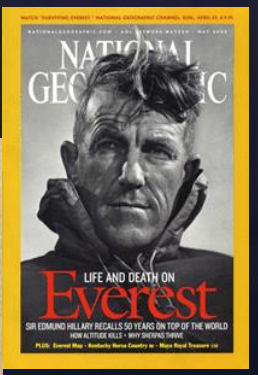
GIRL, 16, STABBED, FRIEND MISSING

AN attractive girl of 16, found dead in the Thames at Richmond yesterday, was murdered and her

Neither cycle has been found.

Duke will watch

Now



AUSTIN
NORTHERN DISTRIBUTORS
MURRAY & CHARLETON
COLLEGE AVE., BARRAS BRIDGE, NEWCASTLE

Newcastle Journal 6 AM
North Mail
No. 33,336 TUESDAY JUNE 2 1953 A KEMSLEY NEWSPAPER 2d

CORONATION PICTURES
See display Coronation photo enlargements by "Manchester Guardian" early tomorrow morning Fenwick windows.
FENWICK OPEN ALL DAY WEDNESDAY

Britain on top of the world on this Elizabeth II day

EVEREST IS CONQUERED

Queen awakened to

COMMENTARY

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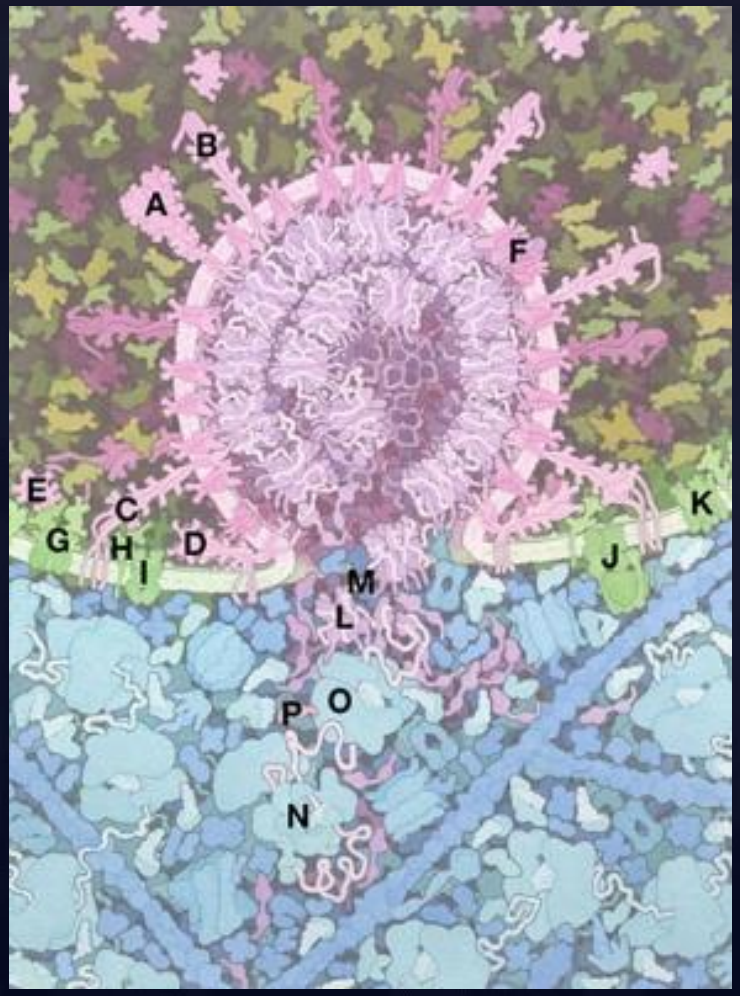
Tensing, the "King" of the Sherpa porters of Mount

Publications/PDB/Google

We have vaccine !!
New drugs are on the way

limited medical and
limited virus knowledge
>266 million cases
>5.2 million deaths

Molecular Landscape: SARS-Cov-2 Fusion (PDB – 101)



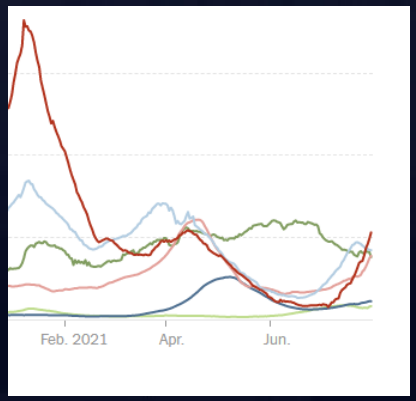
A. Pre-fusion state of the viral spike protein (6crz)
B. Viral spike protein S2 domain, after S1 is released.
C. Viral spike protein inserting into the endosomal membrane
D. Post-fusion state of the viral spike protein (6xra)
E. S1 domain of viral spike
F. Complex of viral M, E (5x29), ORF3a (6xdc) and ORF7a (6w37)
G. ACE2 (6m17)
H. LAMP (5gv0)
I. ABC transporter
J. V-ATPase (5vox)
K. Mucolipin (5wj5)
L. Viral nucleocapsid protein (6m3m, 6wzo)
M. Viral RNA genome
N. Ribosomal initiation complex
O. Translating ribosome
P. Nascent viral polyprotein

AAAS

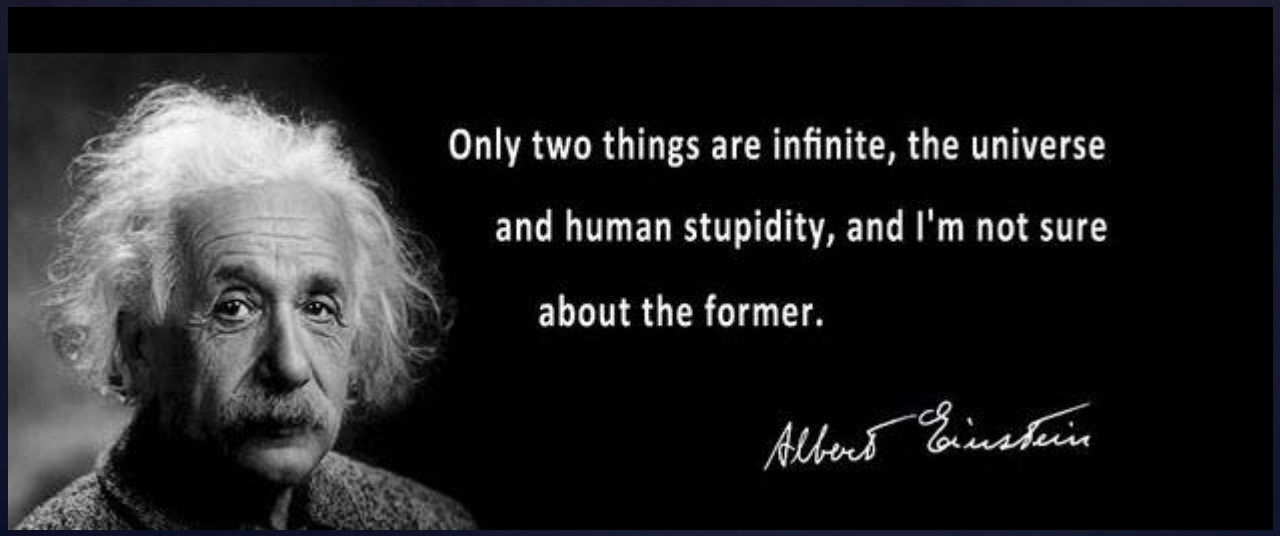
Many (most?) people are getting their news from biased sources.

Misinformation and distrust of science has led to skepticism of the scientific community and its motives.

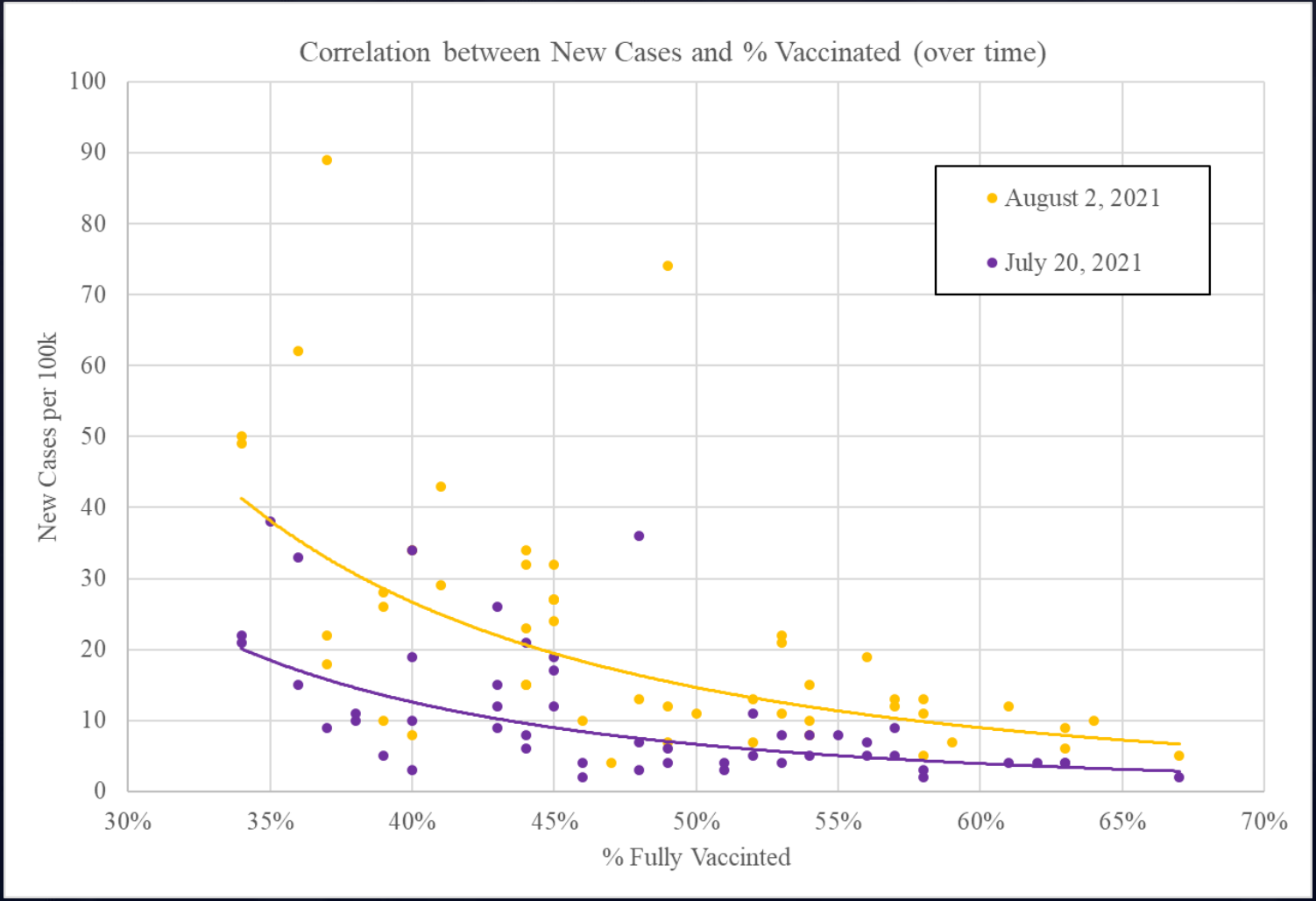
So far we (scientists) have, failed to produce a single message that everyone, even high school dropouts, can easily understand.



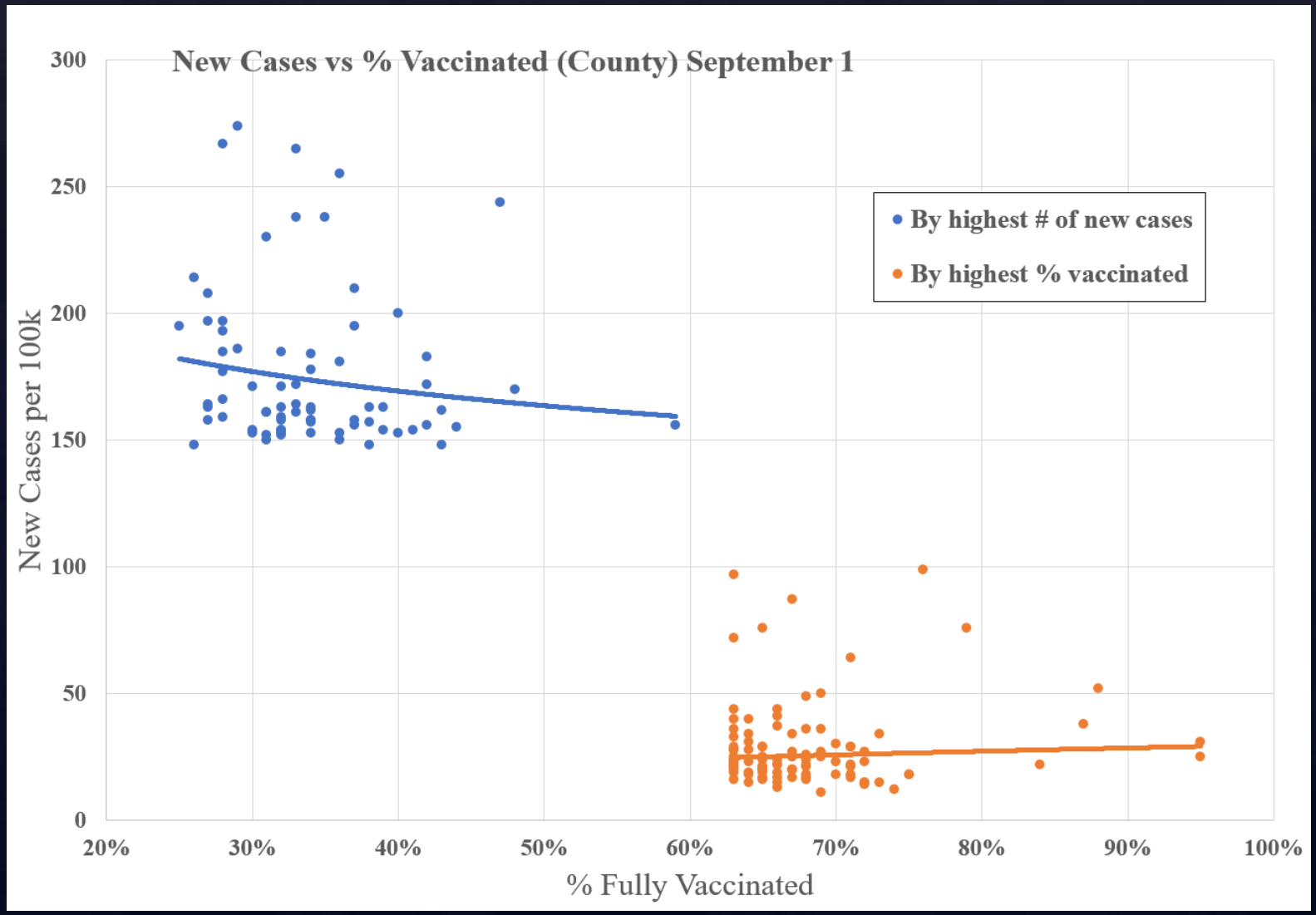
Scientists role ?



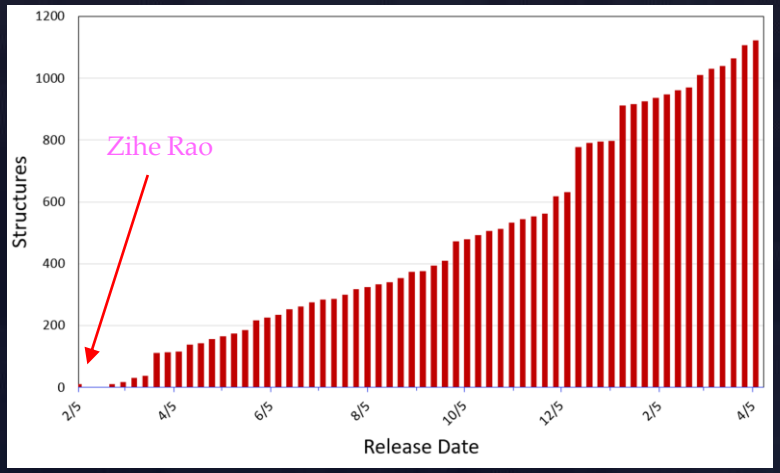
Single message that high school student can understand ?

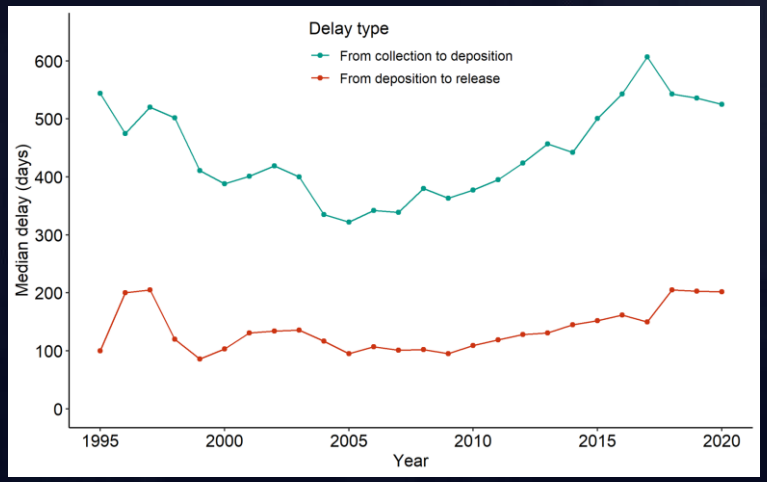


Single message that high school student can understand ?

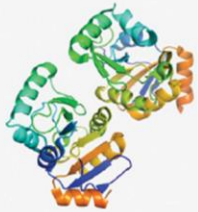


COVID-19 related depositions

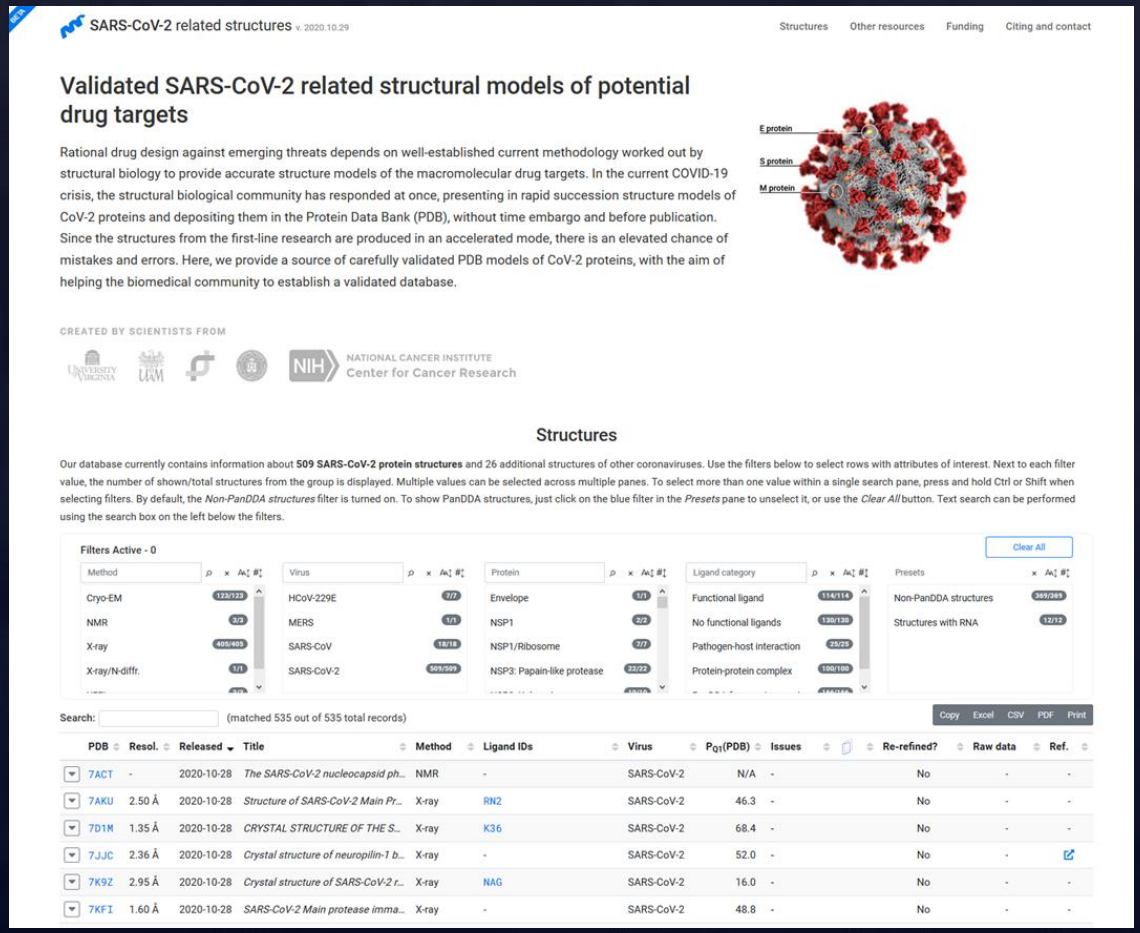




Data collection	
Resolution (Å)	88.12 - 1.17 (1.23 - 1.17)
Wavelength (Å)	0.91188
Space group	P43
a, b, c (Å)	88.12, 88.12, 39.08
α, β, γ (°)	90, 90, 90
Completeness (%)	98.4
Reflections used	100790
<I> / <Sigma I>	3.4
Redundancy	6.3 (5.2)
Rmerge	0.532 !
Rpim	0.231 (5.759) !
CC1/2 last shell	0.36
Wilson B factor (Å²)	11.2
Refinement	
Rwork / Rfree	0.201 / 0.236
Resolution (Å)	88.12 - 1.17
Reflections all	88766
Reflections for Rfree	4499, 5.1%
Bond lengths rmsd (Å)	0.010
Bond angles rmsd (°)	1.12
Mean B value (Å²)	18
Number of protein atoms	2581
Mean B value for protein atoms (Å²)	15
Number of water atoms (expected)	472 (520)
Mean B value for water atoms (Å²)	29
Number of ligand/ion atoms	16
Mean B value for ligand/ion atoms (Å²)	24
Clashscore	3.07
Clashscore percentile (100)	74.8
Rotamer outliers (<1%)	0.70
Ramachandran outliers (<0.2%)	0.00
Ramachandran favored (>98%)	99.09
Residues with bad bonds (<0%)	0.00
Residues with bad angles (<0.1%)	0.45
MolProbity score	1.10

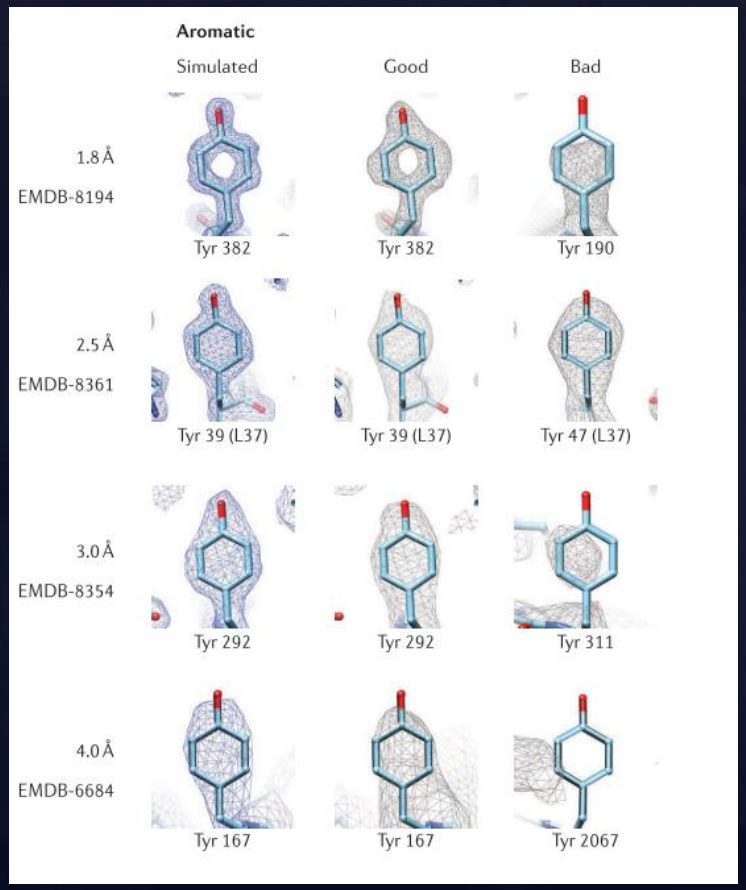


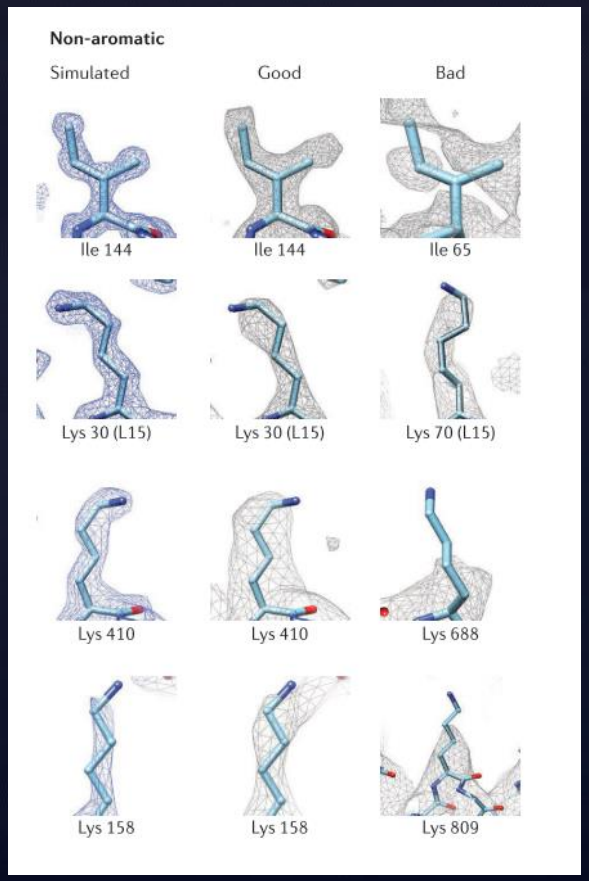
https://covid-19.bioreproducibility.org



A., Wlodawer *et al.*,(2020) *FEBS J.*, **287**, 3703–3718
I., Shabalin *et al.*, (2020). *IUCrJ.*, **7**, 1048–1058.
D. Brzezinski *et al.*, (2021) *Protein Sci.*, 30, 115–124
M. Grabowski *et al.*, (2021) *IUCrJ*, **8**, 395–407
M. Kowiel *et al.*, (2019) *Bioinformatics*, **35**, 452–461

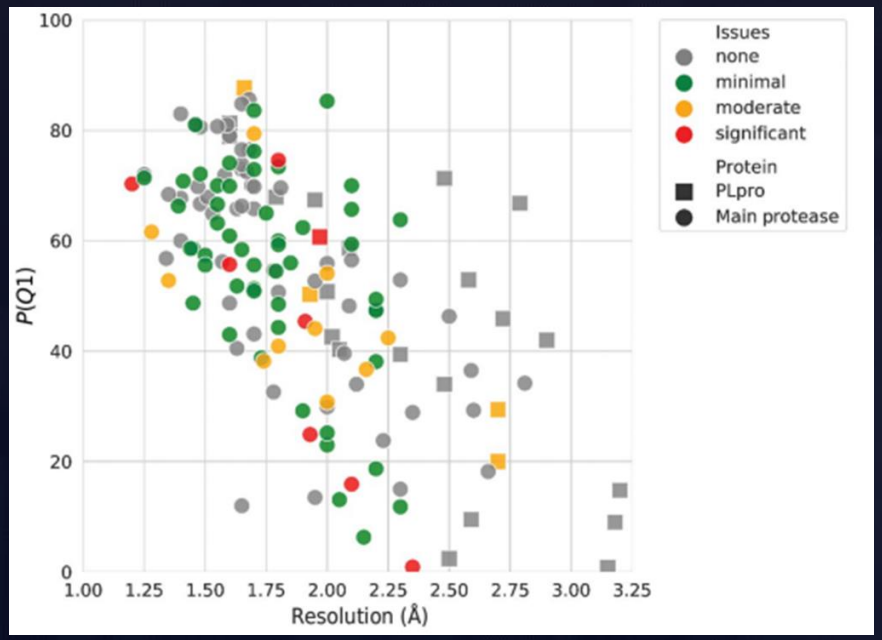
Difficulties to distinguish particle images that may belong to different conformations

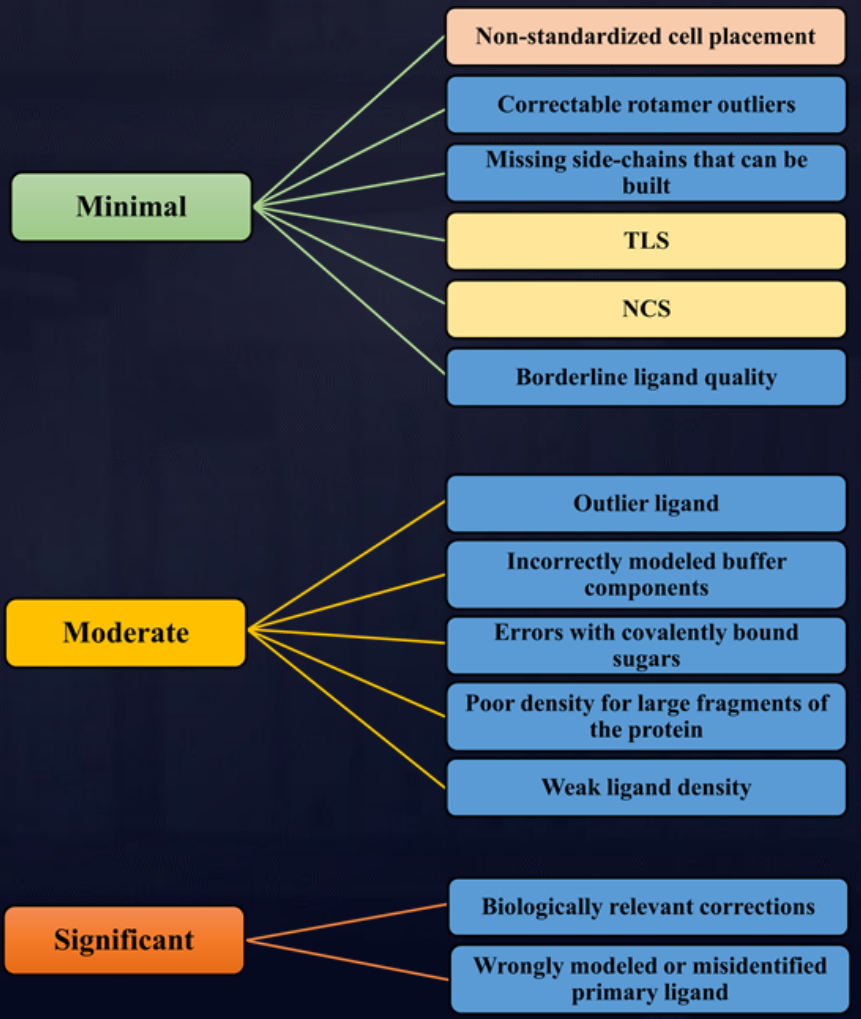


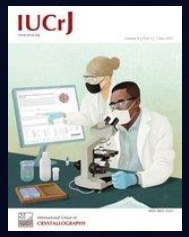


Renaud, J-P et al. *Nature Reviews Drug Discovery (2018)* **17**, 471-492

Possible corrections

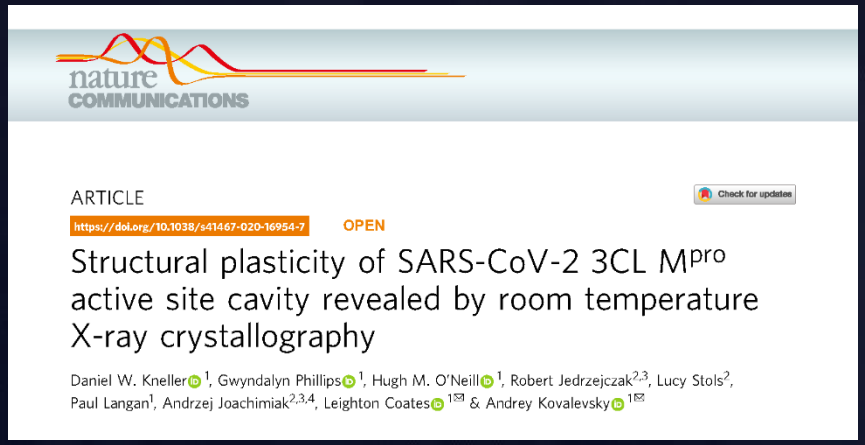






M. Grabowski *et al.*, (2021) *IUCrJ*, **8**, 395–407

Should we trust the model?
Should we blindly follow new methodology?



nature COMMUNICATIONS

ARTICLE

https://doi.org/10.1038/s41467-020-16954-7 OPEN

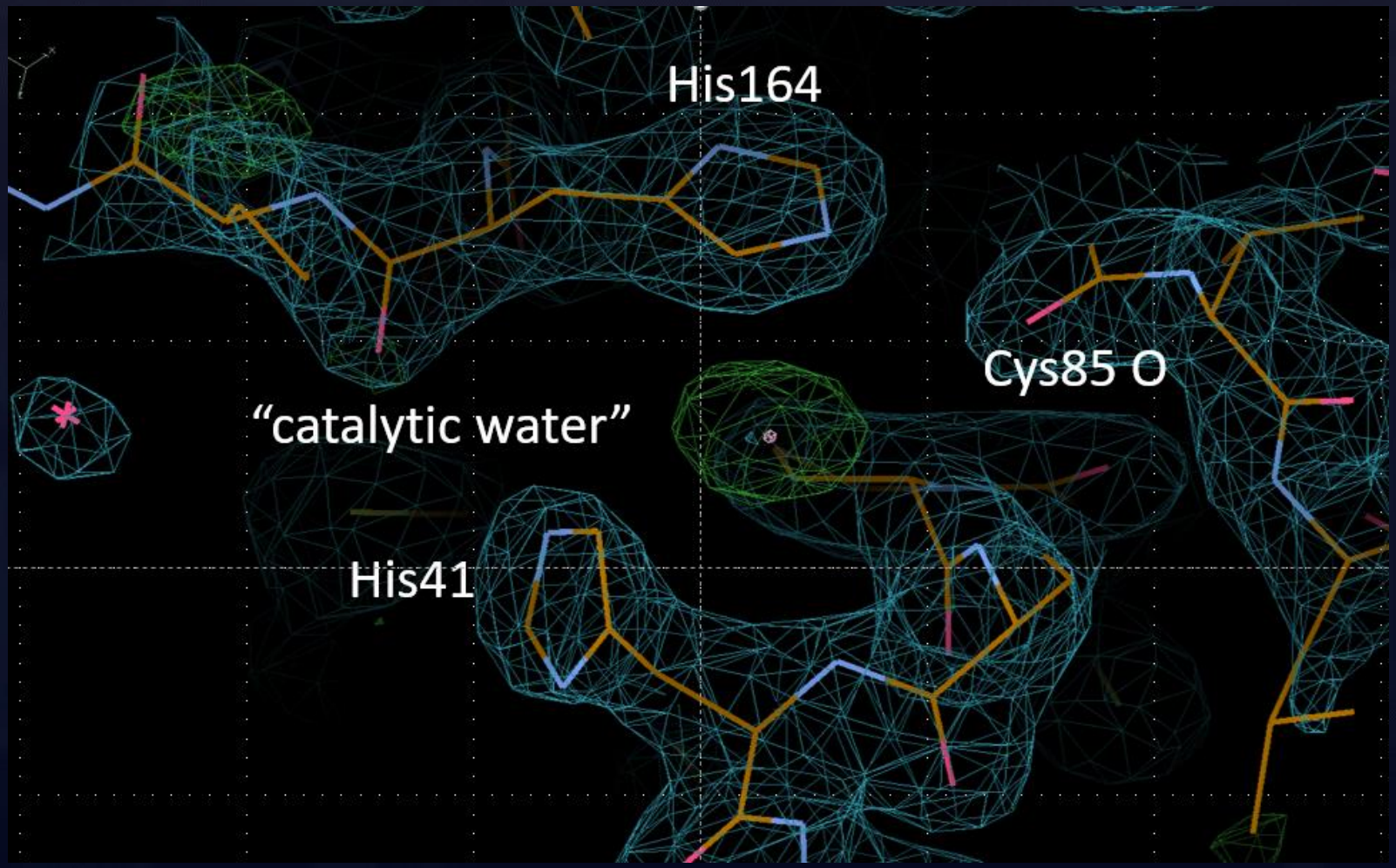
Check for updates

Structural plasticity of SARS-CoV-2 3CL M^{pro} active site cavity revealed by room temperature X-ray crystallography

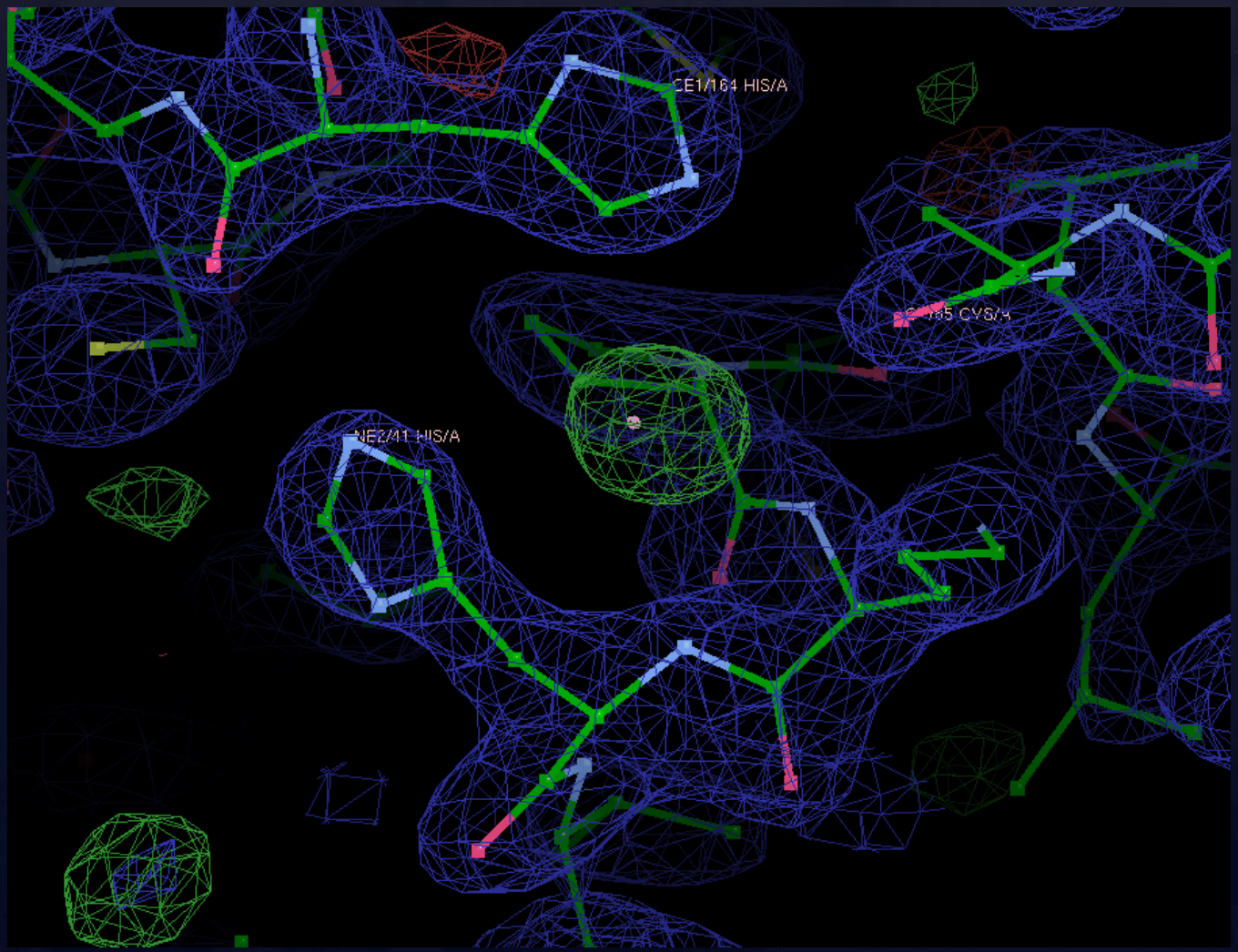
Daniel W. Kneller[1], Gwyndalyn Phillips[1], Hugh M. O'Neill[1], Robert Jedrzejczak[2,3], Lucy Stols[2], Paul Langan[1], Andrzej Joachimiak[2,3,4], Leighton Coates[1✉] & Andrey Kovalevsky[1✉]

H_2O_{cat} is involved in a complex network of interactions, mediating polar contacts between the catalytic His41, a conserved His164, and a conserved Asp187 located in the domain II–III junction. It is not unreasonable to suggest that this water may play a role of the third catalytic residue, completing the non-canonical catalytic triad in 3CL M^{pro} and acting to stabilize the positive charge on His41 by mediating its electrostatic interaction with the negatively charged Asp187 during catalysis. We note that in some X-ray structures of the ligand-free 3CL M^{pro} from SARS-CoV-2 (e.g., PDB ID 6M03) obtained at 100 K, this potentially crucial water molecule is absent.

Should we trust the model or check the map too?



Should we trust the automation ?
PDB_REDO



Enemy of knowledge

The greatest enemy of knowledge is not ignorance, but the illusion of knowledge

Stephen Hawking

Automatic Ligand Recognition CMB server

Bioinformatics, 2018, 1–10
doi: 10.1093/bioinformatics/bty626
Advance Access Publication Date: 17 July 2018
Original Paper

OXFORD

Structural bioinformatics

Automatic recognition of ligands in electron density by machine learning

Marcin Kowiel[1,2], Dariusz Brzezinski[3,2], Przemyslaw J. Porebski[2,4], Ivan G. Shabalin[2,4], Mariusz Jaskolski[1,5] and Wladek Minor[2,4,*]

[1]Center for Biocrystallographic Research, Institute of Bioorganic Chemistry, Polish Academy of Sciences, Poznan 61-704, Poland, [2]Department of Molecular Physiology and Biological Physics, University of Virginia, Charlottesville, VA 22908, USA, [3]Institute of Computing Science, Poznan University of Technology, Poznan 60-965, Poland, [4]Center for Structural Genomics of Infectious Diseases (CSGID), University of Virginia, Charlottesville, VA 22908, USA and [5]Department of Crystallography, Faculty of Chemistry, A. Mickiewicz University, Poznan 61-614, Poland

Misidentified ligands replaced by correct ones and re-refined

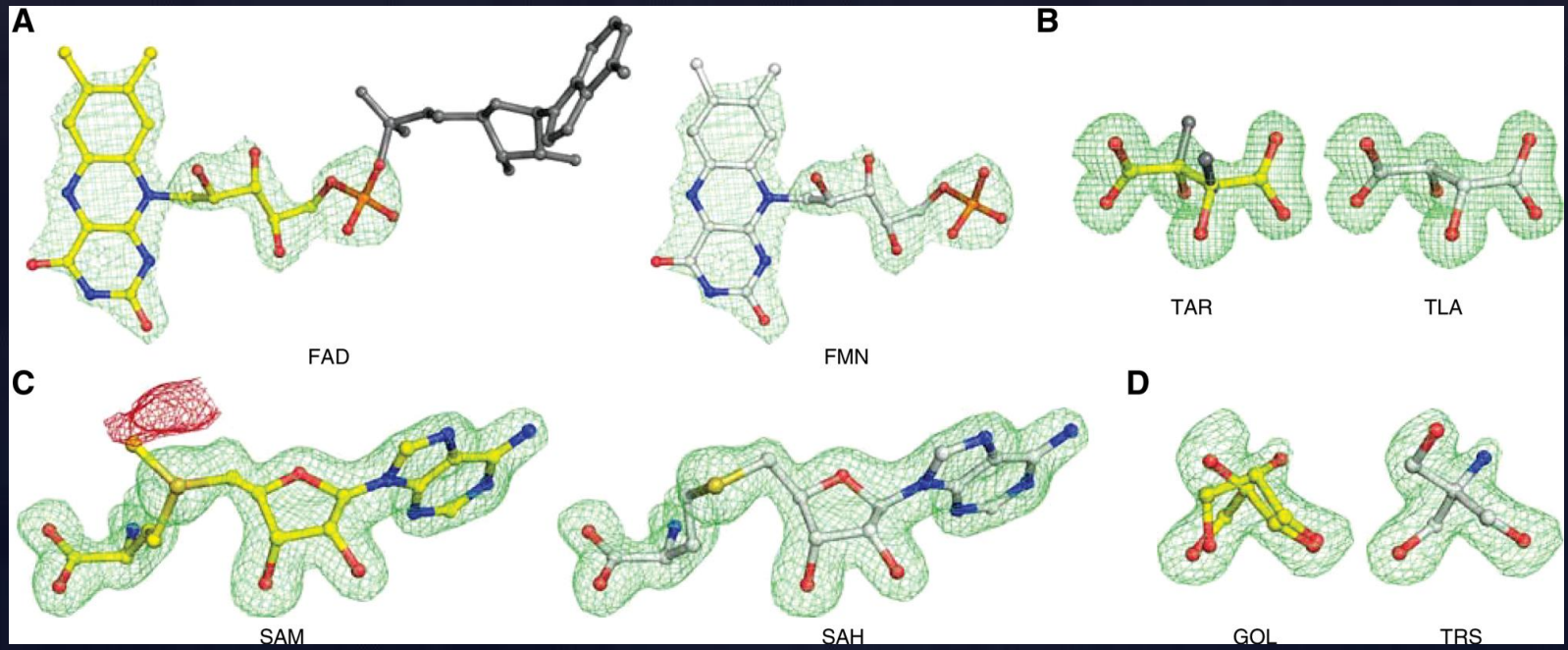


Table 3. Summary of refinement and structure quality statistics for original and re-refined structures

Pdb code^{O}	Wrong ligand	Resolution^{O} [Å]	R/R$_{free}$ ^{O}	Clashscore^{O}	RMSD bonds ^{O} [Å]	Pdb code^{R}	Correct ligand	Resolution^{R} [Å]	R/R$_{free}$ ^{R}	Clashscore^{R}	RMSD bonds^{R} [Å]
2PDT	FAD	2.20	0.234/0.266	21.4	0.008	6CNY	FMN	2.10	0.163/0.204	1.5	0.014
1KWN	TAR	1.20	0.127/0.145	4.7	0.016	6COA	TLA	1.20	0.103/0.117	0.6	0.011
1FPX	SAM	1.65	0.218/0.235	8.3	0.021	6CIG	SAH	1.65	0.146/0.174	4.2	0.013
4RK3	GOL	1.80	0.157/0.200	1.4	0.019	6CHK	TRS	1.80	0.140/0.190	0.7	0.014

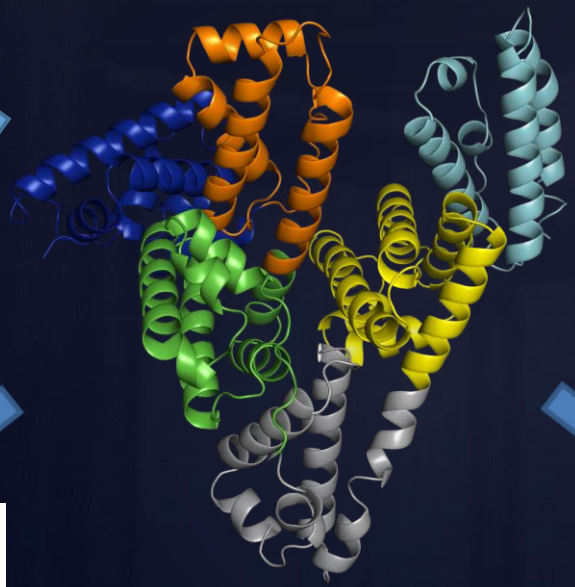
6ynq – 63 authors

```
HETATM 5233  O   HOH A 779      12.134  21.849   2.556  0.99 36.92
HETATM 5234  O   HOH A 780      20.976  16.925 -17.973  1.00 29.65
HETATM 5235  O   HOH A 781       7.156  11.891   0.609  1.00 32.26
HETATM 5236  O   HOH A 782       9.160  13.668   2.975  1.00 39.62
HETATM 5237  O   HOH A 783      -2.844  17.355 -11.320  0.78 44.36
HETATM 5238  O   HOH A 784      -2.690  -1.620  11.824  0.96 47.72
HETATM 5239  O   HOH A 785      21.475 -13.209   1.917  1.00 43.20
HETATM 5240  O   HOH A 786      14.513  26.179   4.420  0.99 48.21
HETATM 5241  O   HOH A 787       7.432  19.965  -0.463  0.92 23.78
HETATM 5242  O   HOH A 788      18.335   3.449 -12.952  1.00 47.72
HETATM 5243  O   HOH A 789      22.196  12.988   5.126  0.96 38.25
HETATM 5244  O   HOH A 790       2.026 -19.646  21.758  1.00 55.79
HETATM 5245  O   HOH A 791      15.784  24.839   7.648  0.92 34.54
HETATM 5246  O   HOH A 792      23.665  -5.935   1.781  0.92 32.14
```

Corrected 7 times between 4/29/20 and 5/19/21

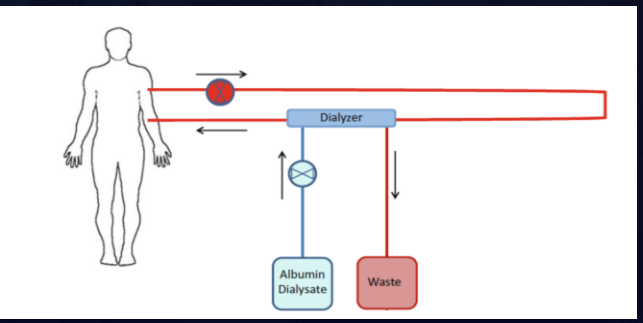
SA – application in medicine

Vaccines



Treatment of various diseases, (e.g., burns, cirrhosis)

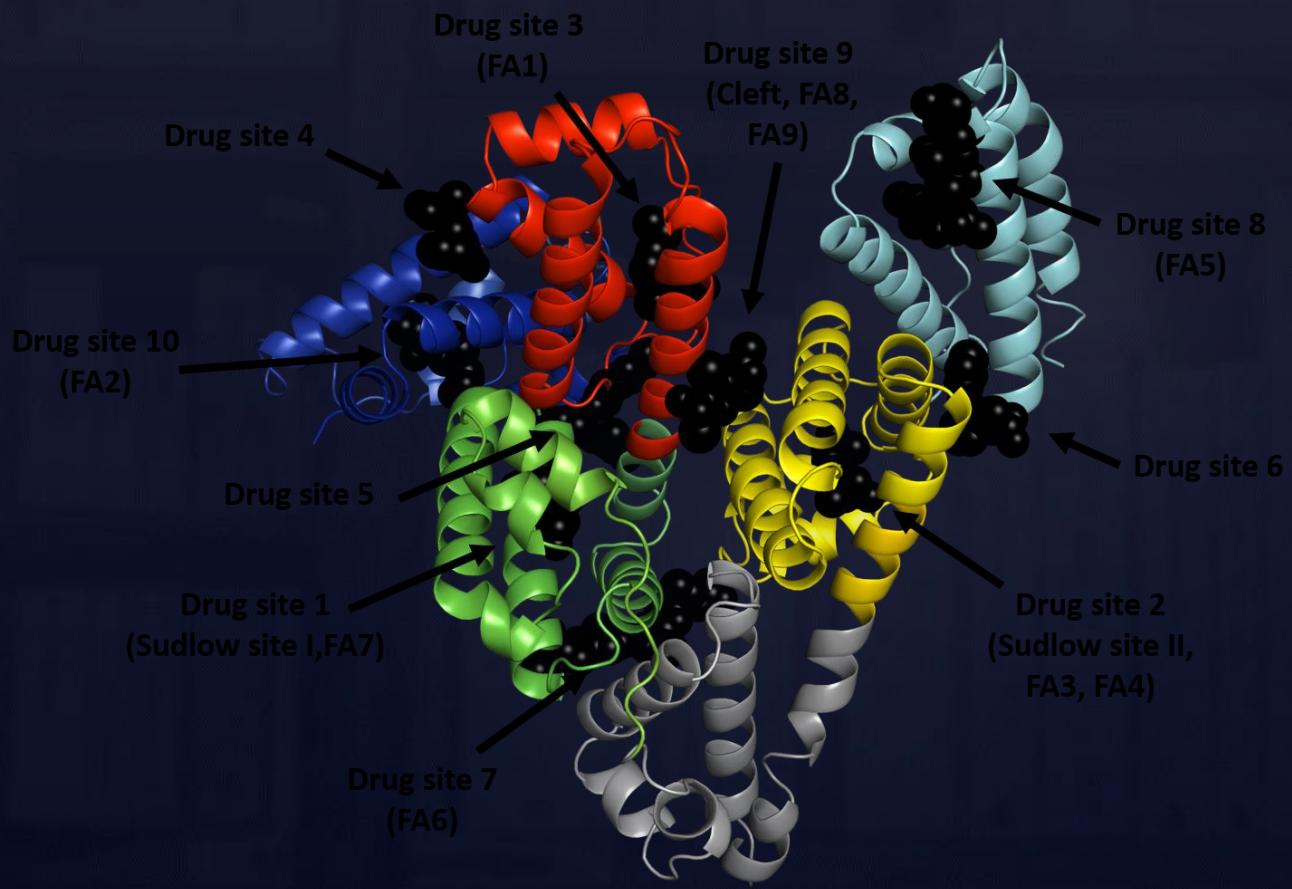
Blood detoxification



Prognostic factor of outcomes in patients

Wiedmann R. T. et al., *Vaccine*, 33, 2132–40 (2015).
Bi C. et al., *Separations*, DOI:10.3390/separations3030027.
Otagiri M. and Chuang V. T., *Albumin in medicine: Pathological and clinical applications*, 2016.
Czub M. P. et al., *J. Med. Chem.*, 63, 6847–6862 (2020).

Summary of known SA drug-binding sites



Drug-binding sites on SA

Czub M. P. et al., *J. Med. Chem.*,(2020) 63, 6847–6862.

Summary of SA drug-binding sites and FDA-approved drugs that were reported to bind in these sites

Drug site 1 (Sudlow site I, FA7)	Drug site 2 (Sudlow Site II, FA3, FA4)	Drug site 3 (FA1)	Drug site 4	Drug site 5	Drug site 6	Drug site 7 (FA6)	Drug site 8 (FA5)	Drug site 9 (Cleft, FA8, FA9)	Drug site 10 (FA2)
Amantadine (HSA)	Aripiprazole (HSA)	**Ampicillin (ESA)**	Cetirizine (ESA)	Etoposide (HSA)	Diclofenac (ESA, OSA, CSA)	**6-MNA (ESA)**	Fusidic acid (HSA)	Diclofenac (CSA)	Halothane (HSA)
Aspirin / salicylic acid (HSA)	Diazepam (HSA)	Azapropazone (HSA)	Diclofenac (OSA, CSA)		**Ketoprofen (ESA, LSA)**	Ampicillin (ESA)	Propofol (HSA)	Iodipamine (HSA)	**Ketoprofen (ESA)**
Azapropazone (HSA)	Diclofenac (ESA, OSA, CSA)	Bicalutamide (HSA)	**Ibuprofen (ESA)**		**Nabumetone / 6-MNA (ESA)**	Cetirizine (ESA)	Thyroxine (HSA)	**Ketoprofen (HSA)**	**Tolbutamide (ESA)**
Diclofenac (HSA)	Diflunisal (HSA)	Diclofenac (HSA, OSA, CSA)	**Ketoprofen (ESA)**		Naproxen (LSA)	**Dexamethasone (ESA)**		Thyroxine (HSA)	
Diflunisal (HSA)	**Haloperidol (ESA)**	**Etodolac (ESA)**	**Progesterone (ESA)**		Oxyphenbutazone (HSA)	Diclofenac (HSA, OSA, CSA)		**Tolbutamide (ESA)**	
Etodolac (ESA)	Halothane (HSA)	Fusidic acid (HSA)	**Testosterone (ESA)**			Diflunisal (HSA)			
Halothane (HSA)	**Ibuprofen (HSA, ESA)**	Idarubicin (HSA)	**Tolbutamide (ESA)**			**Etodolac (ESA)**			
Indomethacin (HSA)	**Ketoprofen (HSA, LSA)**	Indomethacin (HSA)				Halothane (HSA)			
Iodipamine (HSA)	**Nabumetone / 6-MNA (ESA)**	**Ketoprofen (HSA)**				Ibuprofen (HSA, ESA)			
Ketoprofen (BSA)	Naproxen (ESA, BSA, LSA)	Lidocaine (HSA)				Naproxen (ESA, BSA, LSA)			
Naproxen (BSA)	Phenylbutyric acid (HSA)	Naproxen (HSA)				**Testosterone (ESA)**			
Oxyphenbutazone (HSA)	Propofol (HSA)	Salicylic acid (HSA)							
Phenylbutazone (HSA)	Suprofen (ESA)	Teniposide (HSA)							
Thyroxine (HSA)	Thyroxine (HSA)	Zidovudine (HSA)							
Warfarin (HSA)	**Tolbutamide (ESA)**								
Zidovudine (HSA)	**Warfarin (ESA)**								

Structures determined in my lab are shown in red

Czub M. P. et al., *J. Med. Chem.*, 63, 6847–6862 (2020).

Problem solving approach
Integration of Structure and medical data

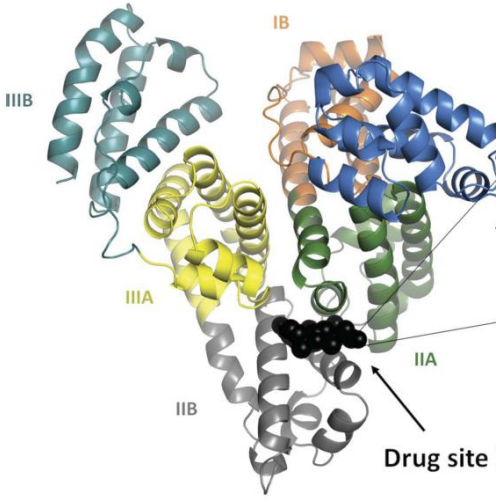


Figure 1
The overall structure of the ESA–dexamethasone complex. The elect
($mF_o - DF_c$ map, calculated after ten refinement cycles without the ligar
with Roman numerals and letters (*e.g.* IA). The dexamethasone molecul
F atom in cyan. The chemical structure of dexamethasone is displayed in
the OMIT maps, and the model can be inspected interactively at https:

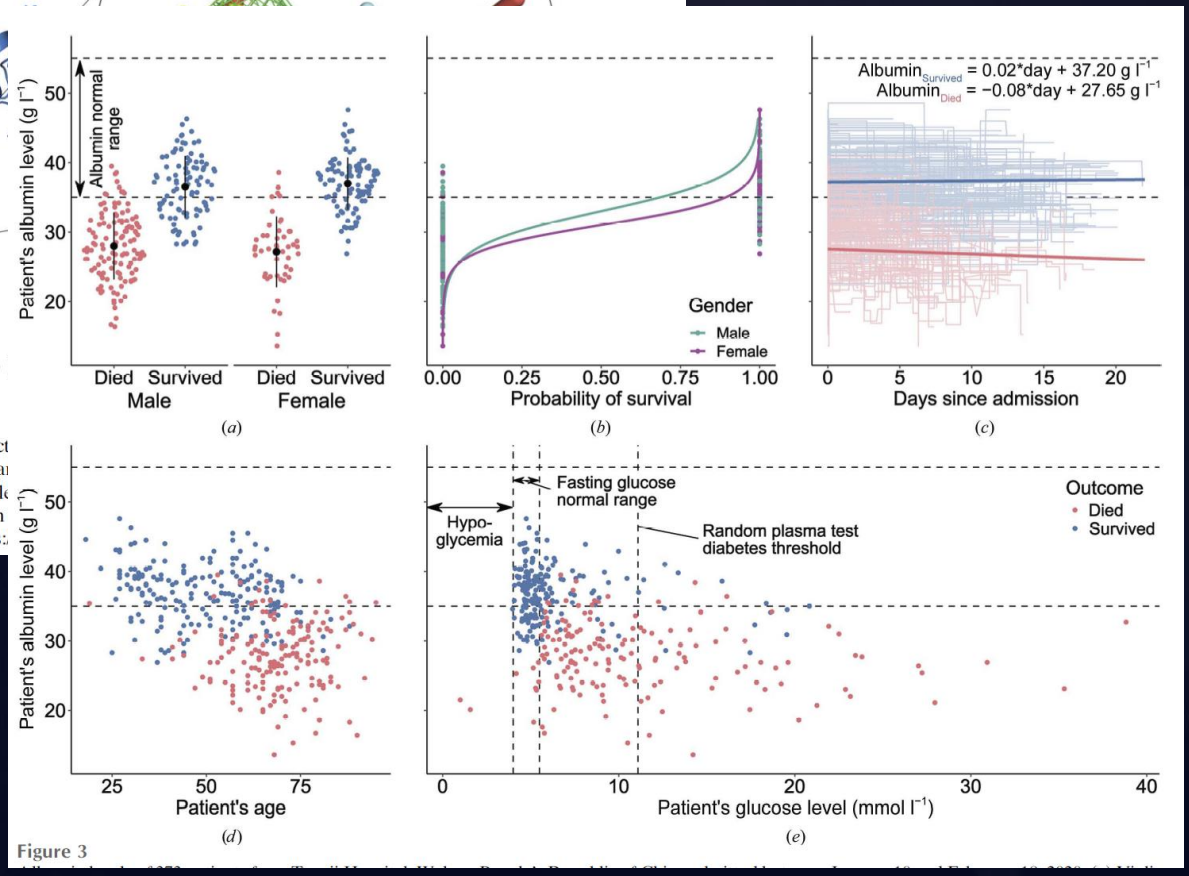
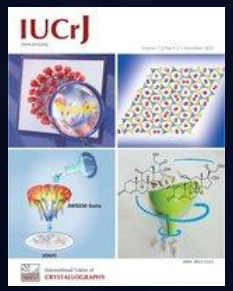
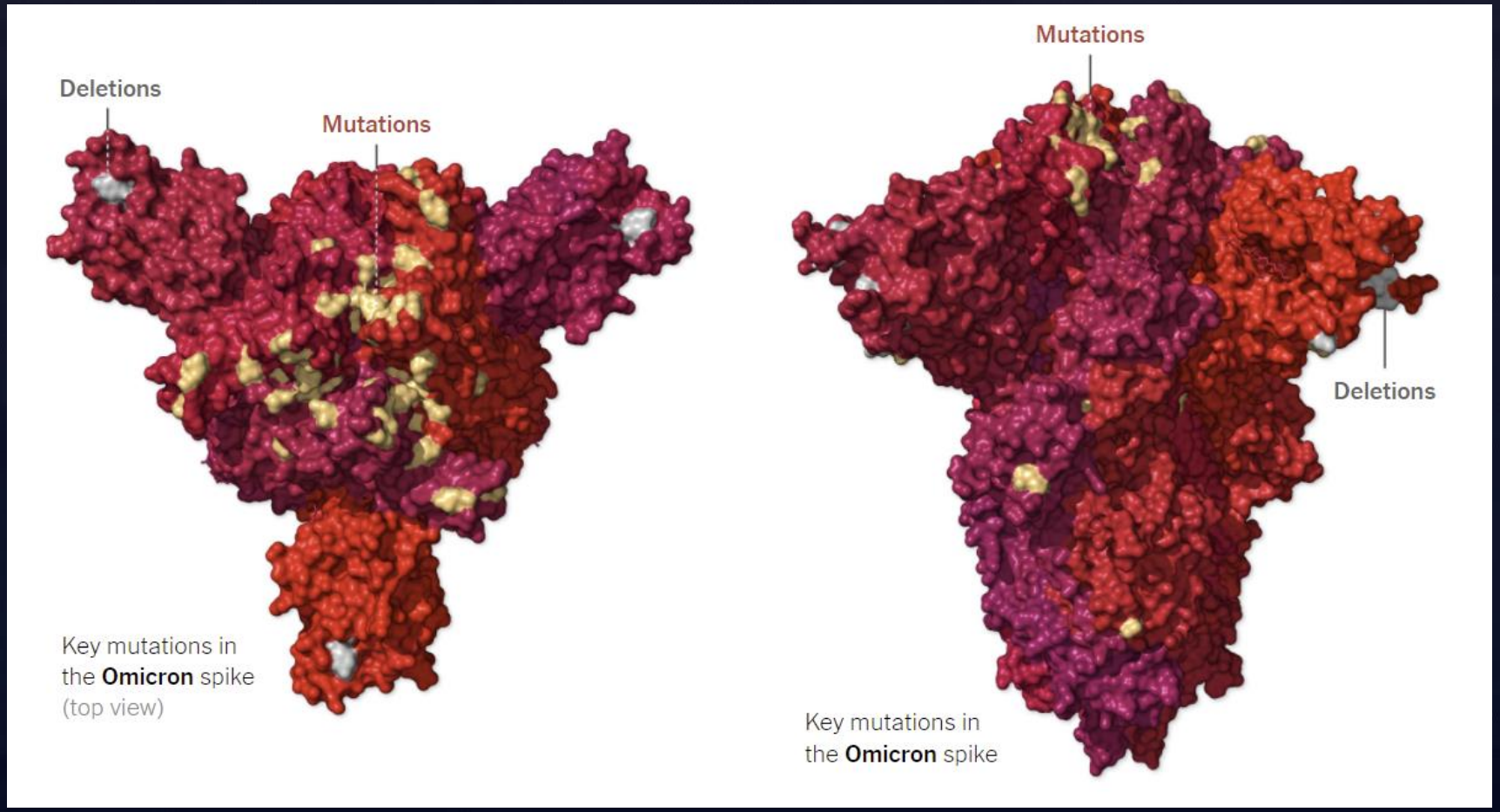


Figure 3



M. Schabalin *et al.*, (2020) *IUCrJ*, **6**, 1048–58

OMICRON


Deletions
Mutations
Key mutations in the **Omicron** spike (top view)
Mutations
Deletions
Key mutations in the **Omicron** spike

Targeting the receptor-binding domain - RDB

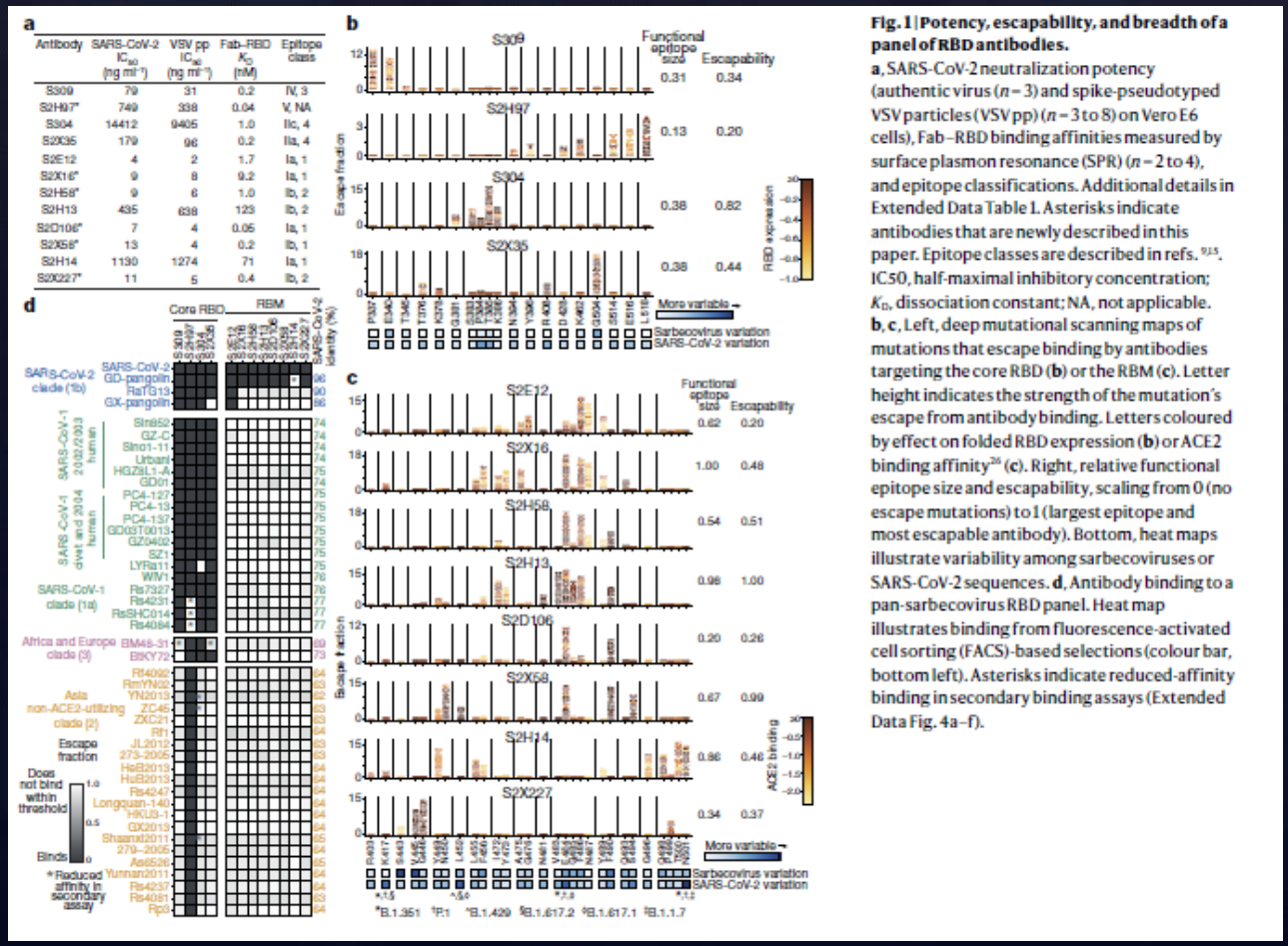


Fig. 1 | Potency, escapability, and breadth of a panel of RBD antibodies.
a, SARS-CoV-2 neutralization potency (authentic virus ($n = 3$) and spike-pseudotyped VSV particles (VSVpp) ($n = 3$ to 8) on Vero E6 cells), Fab–RBD binding affinities measured by surface plasmon resonance (SPR) ($n = 2$ to 4), and epitope classifications. Additional details in Extended Data Table 1. Asterisks indicate antibodies that are newly described in this paper. Epitope classes are described in refs. [9,15]. IC50, half-maximal inhibitory concentration; K_D, dissociation constant; NA, not applicable. **b**, **c**, Left, deep mutational scanning maps of mutations that escape binding by antibodies targeting the core RBD (**b**) or the RBM (**c**). Letter height indicates the strength of the mutation's escape from antibody binding. Letters coloured by effect on folded RBD expression (**b**) or ACE2 binding affinity[26] (**c**). Right, relative functional epitope size and escapability, scaling from 0 (no escape mutations) to 1 (largest epitope and most escapable antibody). Bottom, heat maps illustrate variability among sarbecoviruses or SARS-CoV-2 sequences. **d**, Antibody binding to a pan-sarbecovirus RBD panel. Heat map illustrates binding from fluorescence-activated cell sorting (FACS)-based selections (colour bar, bottom left). Asterisks indicate reduced-affinity binding in secondary binding assays (Extended Data Fig. 4a–f).

Starr, N. *et al*. (2021) *Nature* 597:97-102

SOTROVIMAB and OMICRON

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SARS-CoV-2 RBD antibodies that maximize breadth and resistance to escape.

Starr TN, Czudnochowski N, Liu Z, Zatta F ... Veesler D, Corti D, Bloom JD, Snell G.
Nature 2021 09; 597(7874):97-102

PMID: 34261126 | DOI: 10.1038/s41586-021-03807-6

Recommended ★★★

Wladek Minor
Faculty Member
Faculty Opinions Structural Biology
University of Virginia, Charlottesville, VA, USA.

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3 Sep 2021 | New Finding, Technical Advance

This large international team of researchers (over 50 researchers from 14 institutions) report on a new therapy based on a natural antibody discovered in the blood of a SARS survivor. This antibody called S309 neutralizes not only all known SARS-CoV-2 strains but also the original SARS-CoV virus. Combined X-ray crystallography and cryo-EM studies elucidated structural maps of how these antibodies bind to the SARS-CoV-2 spike protein. Based on structural and other findings, researchers have designed a novel antibody therapy called sotrovimab. Sotrovimab has recently received emergency use authorization from the FDA for the treatment of COVID-19.

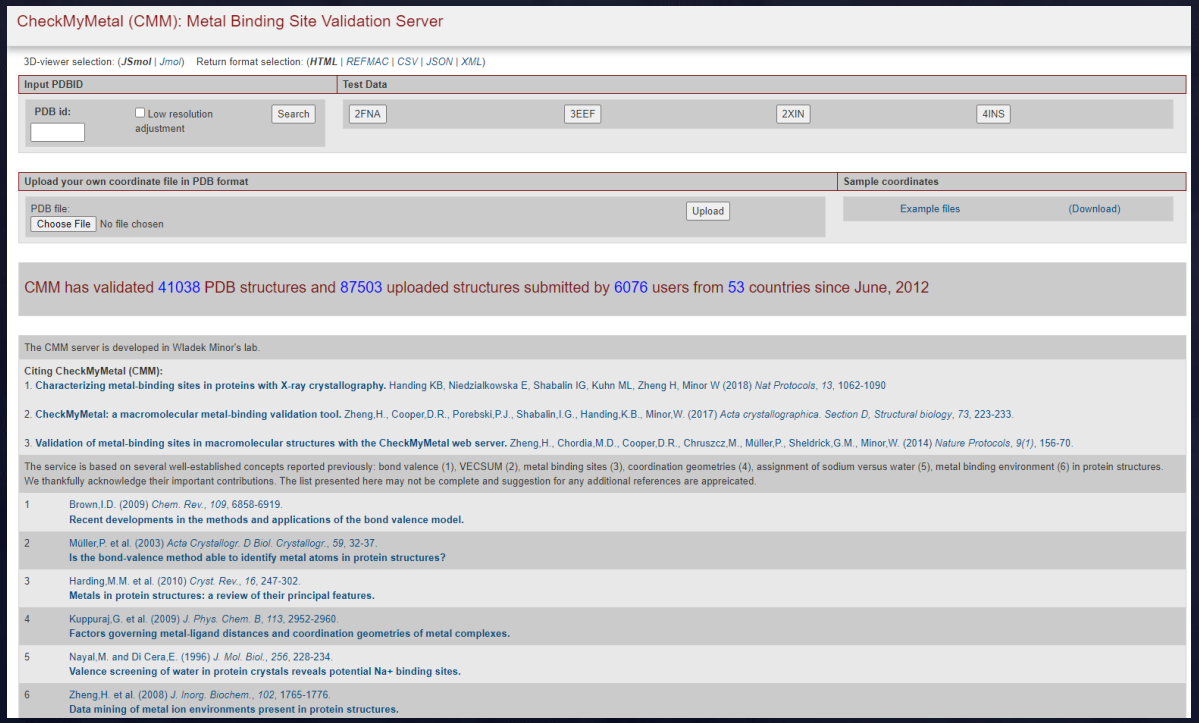
Article

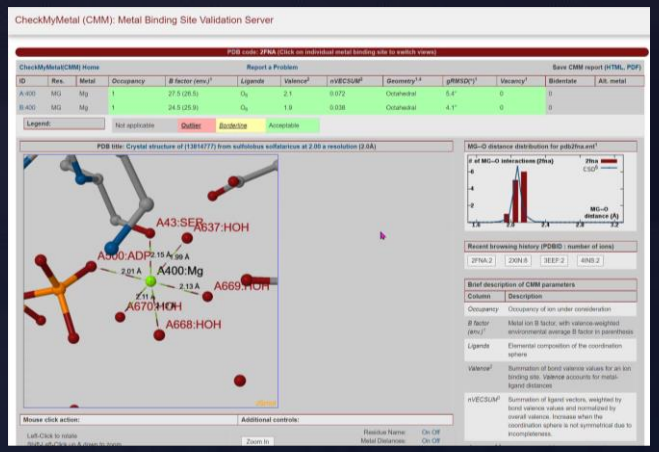
SARS-CoV-2 RBD antibodies that maximize breadth and resistance to escape

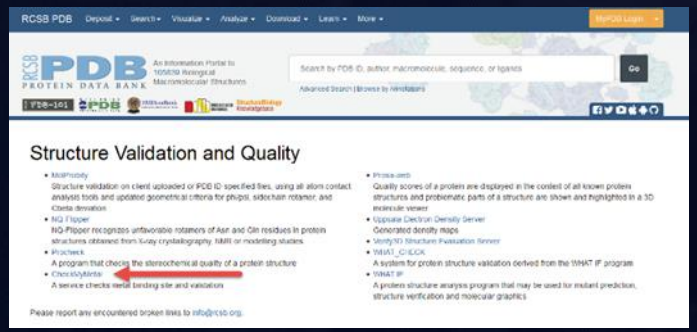
https://doi.org/10.1038/s41586-021-03807-6
Received: 29 March 2021
Accepted: 6 July 2021
Published online: 14 July 2021
Check for updates

Tyler N. Starr[1,15], Nadine Czudnochowski[2,15], Zhuoming Liu[3,15], Fabrizia Zatta[4], Young-Jun Park[5], Amin Addetia[1], Dora Pinto[4], Martina Beltramello[4], Patrick Hernandez[2], Allison J. Greaney[1,6], Roberta Marzi[4], William G. Glass[7], Ivy Zhang[7,8], Adam S. Dingens[1], John E. Bowen[5], M. Alejandra Tortorici[5], Alexandra C. Walls[5], Jason A. Wojcechowskyj[2], Anna De Marco[4], Laura E. Rosen[2], Jiayi Zhou[3], Martin Montiel-Ruiz[2], Hannah Kaiser[2], Josh R. Dillen[2], Heather Tucker[2], Jessica Bassi[4], Chiara Silacci-Fregni[4], Michael P. Housley[2], Julia di Iulio[2], Gloria Lombardo[4], Maria Agostini[2], Nicole Sprugasci[4], Katja Culap[4], Stefano Jaconi[4], Marcel Meury[2], Exequiel Dellota Jr[2], Rana Abdelnabi[9], Shi-Yan Caroline Foo[9], Elisabetta Cameroni[4], Spencer Stumpf[2], Tristan I. Croll[10], Jay C. Nix[11], Colin Havenar-Daughton[2], Luca Piccoli[4], Fabio Benigni[4], Johan Neyts[9], Amalio Telenti[2], Florian A. Lempp[2], Matteo S. Pizzuto[4], John D. Chodera[7], Christy M. Hebner[2], Herbert W. Virgin[2,12,13], Sean P. J. Whelan[3], David Veesler[5], Davide Corti[4] ✉, Jesse D. Bloom[1,6,14] ✉ & Gyorgy Snell[2] ✉

Check My Metal CMM







Zheng et al. *Nature protocols* (2014)9: 156-70
Zheng et al. *Acta Cryst. D.* (2017)9: 156-70
Handing et al. *Nature protocols* (2018)13: 1062-1090

4YPM Mg ? - no

CheckMyMetal (CMM): Metal Binding Site Validation Server

PDB code: **UNKNOWN** (Click on individual metal binding site to switch views)

CheckMyMetal(CMM) Home | Report a Problem | Save CMM report (HTML, PDF)

ID	Res.	Metal	*Occupancy*	*B factor (env.)*[1]	*Ligands*	*Valence*[2]	*nVECSUM*[3]	*Geometry*[1,4]	*gRMSD*(°)[1]	*Vacancy*[1]	Bidentate	Alt. metal
A:801	BO2	B26	1	16.2 (15.8)	O_3	1.9	0.44	Tetrahedral	7.9°	25%	0	
A:802	MG	Mg	1	25.3 (15.2)		N/A	N/A	Free	N/A	N/A	N/A	Mg

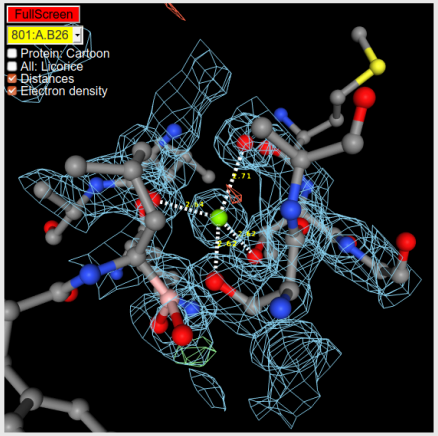
Legend: Not applicable | Outlier | *Borderline* | Acceptable

Generate a model with alt. metal: Select the metal(s) above and Change Without Refinement | Change With Refinement

Timing: Instant | 1 min-few mins

PDB title: Crystal structure of a lona protease domain in complex with

Warning: *Valence* and *nVECSUM* parameters should be interpreted with great care due to the presence of multi-nuclear metal clusters around A:801



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Crystallization conditions:

0.2 M SODIUM CITRATE PH 6.5 AND 10 %
PEG 3350, EVAPORATION, TEMPERATURE 295K

Brief description of CMM parameters

Column	Description
Occupancy	Occupancy of ion under consideration
B factor (env.)[1]	Metal ion B factor, with valence-weighted environmental average B factor in parenthesis
Ligands	Elemental composition of the coordination sphere
Valence[2]	Summation of bond valence values for an ion binding site. *Valence* accounts for metal-ligand distances
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Geometry[1,4]	Arrangement of ligands around the ion, as defined by the *NEIGHBORHOOD* algorithm
gRMSD(°)[1]	R.M.S. Deviation of observed geometry angles (L-M-L angles) compared to ideal geometry, in degrees
Vacancy[1]	Percentage of unoccupied sites in the coordination sphere for the given geometry
Bidentate	Number of residues that form a bidentate interaction instead of being considered as multiple ligands
Alt. metal	A list of alternative metal(s) is proposed in descending order of confidency, assuming metal environment is accurately

4YPM Na (very possible)

CheckMyMetal (CMM): Metal Binding Site Validation Server

PDB code: **UNKNOWN** (Click on individual metal binding site to switch views)

CheckMyMetal(CMM) Home | Report a Problem | Save CMM report (HTML, PDF)

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A:801	BO2	B26	1	19.1 (16.3)	O_3	2.3	0.45	Trigonal Bipyramidal	5.9°	40%	0	
B:1	NA	Na	1	25.2 (15.7)	O_3	0.3	0.39	Tetrahedral	8.9°	25%	0	Na

Legend: Not applicable | Outlier | Borderline | Acceptable

Generate a model with alt. metal: Select the metal(s) above and Change Without Refinement / Change With Refinement

Timing: Instant / 1 min-few mins

PDB title: Crystal structure of a lona protease domain in complex with

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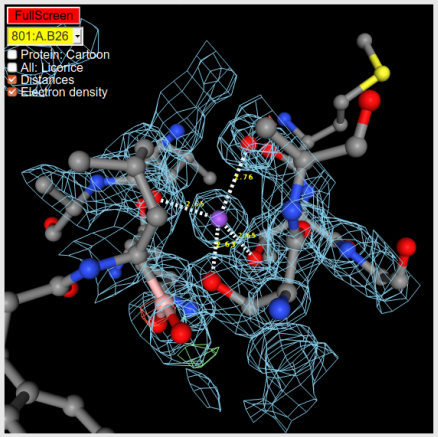
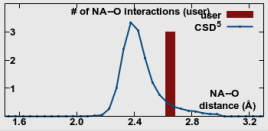


NA--O distance distribution for hkl_refine_3.pdb[1]



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Mouse click action:

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Shift-Left-Click left & right to rotate on Z
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Crystallization conditions:

0.2 M SODIUM CITRATE PH 6.5 AND 10 %
PEG 3350, EVAPORATION, TEMPERATURE 295K

4YPM K - no

CheckMyMetal (CMM): Metal Binding Site Validation Server

PDB code: **UNKNOWN** (Click on individual metal binding site to switch views)

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B:1	K	K	1	37.5 (15.5)	O_5	0.9	0.11	Trigonal Bipyramidal	12.3°	0	0	K

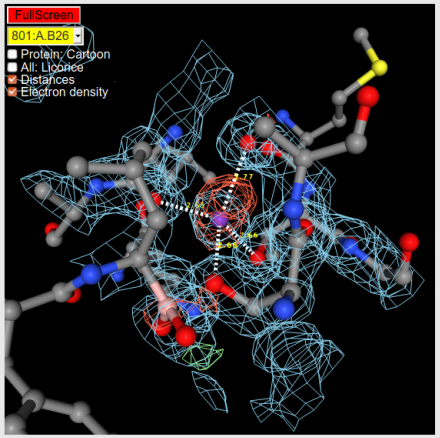
Legend: Not applicable | Outlier | Borderline | Acceptable

Generate a model with alt. metal: Select the metal(s) above and Change Without Refinement | Change With Refinement

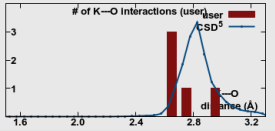
Timing: Instant | 1 min-few mins

PDB title: Crystal structure of a Iona protease domain in complex with

Warning: *Valence* and *nVECSUM* parameters should be interpreted with great care due to the presence of multi-nuclear metal clusters around A:801



K---O distance distribution for hkl_refine_4.pdb[1]



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Crystallization conditions:

0.2 M SODIUM CITRATE PH 6.5 AND 10 %
PEG 3350, EVAPORATION, TEMPERATURE 295K

4YPM

CellPress

Structure
Article

Structural Basis for the Magnesium-Dependent Activation and Hexamerization of the Lon AAA+ Protease

Shih-Chieh Su,[1,2,7] Chien-Chu Lin,[1,3,7] Hui-Chung Tai,[4] Mu-Yueh Chang,[1] Meng-Ru Ho,[1] C. Satheesan Babu,[4] Jiahn-Haur Liao,[1] Shih-Hsiung Wu,[1,2] Yuan-Chih Chang,[5] Carmay Lim,[4,6] and Chung-I Chang[1,2,*]

[1]Institute of Biological Chemistry, Academia Sinica, Taipei, Taiwan 11529, ROC
[2]Institute of Biochemical Sciences, National Taiwan University, Taipei, Taiwan 10617, ROC
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[4]Institute of Biomedical Sciences, Academia Sinica, Taipei, Taiwan 11529, ROC
[5]Institute of Cellular and Organismic Biology, Academia Sinica, Taipei, Taiwan 11529, ROC
[6]Department of Chemistry, National Tsing Hua University, Hsinchu, Taiwan 30013, ROC
[7]Co-first author
*Correspondence: chungi@gate.sinica.edu.tw
http://dx.doi.org/10.1016/j.str.2016.03.003

SUMMARY

The Lon AAA+ protease (LonA) plays important roles in protein homeostasis and regulation of diverse bio-

A LonA protomer contains three functional domains: (1) the N-terminal domain involved in substrate recognition, (2) the central AAA+ module with ATP-binding and hydrolysis activity, and (3) the C-terminal protease domain with a serine-lysine catalytic

The Washington Post
Democracy Dies in Darkness

Health

Messy, incomplete U.S. data hobbles pandemic response

The nation's decentralized, underfunded reporting system hampers efforts to combat the coronavirus.

The U.S. Capitol dome seen reflected in the window of a medical vehicle. (Jabin Botsford/The Washington Post)

By Joel Achenbach and Yasmeen Abutaleb

September 30, 2021 at 9:30 a.m. EDT

The contentious and confusing debate in recent weeks over coronavirus booster shots has exposed a fundamental weakness in the United States' ability to respond to a public health crisis: The data is a mess.

'A largely 19th-century system'

The CDC compiles national statistics by collecting data from every state and locality, but these jurisdictions often have different ways of counting tests, infections and even deaths. The data may not be submitted to the CDC for days or weeks. Many smaller jurisdictions still share that data via fax, an outdated technology.

MOST READ HEALTH ›

1 As covid persists, nurses are leaving staff jobs — and tripling their salaries as travelers

2 Over half of young adults are obese or overweight, study says

3 U.S. coronavirus cases approach 50 million as New York City imposes new vaccine mandate

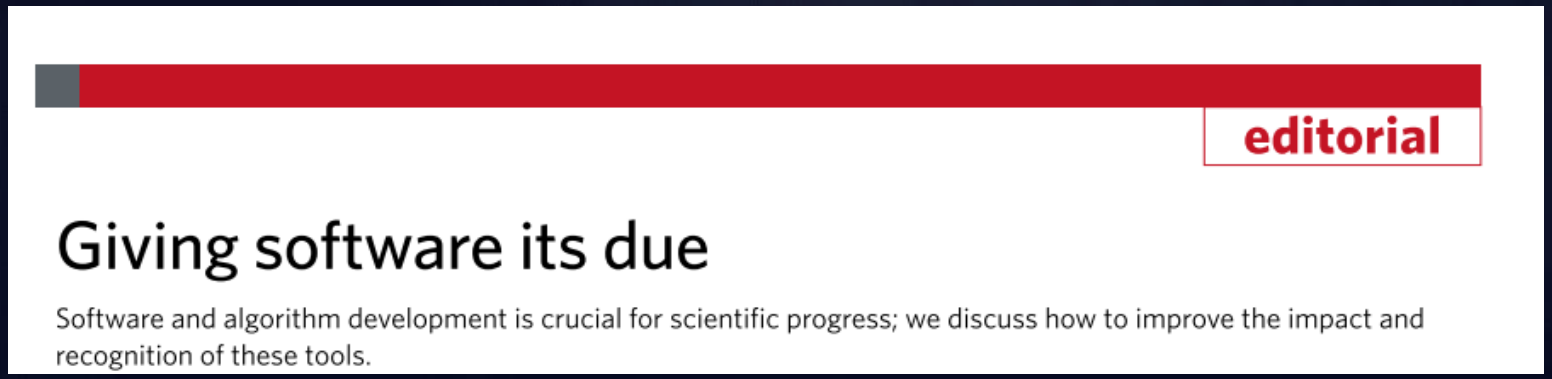
5 How scary is omicron? Scientists are racing to find answers.

Joel Achenbach, Yasmeen Abutaleb *Washington Post*, Sept 30, 2021

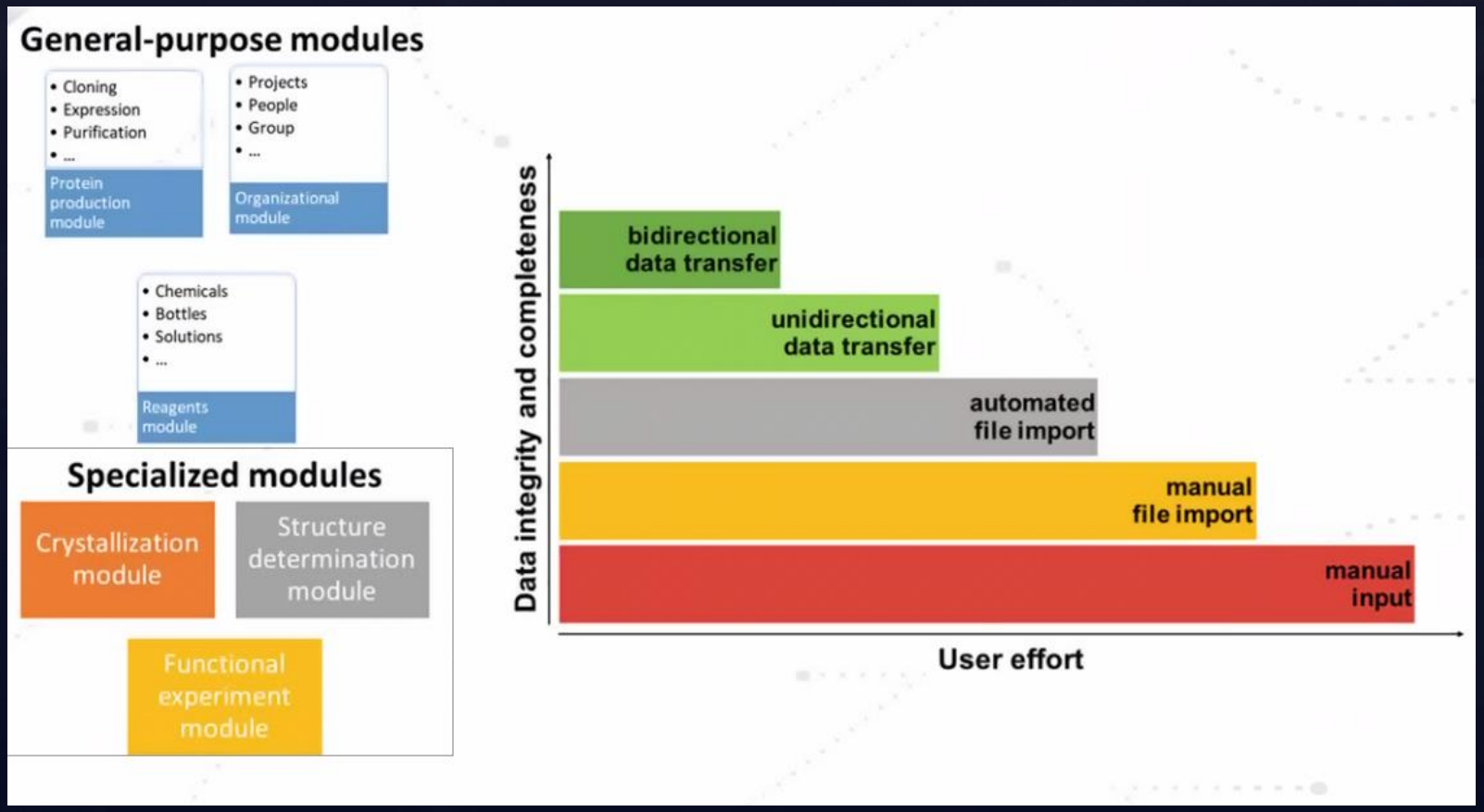
Software is easy ??

737MAX - we will fix software in 2 weeks (supervisor)

I can not do anything – this is computer fault (employee)

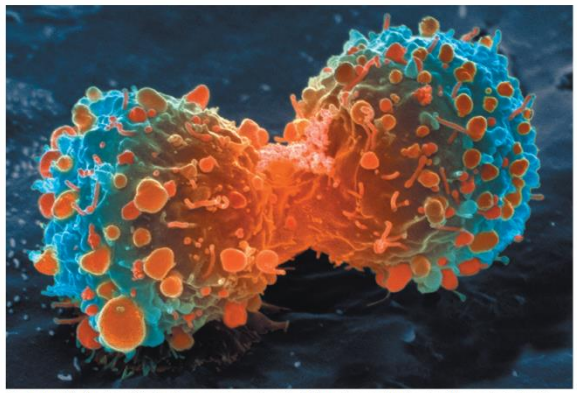


Experimental data management



Reproducibility

The **unspoken rule is that at least 50% of the studies published even in top tier academic journals – *Science, Nature, Cell, PNAS,* etc… – can't be repeated** with the same conclusions by an industrial lab. In particular, key animal models often don't reproduce. This 50% failure rate isn't a data free assertion: it's backed up by dozens of experienced R&D professionals who've participated in the (re)testing of academic findings. This is a huge problem for translational research and one that won't go away until we address it head on.

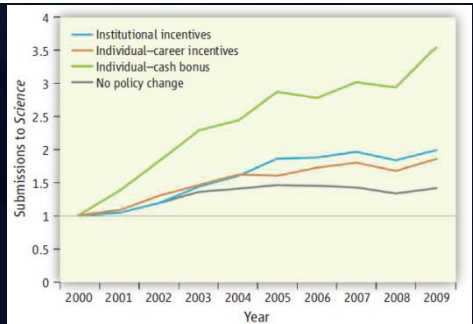


Many landmark findings in preclinical oncology research are not reproducible, in part because of inadequate cell lines and animal models.

NIH plans to enhance reproducibility

Francis S. Collins and **Lawrence A. Tabak** discuss initiatives that the US National Institutes of Health is exploring to restore the self-correcting nature of preclinical research.

Raise standards for preclinical cancer research



CORRESPONDENCE

Believe it or not: how much can we rely on published data on potential drug targets?

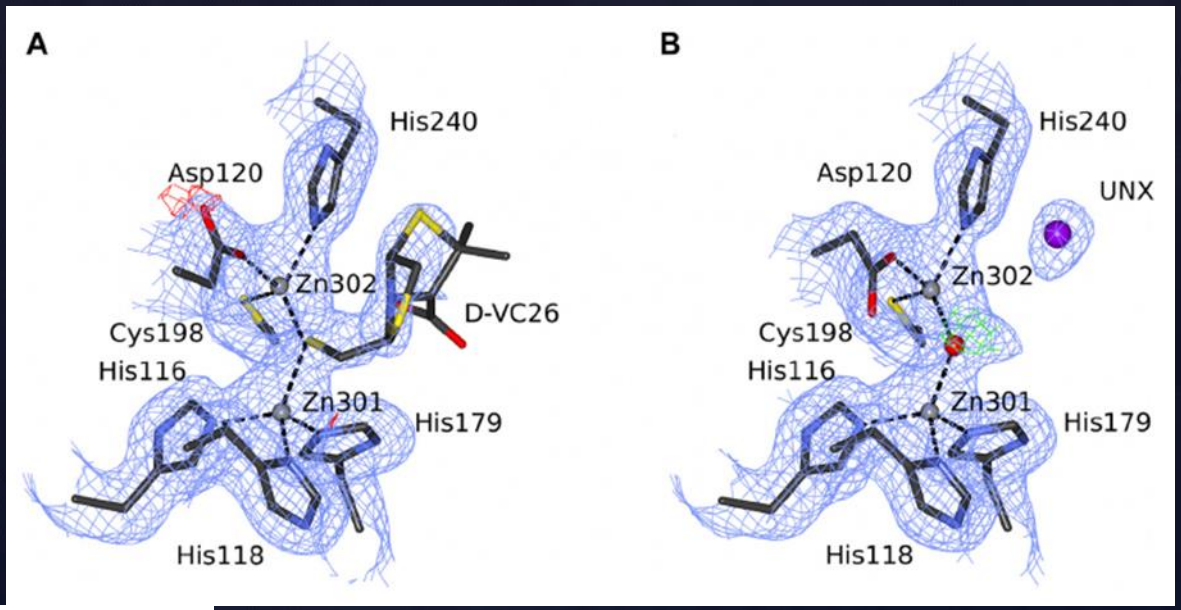
Florian Prinz, Thomas Schlange and Khusru Asadullah

EDITORIAL

Raising the bar

Numbers. Lots and lots of numbers. It is hard to find a paper published in *Science* or any other journal that is not full of numbers. Interpretation of those numbers provides the basis for the conclusions, as well as an assessment of the con-

Reproducibility and antibiotic resistance



CRYSTALLOGRAPHY REVIEWS
https://doi.org/10.1080/0889311X.2018.1521805
Taylor & Francis
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Refining the macromolecular model – achieving the best agreement with the data from X-ray diffraction experiment

Ivan G. Shabalin [a,b], Przemyslaw J. Porebski [a,b] and Wladek Minor [a,b]

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Drug Resistance Updates 40 (2018) 1–12

Contents lists available at ScienceDirect

Drug Resistance Updates

journal homepage: www.elsevier.com/locate/drup

A close look onto structural models and primary ligands of metallo-β-lactamases☆

Joanna E. Raczynska[a,1], Ivan G. Shabalin[b,c,1], Wladek Minor[b,c], Alexander Wlodawer[d], Mariusz Jaskolski[a,e,*]

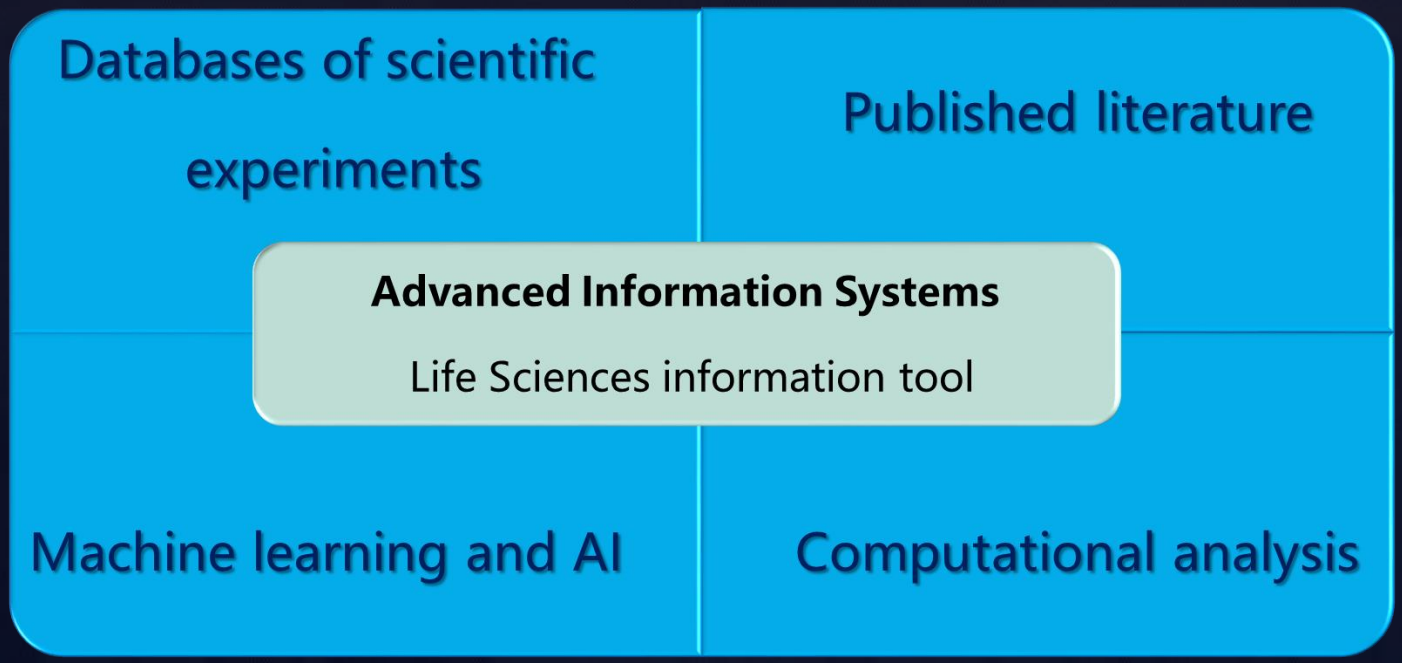
Check for updates

Categories of Data Resources

	Archives	Repositories	Databases	Advanced Information Systems (AIS)
Complexity	Low	Medium	High	High
Content	"Raw" (deposited) data with little or no metadata	Probably include some metadata	Extensively curated metadata	Extensively curated metadata, integrated with external resources
Searches and Retrieval	Data not necessarily indexed, searching cumbersome	Data is indexed, facilitating searches	Search usually driven by a database (in a technical sense)	Efficient search and retrieval
Data mining	Very difficult	Limited to basic statistics	Built-in data analysis and report generation tools. Precalculated result	Customizable tools for analysis of user data
Data validation	No validation	Limited validation	Full validation	Full validation; Mechanism for moderated user's corrections
Data architecture	No organization; typically just a set of files	Partial organization (e.g. subfolders)	Data is structured and maybe distributed	Data is structured and maybe distributed
Users / Audience	Usually limited to a single lab or institution	Collaborative /Public access	Single lab, Organization or Public	Organization or Public
Cost				
Setup	Low	Medium - High	High	Very High
Storage	Low - Medium	Medium	Medium	Medium
Maintenance	Low	Medium - High	High - Very High	Very High
Annotation	N/A	Medium - High	High	Very High
Curation	N/A	Low - Medium	Medium - Very High	Very High

Zheng H *et al*. (2017). *Methods Mol. Biol.* **1607**, 643–665.

Advanced Information Systems



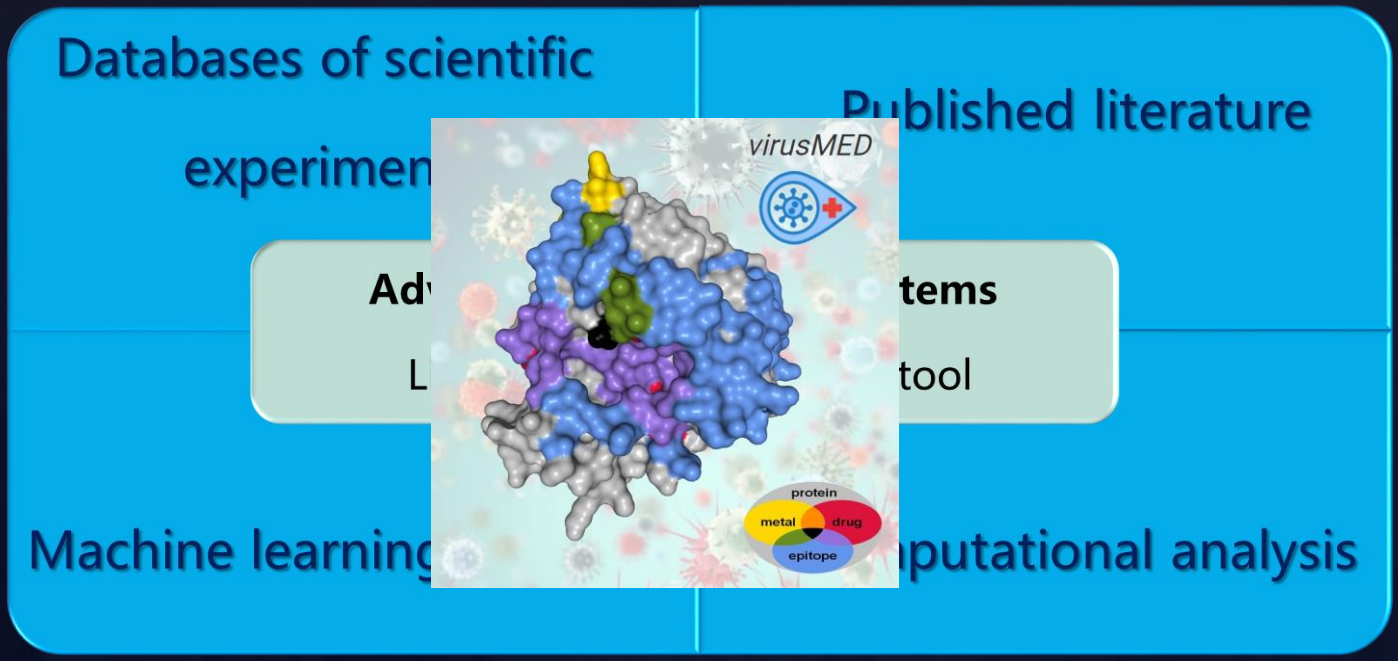
Clear communication problem

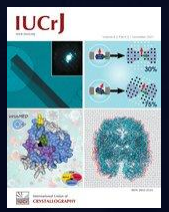
Tower of Babel

we need to understand each other

Pieter Bruegel the Elder

A Prototype of Advanced Information System

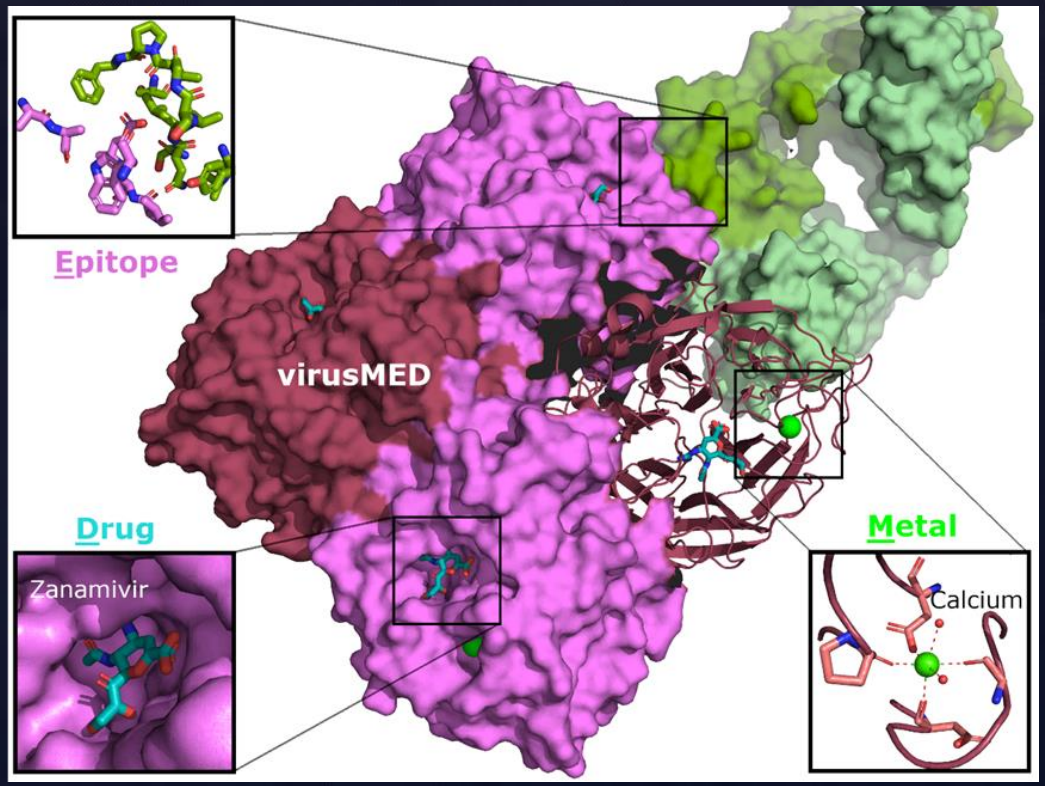


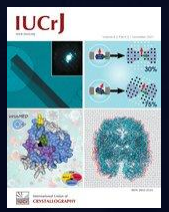


Zhang, H. *et al*. (2021) IUCrJ 8:1-12

virusMED
virus Metals, Epitopes, & Drugs

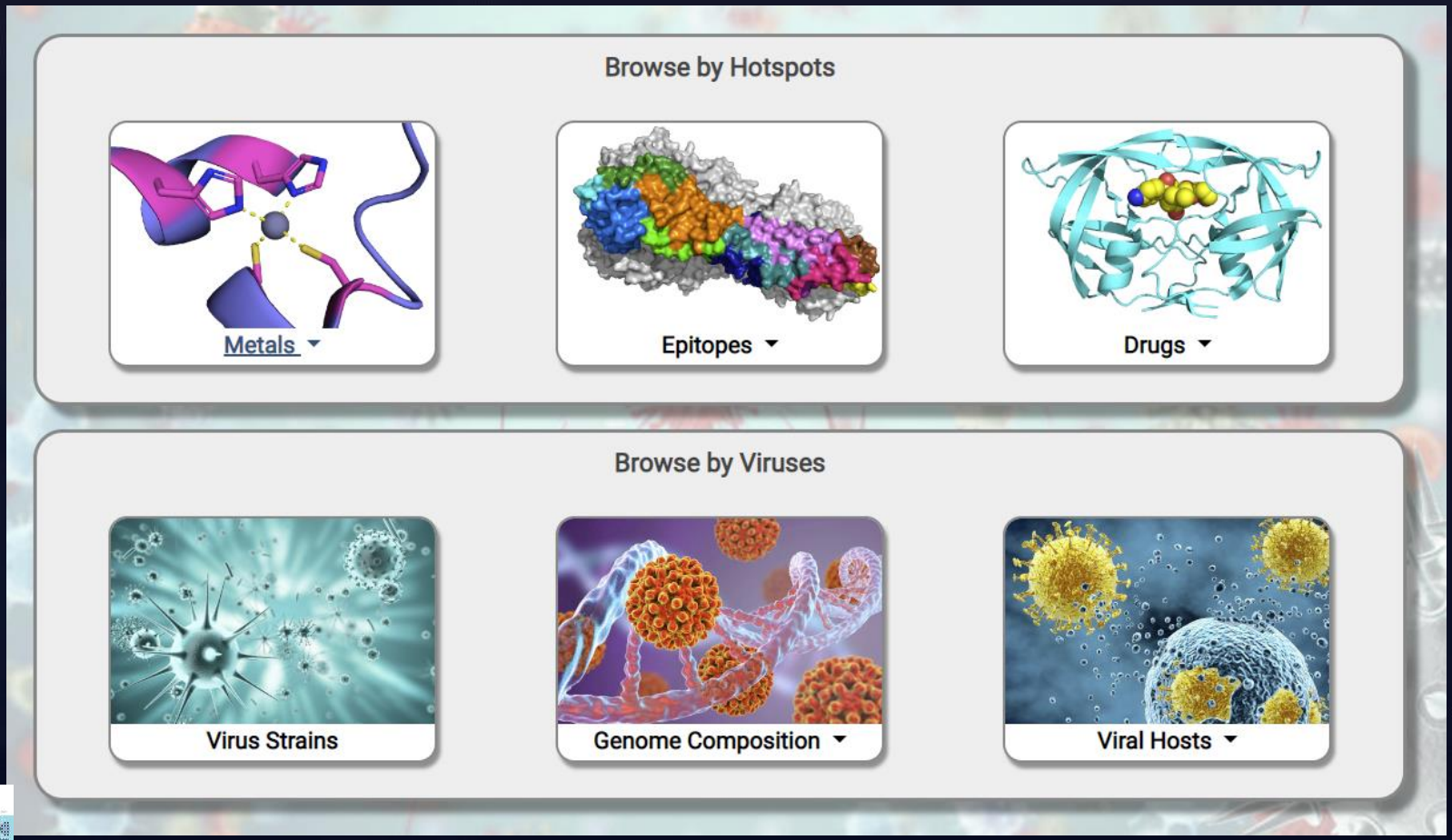
- 25,306 Hotspots
- 7,041 Structures
- 805 Virus strains
- 75 Virus families

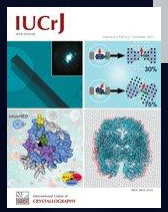




Zhang, H. *et al*. (2021) IUCrJ 8:1-12

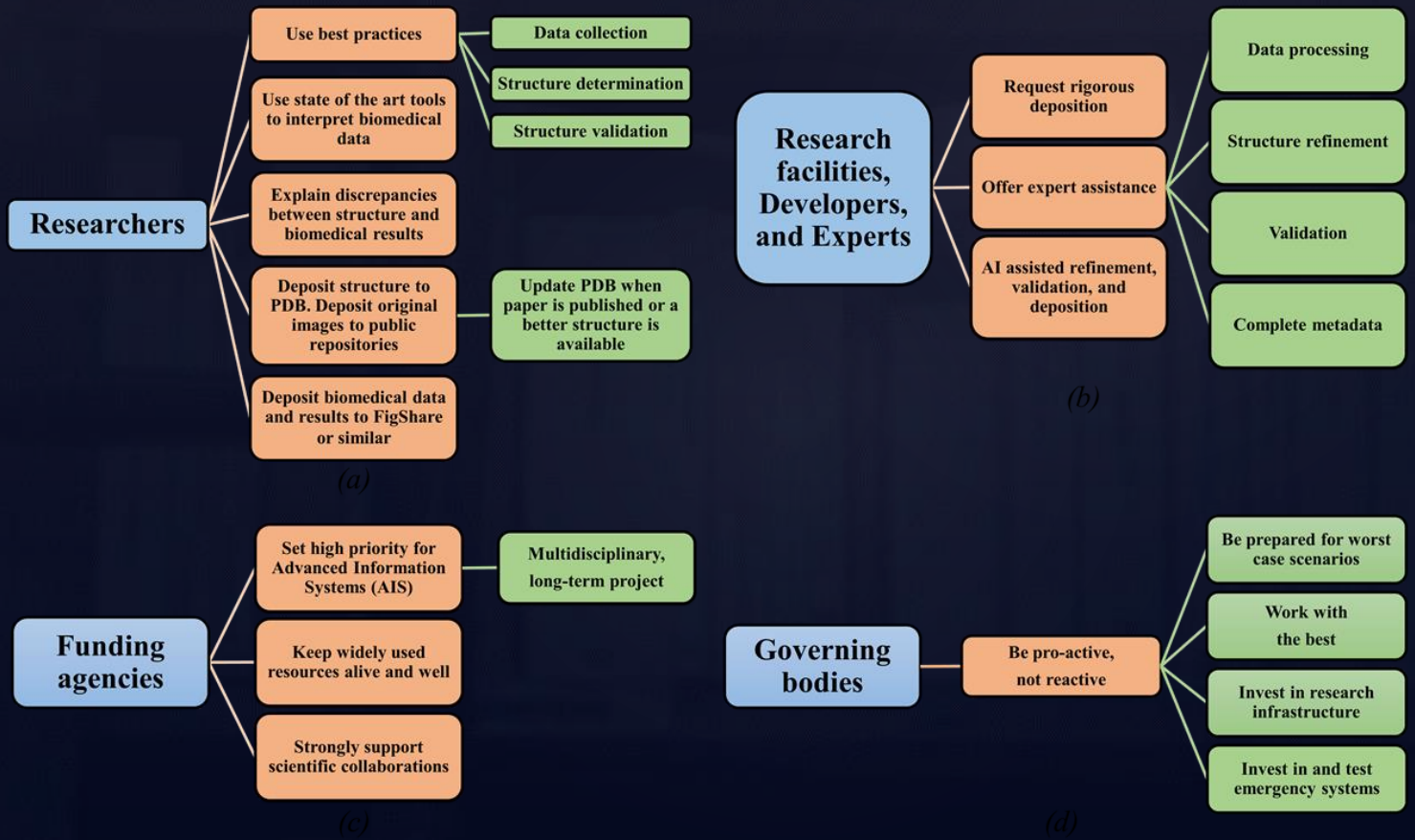
Browsing in virusMED





Zhang, H. *et al*. (2021) IUCrJ 8:1-12

Toward the optimal response



M. Grabowski *et al.*, (2021) *IUCrJ*, **8**, 395–407

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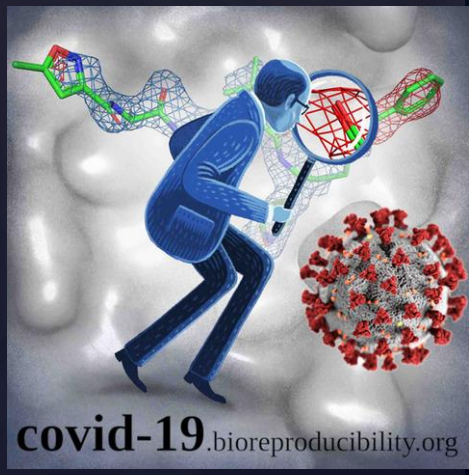

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