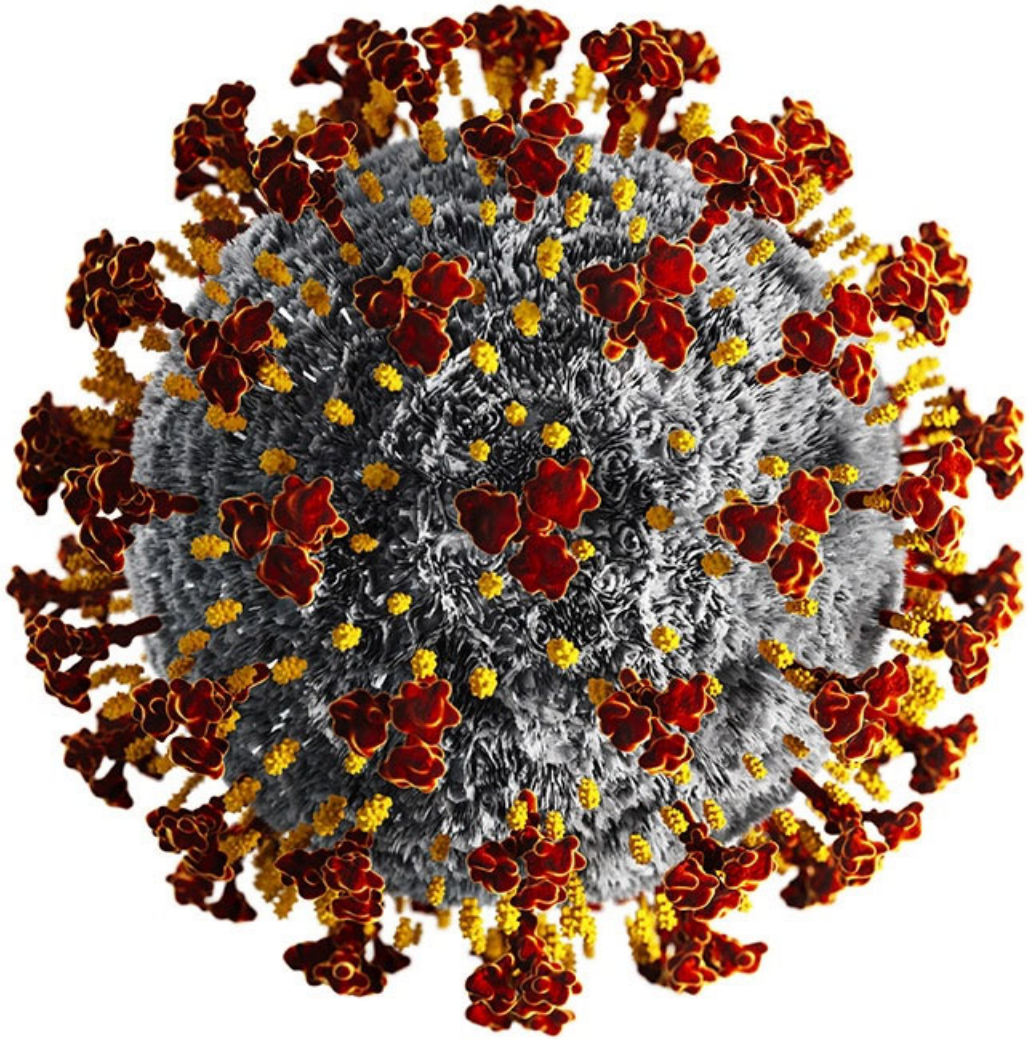


David Winkler | Professor, Biochemistry & Chemistry, La Trobe Institute for Molecular Science | Monash Institute of Pharmaceutical Sciences | School of Pharmacy, University of Nottingham

Computational design and repurposing of drugs for coronaviruses and drug-resistant pathogens

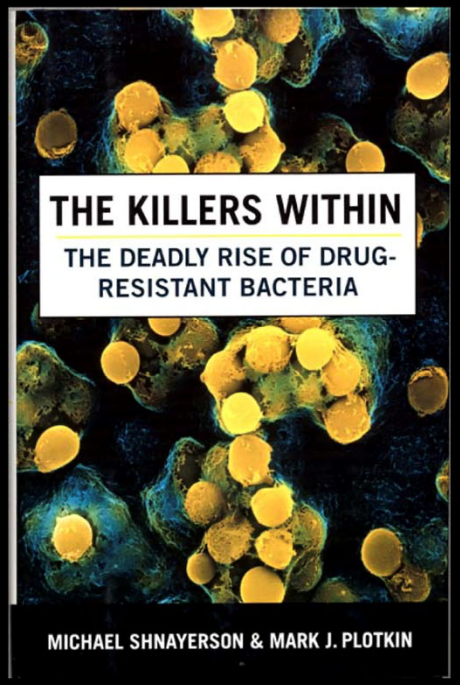
latrobe.edu.au

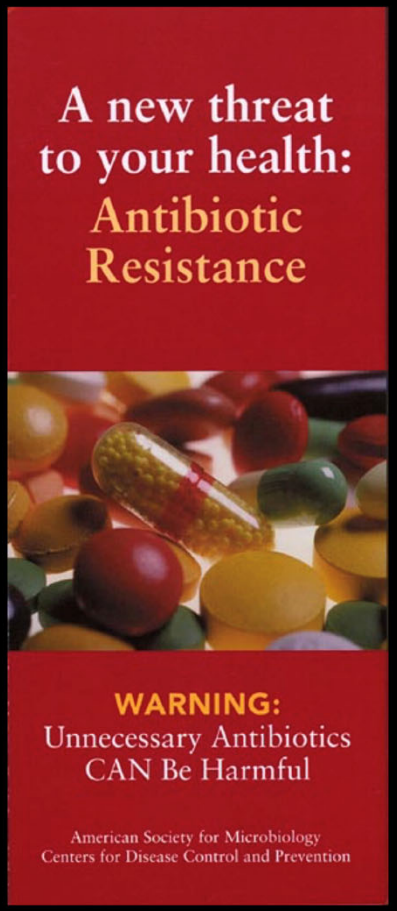
Tropical diseases and their burden

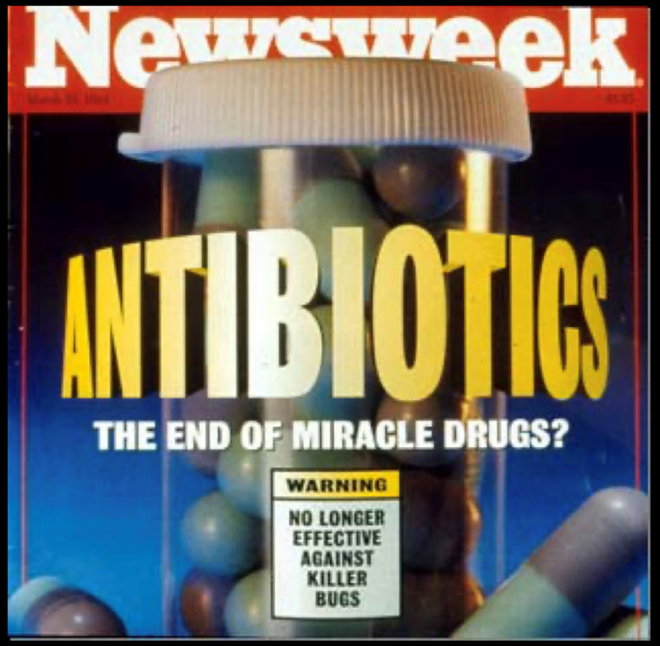
TABLE 2 | Global burden of disease due to major tropical infectious diseases (Njogu et al., 2016).

Infection	Global prevalence (millions)	Population at risk (millions)	Annual mortality (thousands)	Disability-adjusted life years (millions)	Regions of highest prevalence
Malaria	198	3,200	584	46.5	Sub-Saharan Africa, Asia, South and Latin America, Middle East, and Pacific Islands
tuberculosis	11	2000	1,100	34.7	Sub-Saharan Africa and Southeast Asia
Leishmaniasis	12	350	51	2.1	India, South Asia, Sub-Saharan Africa, Latin America, Caribbean, and Mediterranean region
Human African trypanosomiasis	0.3	60	48	1.5	Sub-Saharan Africa
Chagas' disease	10	120	15	0.7	Latin American and Caribbean

The rise of multidrug resistance in antimicrobials



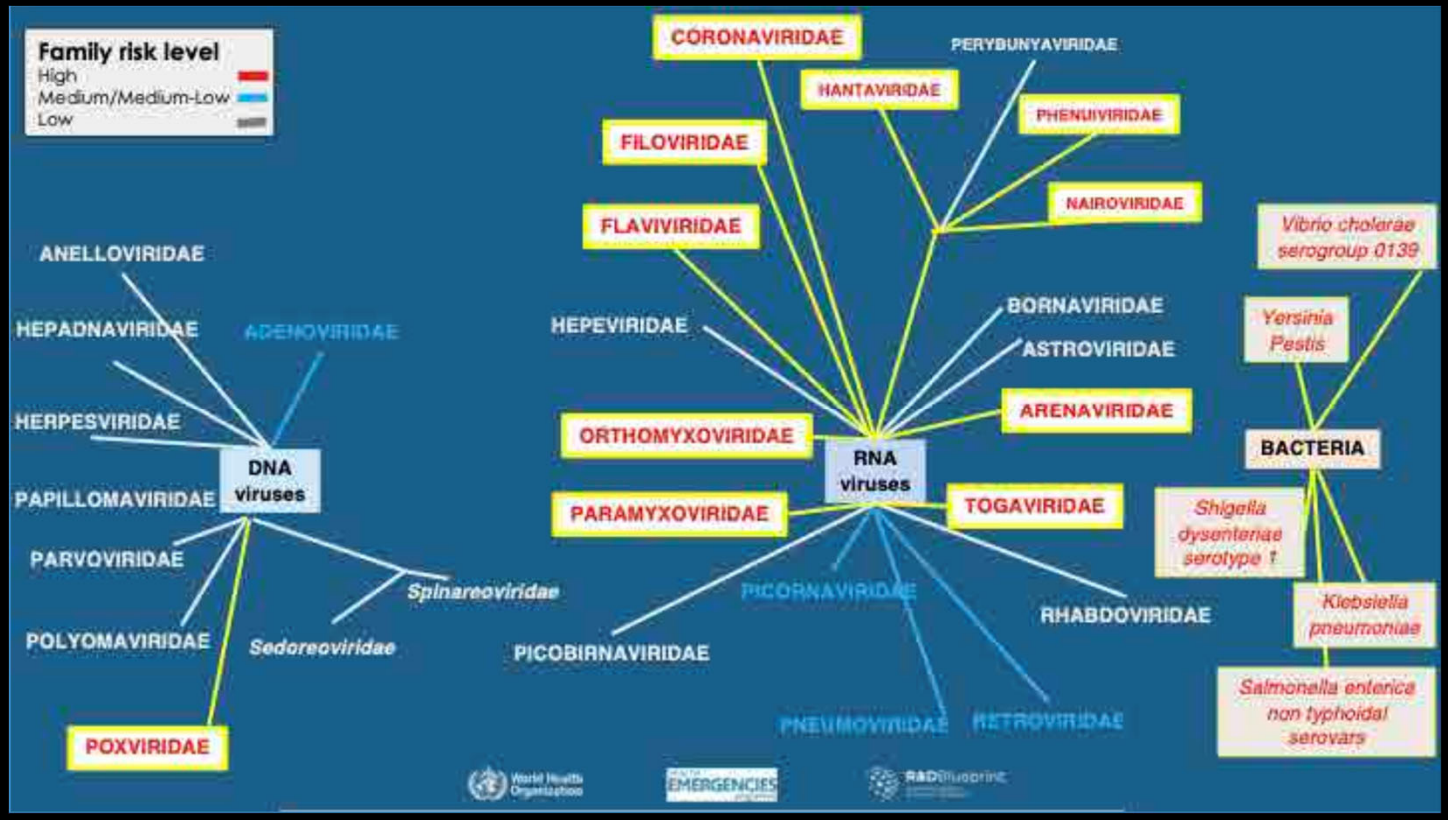




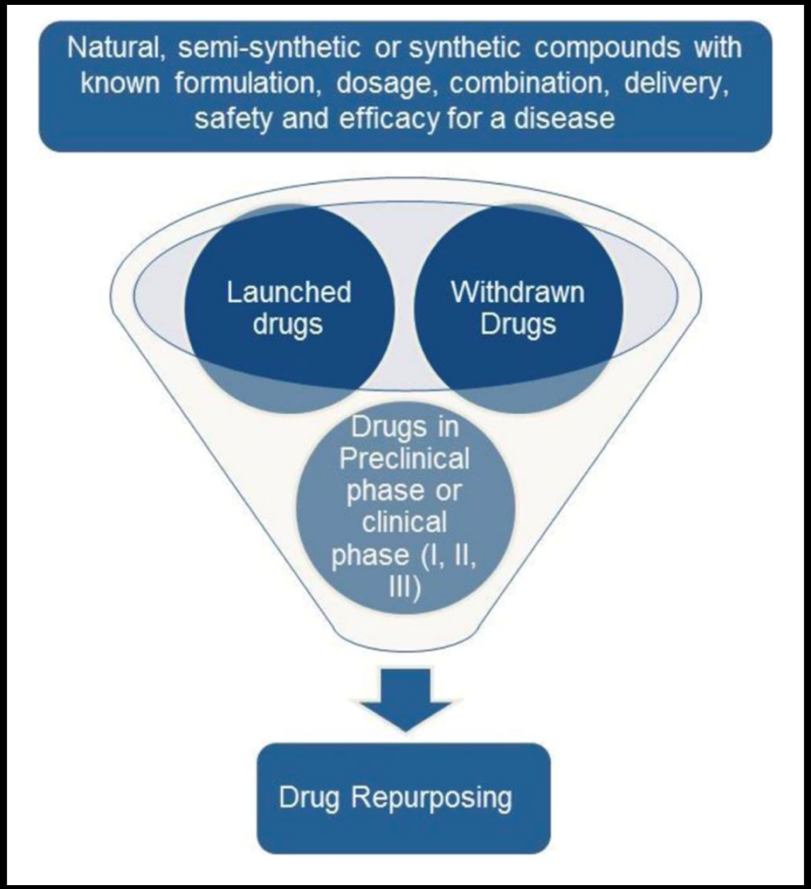
Pandemics in the past century

VIRUS24-May	YEAR	CASES	DEATHS	FATALITY RATE %	NUMBER OF COUNTRIES
Spanish flu H1N1	1918	500M	20-50M	4–10	all
Marburg	1967	466	373	80.0	11
Ebola	1976	33,577	13,562	40.4	9
Hendra	1994	7	4	57.0	1
Bird Flu H5N1	1997	861	455	52.8	18
Nipa	1998	513	398	77.6	2
SARS CoV	2002	8,096	774	9.6	29
Swine flu H1N1**	2009	700M-1.4Bn	152,000–575,000	0.01 based on age	214
MERS CoV***	2012	2,494	858	34.4	28
H7N9 Bird Flu	2013	1,568	616	39.3	3
COVID-19*	2024	705M	7M	1	all

WHO risk profile for future pandemics 2024



Why computational drug discovery and repurposing?

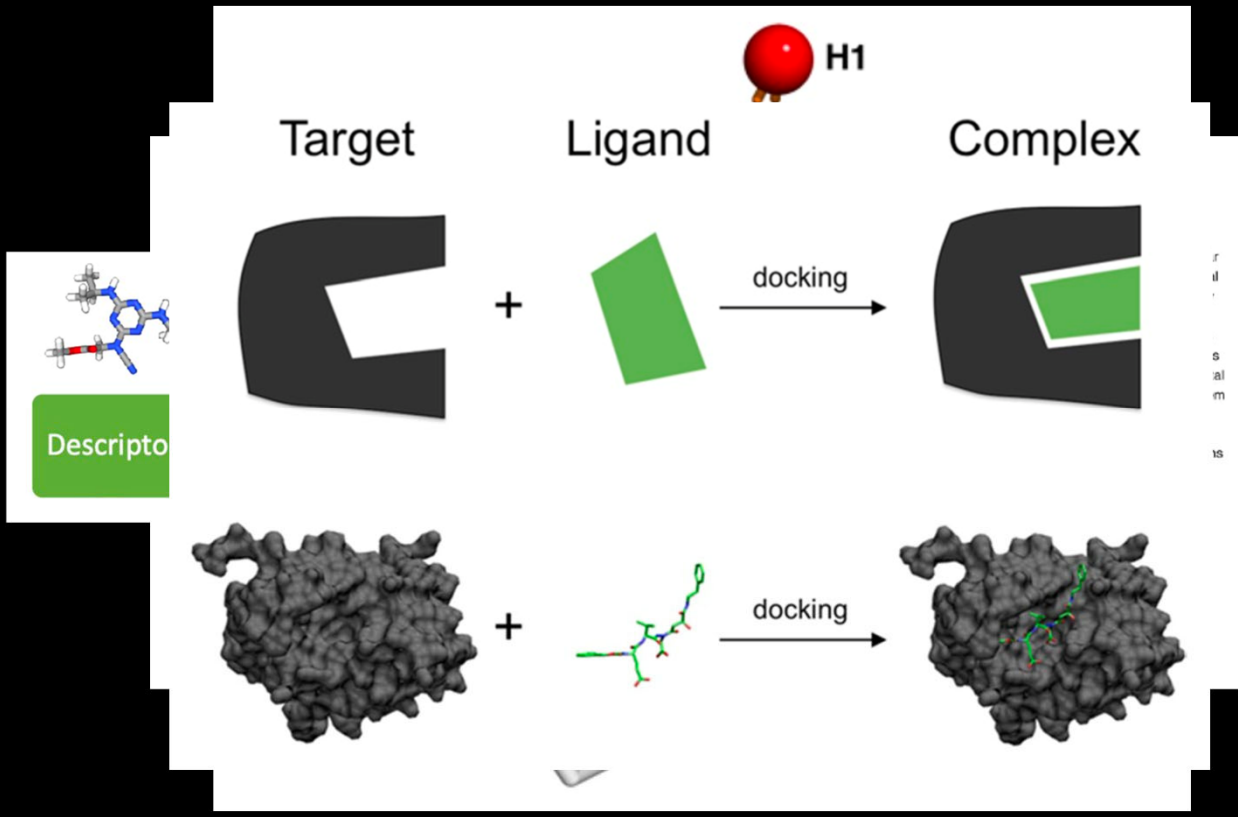


Why computational drug repurposing

- Often, no vaccines or effective drugs are available. Traditionally, drugs require **10-15 years** to reach patients– useless in a pandemic.
- ~12,000 registered drugs, clinical trials candidates, and natural products with human **ADMET data available that** can be used **immediately off label**. Generic versions often **inexpensive**.
- High throughput experimental drug screening on pandemic or other disease protein targets or pathogens has previously been **largely intractable** for finding leads.
- Computational methods are very fast and **accurate enough** to identify potential repurposing candidates
- Homology modelling (or AlphaFold), molecular docking, and dynamics simulations calculate binding energies for many disease target proteins and identify repurposing candidates. **AI and machine learning promise a paradigm shift**

Computational methods used to repurpose drugs

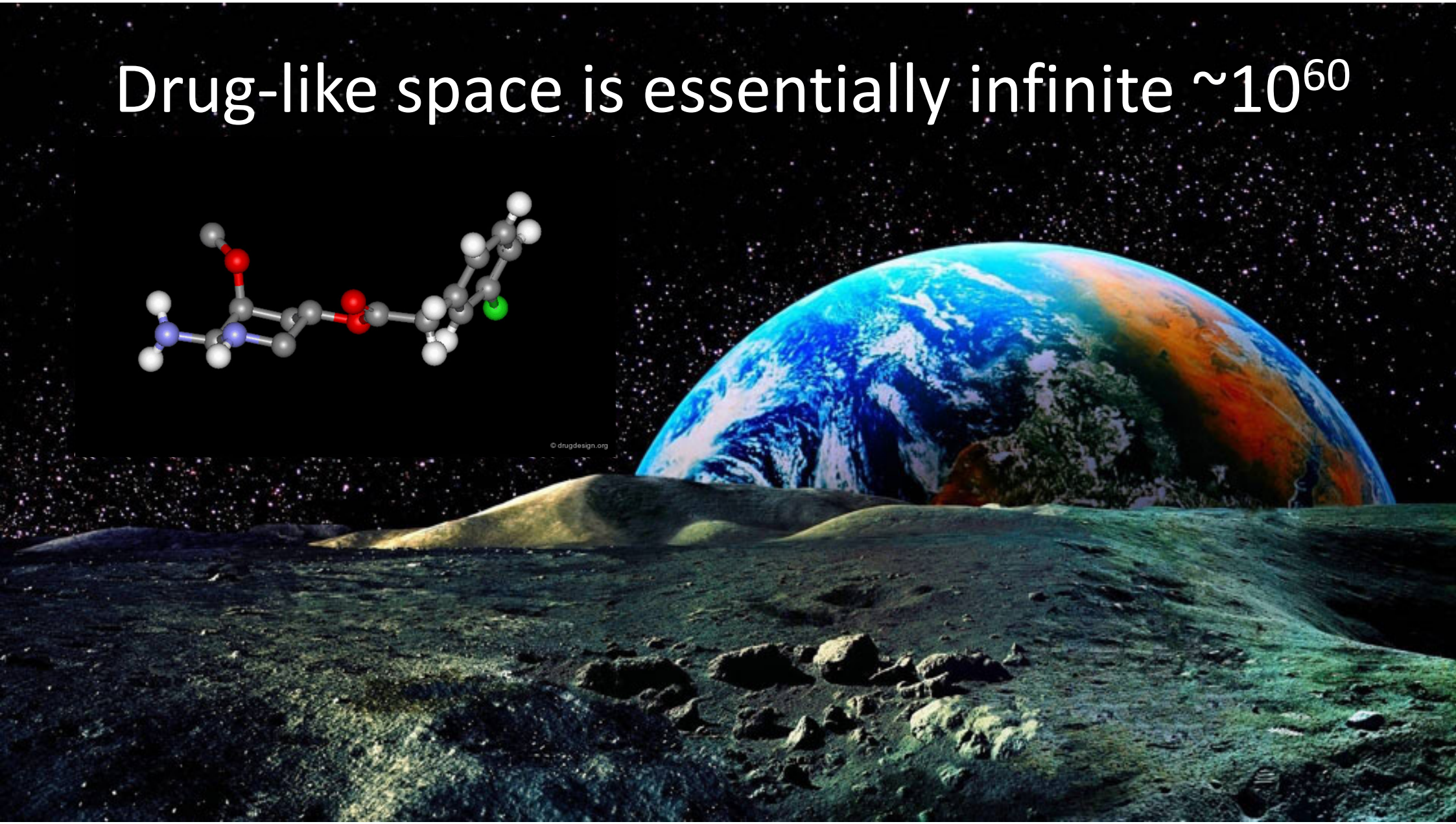
Molecular docking is largely
Docking – using 3D coordinates of a
validated protein target to model the
interactions of small drug-like organic
molecules with putative binding sites
protein targets.



Winkler, Computational repurposing of drugs for viral diseases and current and future pandemics, J. Math. Chem. 2024

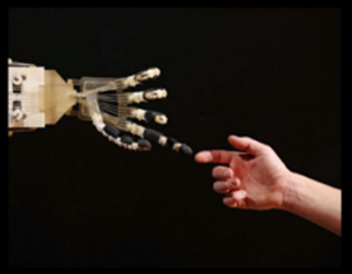
Why use AI, or build machine learning models for drug discovery?

Drug-like space is essentially infinite ~10^{60}



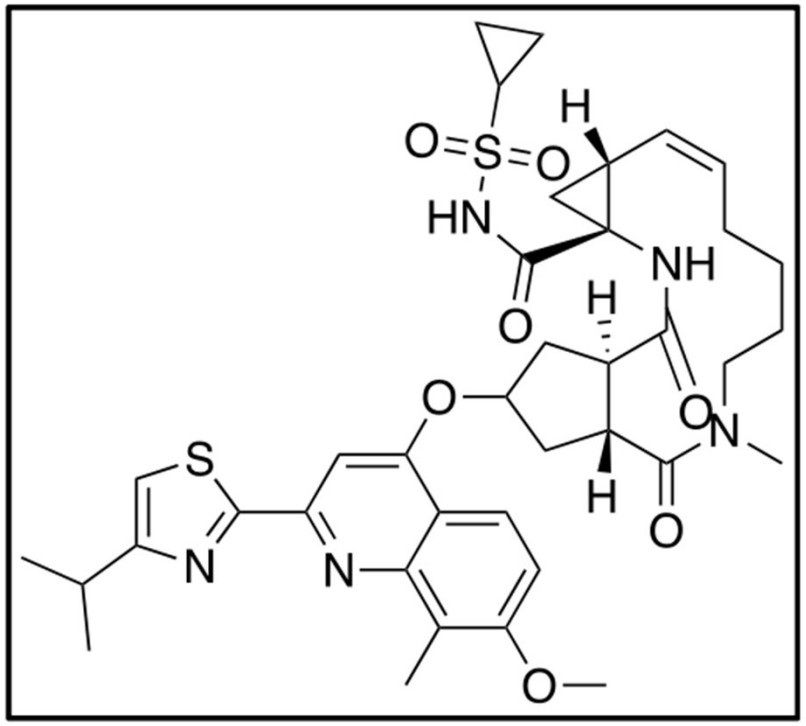
Why use computational methods for drug discovery?

- Allows exploration of larger regions of drug-like space than experiments
- Leverages limited experimental data into larger chemical space
- Extracts knowledge from very large and complex, high dimensional data
- Enables property prediction for novel small molecules and peptides
- Elucidates important properties driving biological responses
- Provides mechanistic insights into drug-biology interactions
- Designs superior bioactive agents faster than by experiments alone



Example : Repurposing drugs for Mpox

Gene	Protein Funct
A48R	Thymidylate kin
A50R	DNA ligase [1
D13L	Viral capsid prote
F13L	EEV formation prot
I7L	Protease [19



8 simeprevir

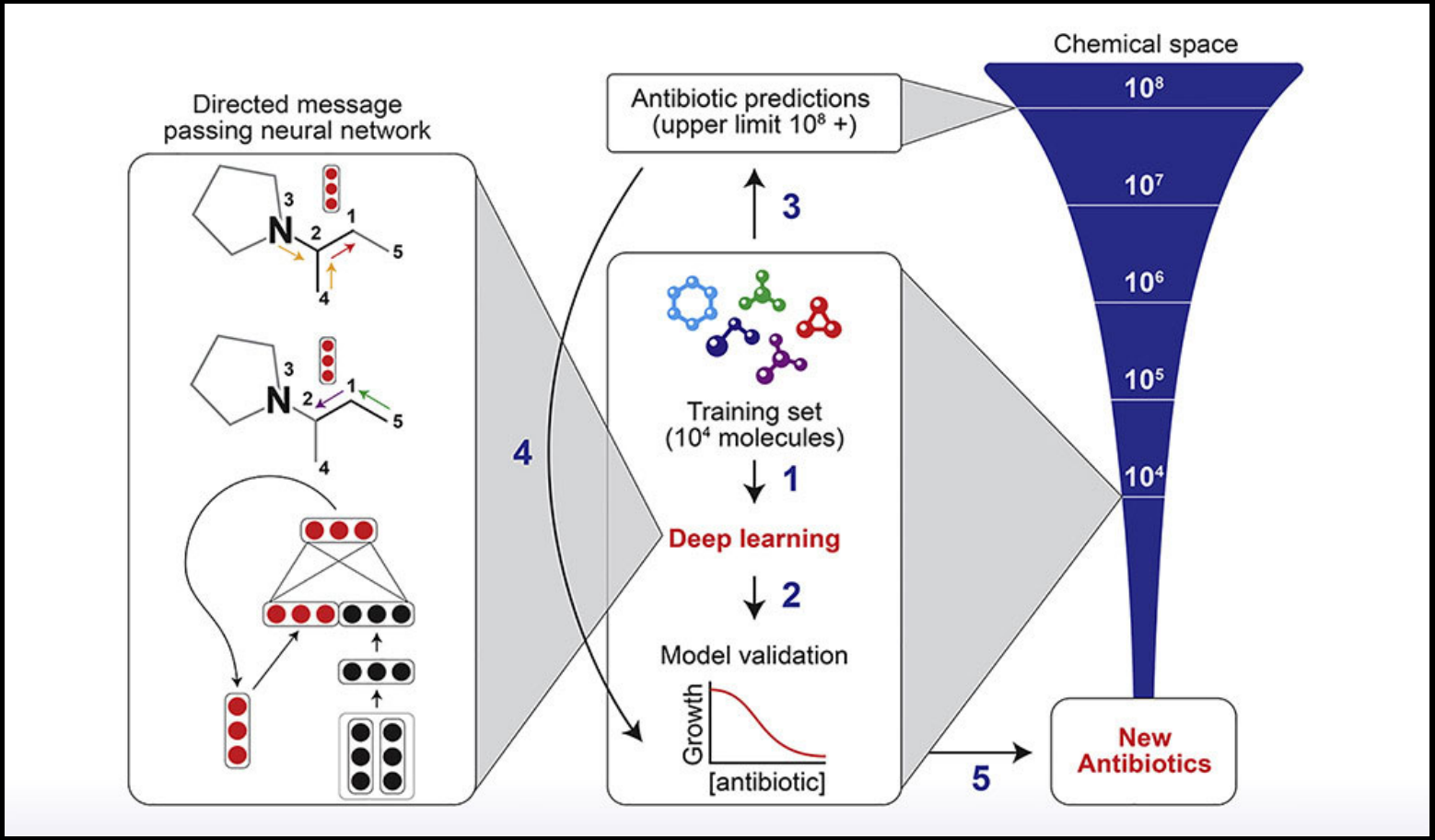
Repurposable Drug	Drug Structure
NMCT	
Rutaecarpine	
Nilotinib	
Simeprevir	
Hypericin	
Naldemedine	
Fosdagrocorat	
Lixivaptan	

Docking virtual screening (AutoDock Vina) and molecular dynamics simulations (Gromacs) to repurpose multiple drugs for poxviruses, exploiting several protein targets (Alphafold)

H.Y.I. Lam, J.S. Guan, Y.G. Mu, Molecules (2022)

Winkler, D.A., Computational repurposing of drugs for viral diseases and current and future pandemics, J. Math. Chem. 2024.

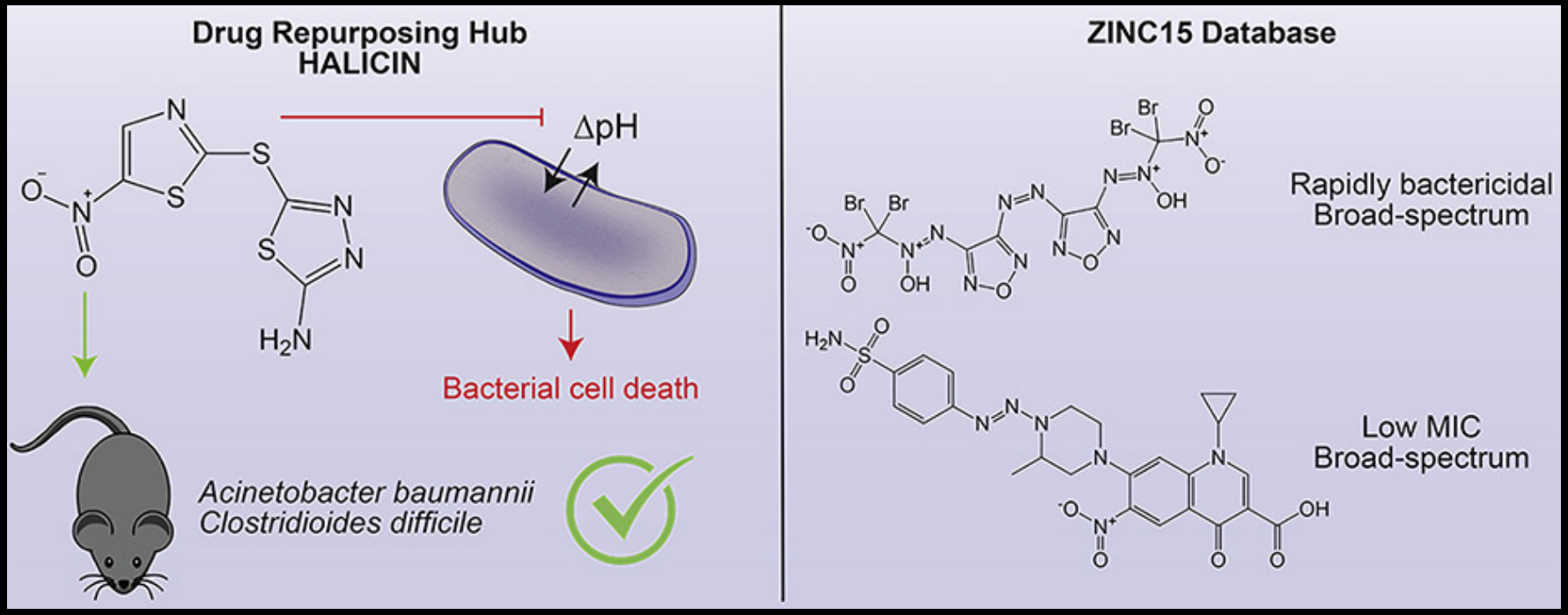
Example : Deep learning screening of virtual libraries for drugs



Stokes et al. A deep learning approach to antibiotic discovery. Cell. 180, 688–702.e13 (2020).

Winkler, Use of AI and Machine Learning for Discovery of Drugs for Neglected Tropical Diseases. Front. Chem. 9:614073 (2021).

Deep learning models screen virtual libraries for new antibiotics



Winkler, Use of AI and Machine Learning for Discovery of Drugs for Neglected Tropical Diseases. Front. Chem. 9:614073 (2021)

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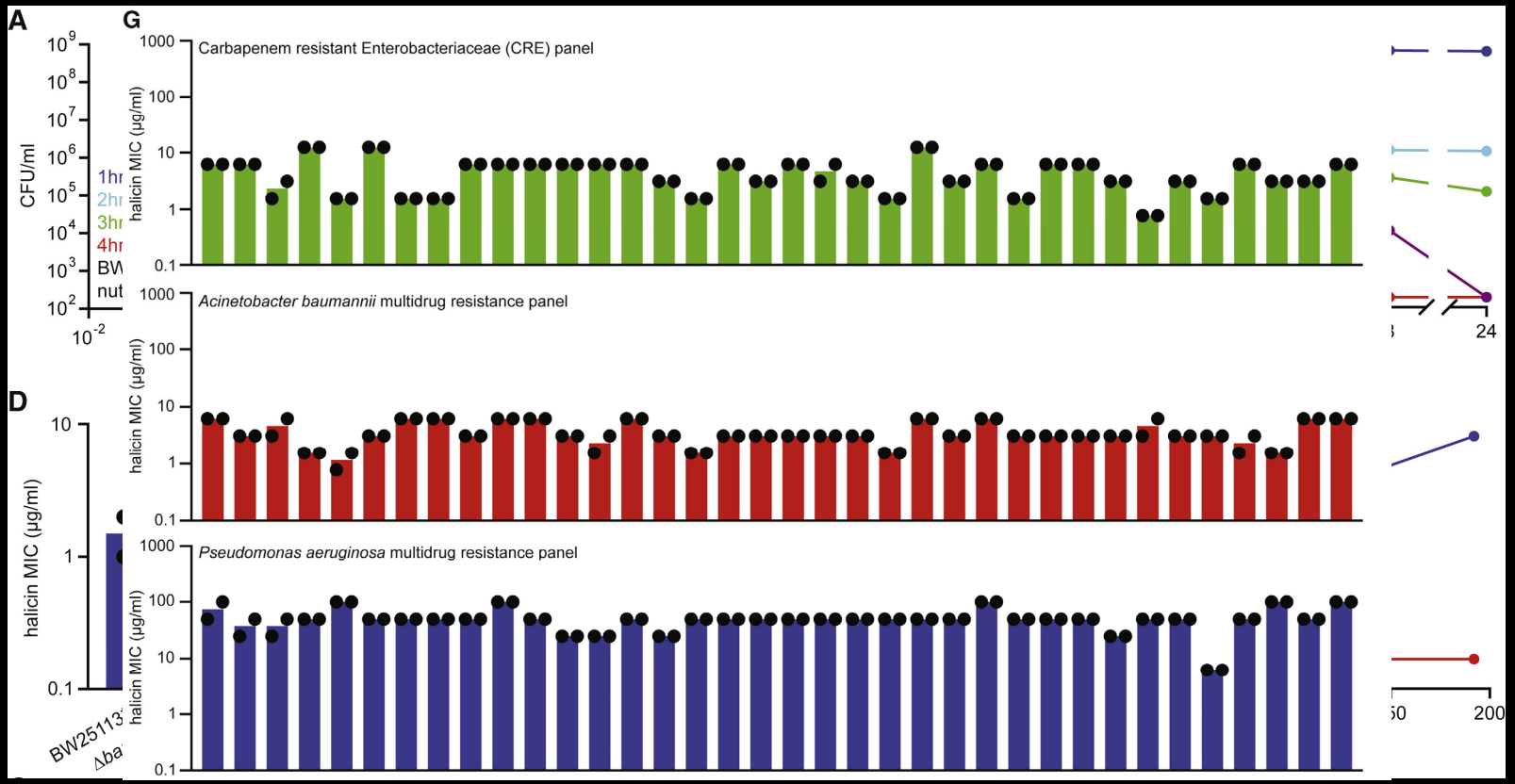
Deep learning models screen virtual libraries for new antibiotics



Stokes et al. A deep learning approach to antibiotic discovery. Cell. 180, 688–702.e13 (2020).

Winkler, Use of AI and Machine Learning for Discovery of Drugs for Neglected Tropical Diseases. Front. Chem. 9:614073 (2021).

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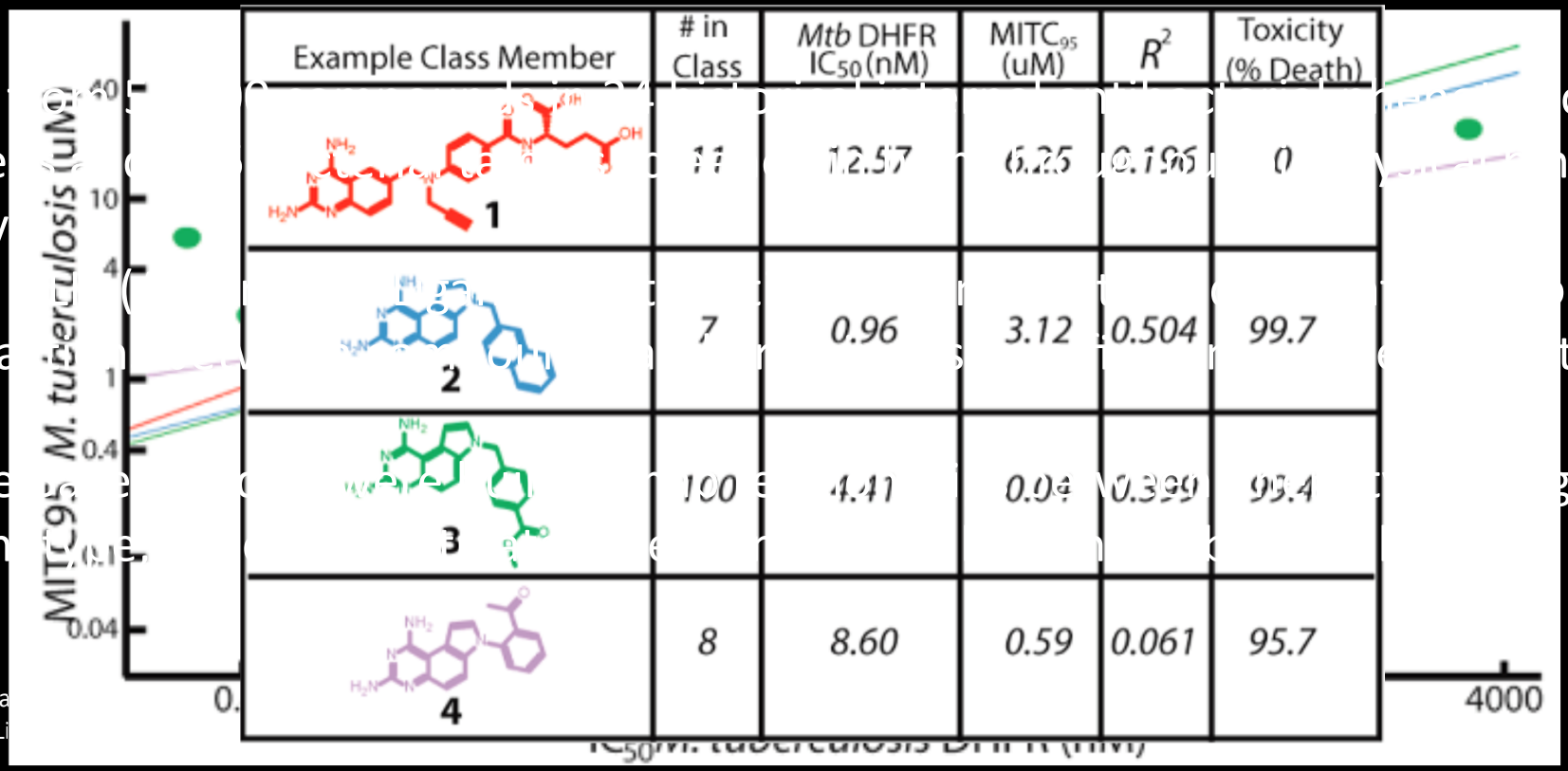
Example: Computational discovery of novel TB drug leads

- Data
- Used
- Naïve

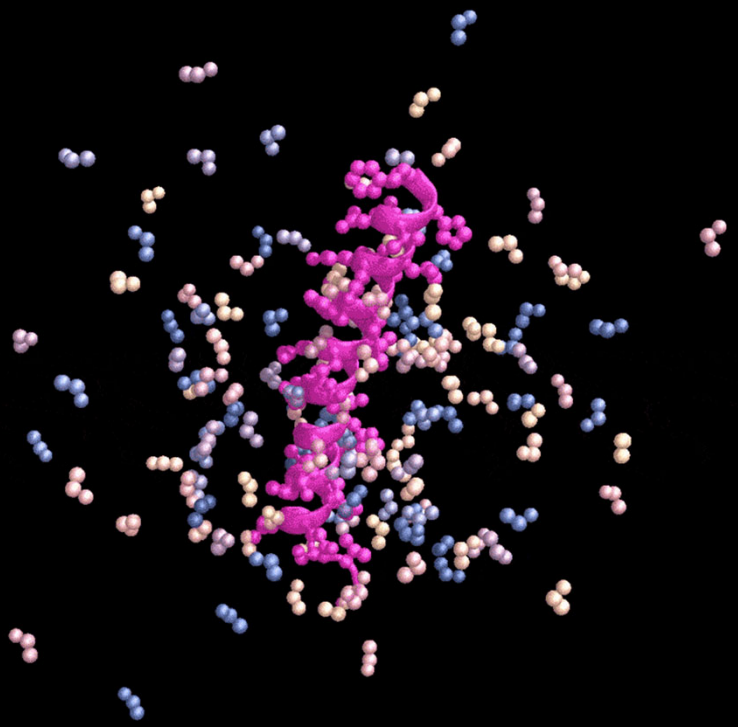


Example Class Member	# in Class	*Mtb* DHFR IC_{50}(nM)	$MITC_{95}$ (uM)	R^2	Toxicity (% Death)
1	11	12.57	6.25	0.196	0
2	7	0.96	3.12	0.504	99.7
3	100	4.41	0.04	0.399	99.4
4	8	8.60	0.59	0.061	95.7

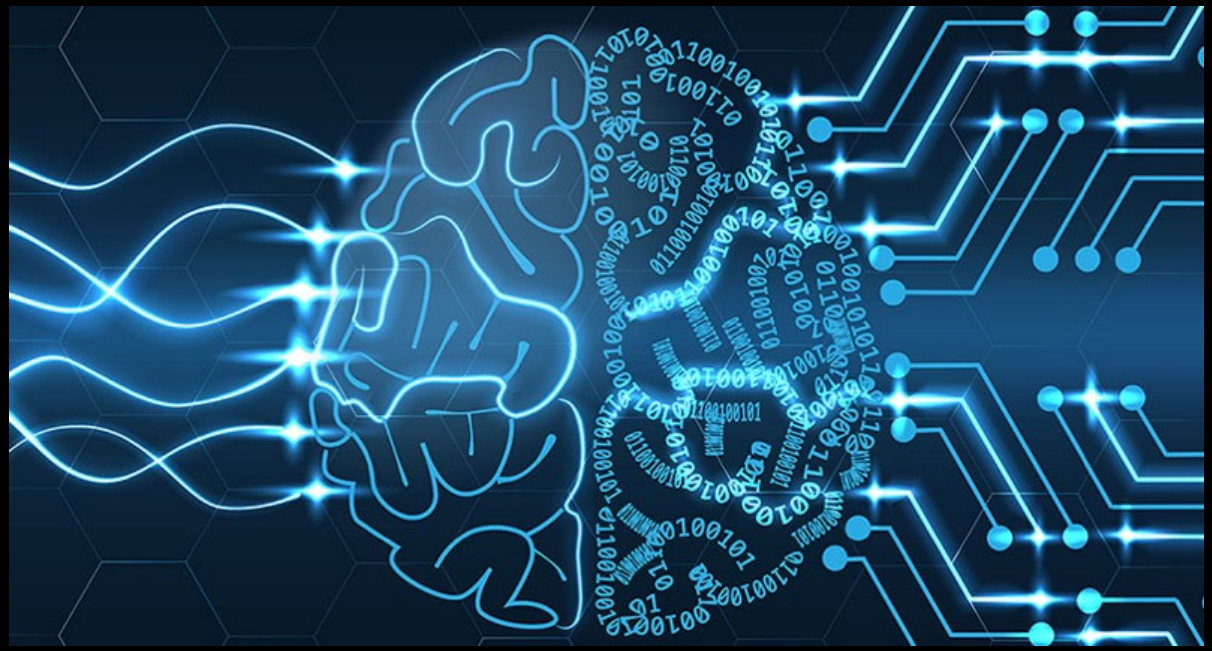
Winkler, Use of AI a
Santa Maria et al. Li

Large language models and drug discovery

An artificial-intelligence tool called RFdiffusion designed a protein that binds to the parathyroid hormone, shown in pink. Credit: Haydon/UW Institute for Protein Design



Computational drug repurposing for pandemics



Need for computational repurposing during a pandemic

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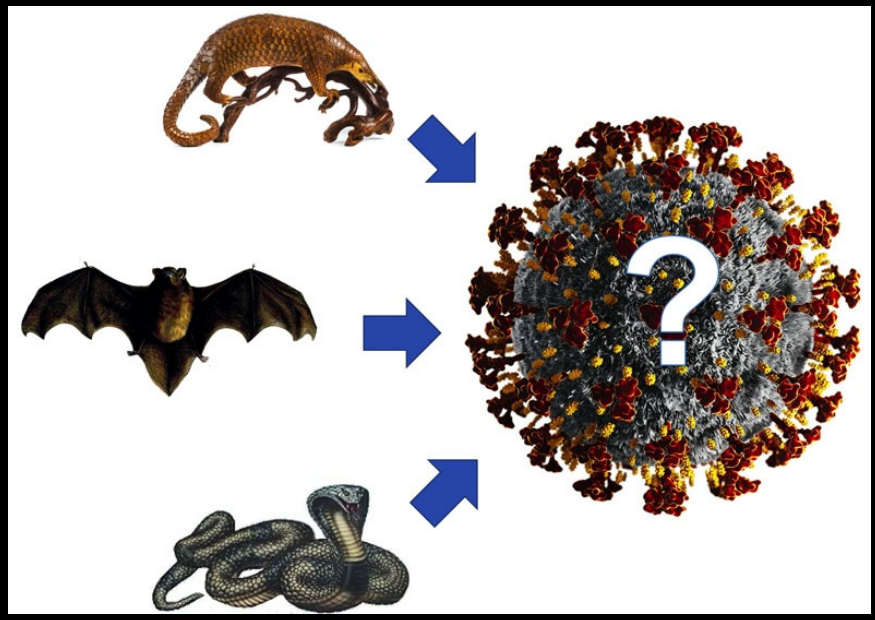
- **No vaccines or effective drugs available for the first half of the pandemic**
- Traditional de novo drug design or discovery takes **10-15 years** to pass though drug pipeline and receive registration – useless in a pandemic (but essential for the next pandemic).
- ~12,000 registered drug, clinical trials candidates and approved natural products that have been in man and have **pharmacokinetic, toxicity, and metabolism data available**.
- If found to be effective for COVID-19 treatment, they could be used **immediately**
- HT drug screening on SARS-CoV-2 protein targets or the virus itself could discover effective repurposing leads but has been largely intractable for this pandemic
- Computational methods are **sufficiently accurate** to quickly identify repurposing candidates
- A combined homology modelling, molecular docking, and molecular dynamics simulations can calculate the binding energies of ACE2 receptors of many species with the spike protein. They can also identify target-based repurposing candidates, **validated experimentally**

SARS-CoV-2 spike interaction with ACE2 of diverse species – virus origin and susceptible species



Lab Leak: A Scientific Debate Mired in Politics — and Unresolved

More than a year into the SARS-CoV-2 pandemic, some scientists say the possibility of a lab leak never got a fair look.

BY CHARLES SCHMIDT (HTTPS://UNDA AUTHOR/CHAR SCHMIDT/)

03.17.2021

Top: Security personnel stand guard outside the Wuhan Institute of Virology in Wuhan in February, as members of the World Health Organization (WHO) team investigating the origins of the Covid-19 coronavirus pay a visit. Visual: Hector Retamal / AFP via Getty Images

NIKOLAI PETROVSKY was scrolling through social media after a day on the ski slopes when reports describing a mysterious cluster of pneumonia cases

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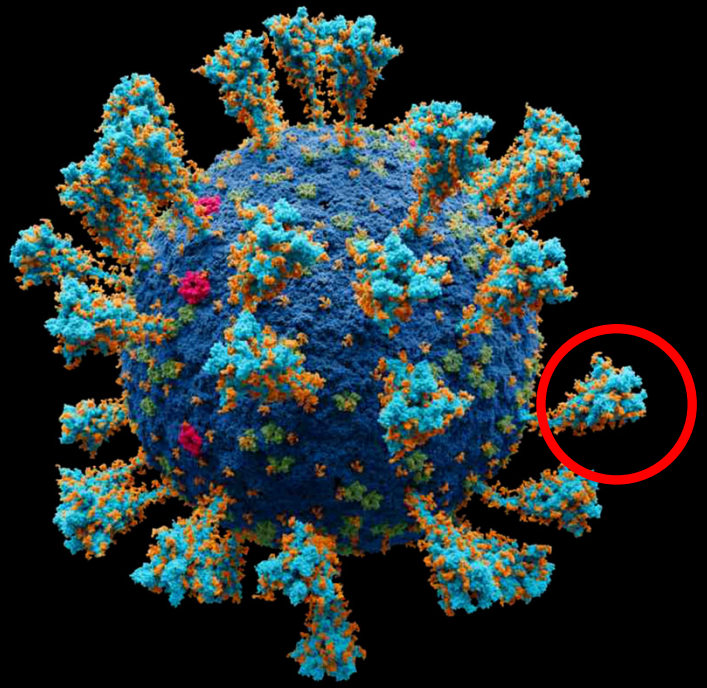
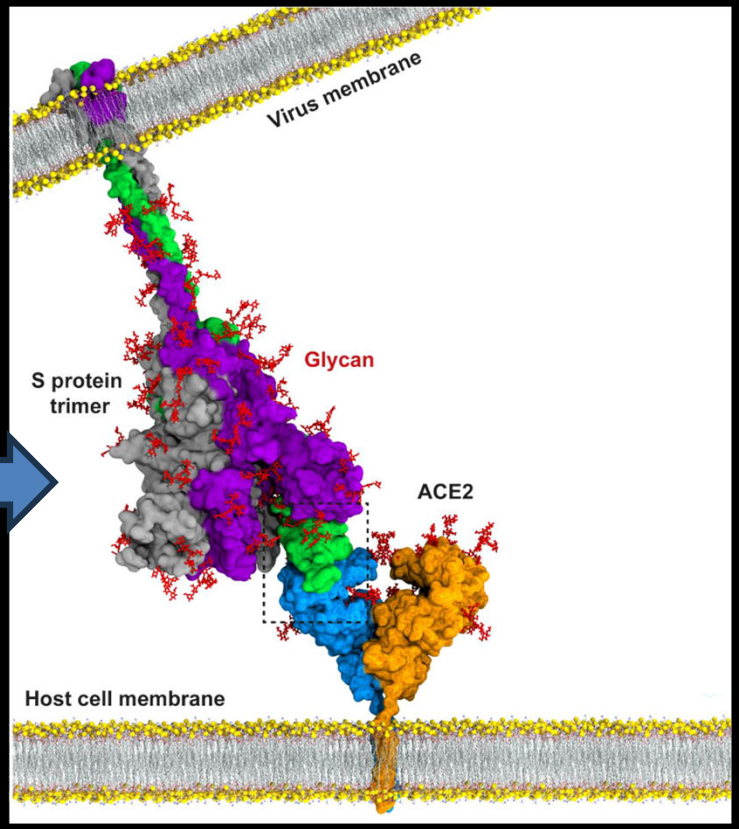
BCADD plenary | Moscow, Russia| September 2024

Infection-initiating event: spike interaction with angiotensin converting enzyme 2 (ACE2)





Piplani, S.; Singh, P.K.; Winkler, D.A.; Petrovsky.N. *In silico comparison of SARS-CoV-2 virus spike protein-ACE2 binding affinities across species; significance for animal susceptibility and viral origin,* **npj Sci Rep.**, 11, 18610 (2021).

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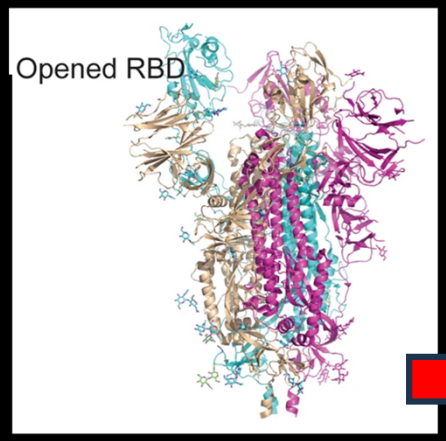
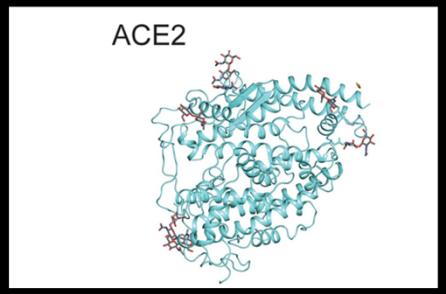
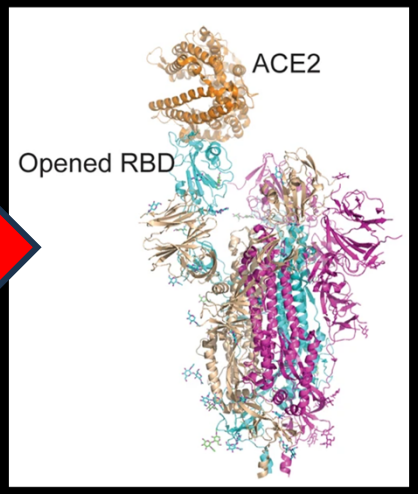
Computational simulation of spike-ACE2 binding strength





Multiple species

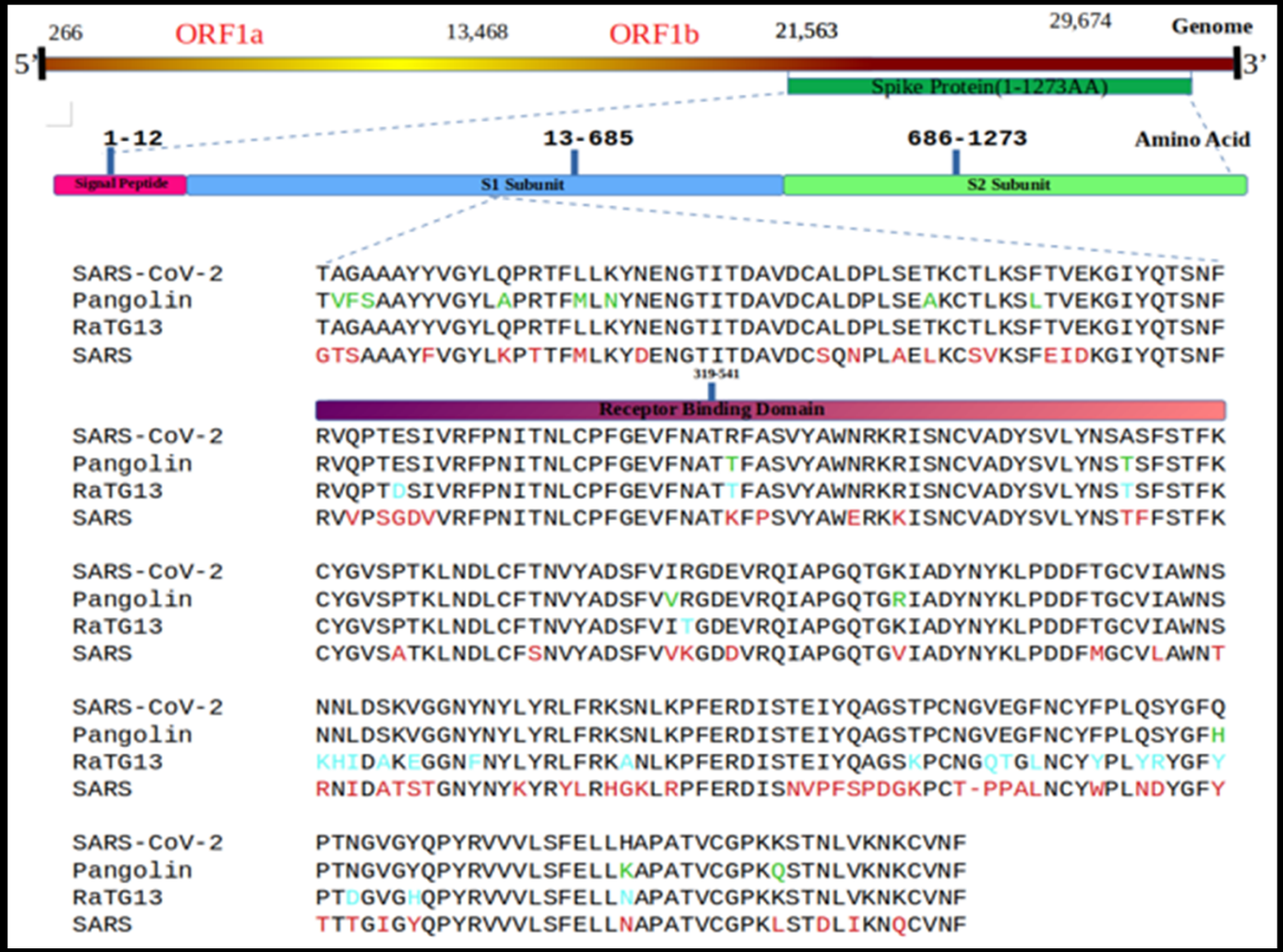
Protein-protein docking (HDOCK, AlphaFold)



Molecular dynamics simulations and ΔG of binding

Piplani et al. **npj Sci Rep**., 11, 18610 (2021).

Sequence alignment of S1 subunit of four closely related spike proteins



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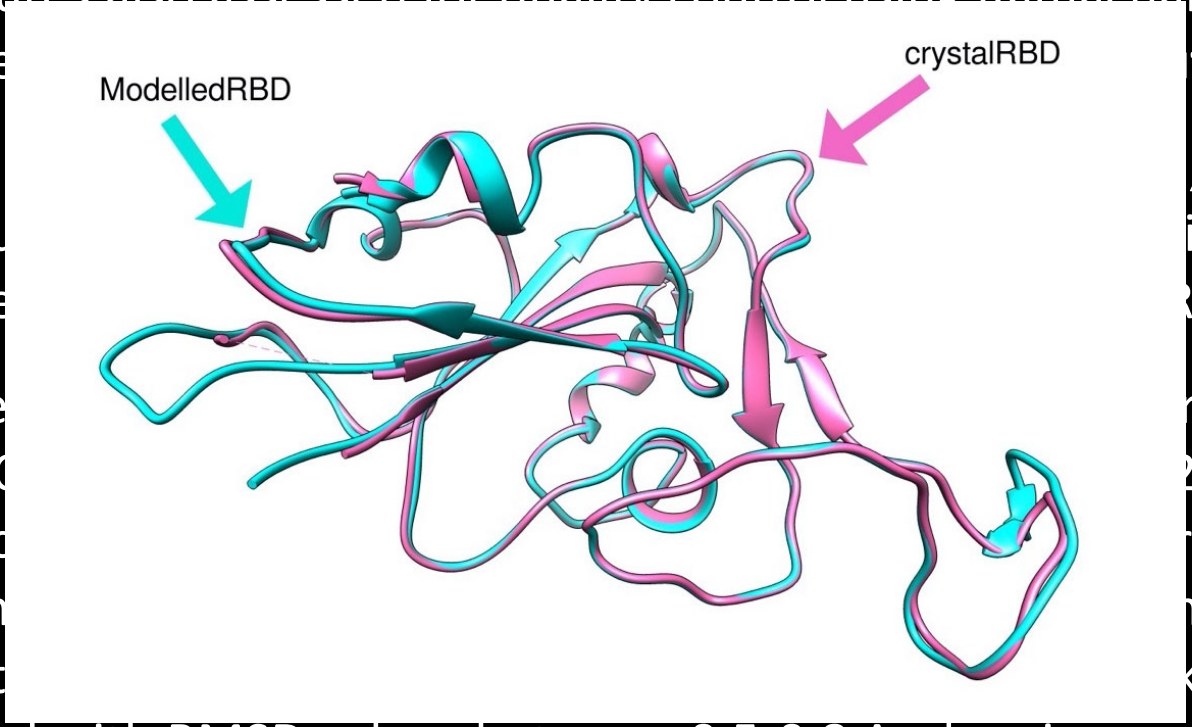
SARS-CoV-2 spike and ACE models

- **No** 3D structure of the SARS-CoV-2 S protein available at start of project
- Spike homology structure using YP_009724390.1 sequence from NCBI Genbank Database, January 2020.
- PSI-BLAST search identified structure of SARS coronavirus S template (PDB ID 5XLR) with ~80% sequence similarity to spike protein
- 3D-structures of RBD of spike and non-human ACE2 proteins were built using Modeller 9.23
- ACE2 receptors of species were homology modelled using the 1R42 (human ACE2), 3CSI (human glutathione transferase) and 3D0G (from spike protein receptor-binding domain of 2002-2003 SARS CoV human strain complexed with human-civet chimeric ACE2) templates
- Quality of models evaluated by GA341 and DOPE ((Discrete Optimized Protein Energy) scores
- Structures with lowest DOPE scores refined by MD and used for further analysis. Generated 10 homology models per protein that were subsequently refined and optimized in GROMACS.

SARS-CoV-2 spike and ACE2 models

- Modelled structures also assessed for quality control using Ramachandran Plot and molprobity score **tliers** in the RBD
- Structure of the , PDB ID 6VYB). Very high structu in structure with the EM structure RMSD of 0.36 Å
- Homology mode rotein structure using hybrid HDO 2 complexes from non-human spec ructure as a template. To elin n HDOCK compared with t kbones of ACE2 structures aligned with RMSD values between 0.5-0.8 A, showing very strong structural similarities.



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Quality and consistency of modelled ACE2 structures

Species	RMSD Å Cα ACE2	RMSD Å complex
Bat	0.82	0.88
Cat	0.54	0.85
Cattle	0.77	0.79
Civet	0.74	0.85
Dog	0.69	0.82
Ferret	0.59	0.84
Hamster	0.60	0.85
Horse	0.82	0.84
Monkey	0.56	0.85
Pangolin	0.54	0.86
Snake	0.84	0.89
Tiger	0.87	0.85
Mouse	0.54	0.86

RMSD for alignments of Cα backbones of modelled ACE2 with its corresponding ACE2 in the HDOCK generated ACE2-S protein complexes, and all-atom RMSDs for modelled ACE2 with its corresponding ACE2 in the HDOCK generated ACE2-spike protein complexes

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MD simulations

- Complexes were subjected to molecular dynamics simulation to wash out any template-induced bias.
- Final docked SARS-CoV-2 spike/ACE2 protein complexes were optimized using the AMBER99SB-ILDN force field in GROMACS2020 using the GPU accelerated version of the program and periodic boundary conditions in an ORACLE server.
- Docked complexes were immersed in a truncated octahedron box of TIP3P water molecules. The solvated box was further neutralized with Na+ or Cl− counter ions using the tleap program.
- Particle Mesh Ewald (PME) was employed to calculate the long-range electrostatic interactions. The cut-off distance for the long-range van der Waals (VDW) energy term was 12.0 Å.

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MD simulations

- System minimized without restraints. Applied 2500 cycles of steepest descent minimization followed by 5000 cycles of conjugate gradient minimization.
- After system optimization, MD simulations was initiated by heating each system in the NVT ensemble from 0 to 300 K for 50 ps using a Langevin thermostat with a coupling coefficient of 1.0/ps and a force constant of 2.0 kcal/mol·Å2 on the complex.
- Productions run of 100 ns of MD simulation were performed at 300 K in the NPT ensemble with periodic boundary conditions for each system. The time step was 2 fs. Structural stability of complexes were monitored by the RMSD and RMSF values of the backbone atoms of the entire protein.
- Finally, the free energies of binding were calculated for all simulated docked structures.

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Spike–ACE2 binding free energies and observed infection susceptibilities

Species	ΔG_{eqn1} (kcal/mol)	ΔG_{MMPBSA} (kcal/mol)	SARS-Cov-2 infectivity
Homo sapiens (human)	-52.8	-57.6 ± 0.25	Permissive, high infectivity, severe disease in 5-10%,
Manis javanica (pangolin)	-52.0	-56.3 ± 0.4	Permissive [23,24]
Canis luparis (dog)	-50.8	-49.5	Permissive, low/mod infectivity, no overt disease [25,26]
Macaca fascicularis (monkey)	-50.4	-50.8	Permissive, high infectivity, lung disease [11]
Mesocricetus auratus (hamster)	-49.7	-50.0	Permissive, high infectivity, lung disease [27,28]
Mustela putorius furo (ferret)	-48.6	-49.2	Permissive, moderate infectivity, no overt disease [28-30]
Felis catus (cat)	-47.6	-48.9	Permissive, high infectivity, lung disease [26,29,31]
Panthera tigris (tiger)	-47.3	-42.5	Permissive, overt disease, RNA positive[26]
Rhinolophus sinicus (bat)	-46.9	-50.1 ± 1.0	Not permissive [11]
Paguma larvata (civet)	-45.1	-46.1	No reported infection
Equus ferus caballus (horse)	-44.1	-49.2	No naturally occurring infections[26]
Bos taurus (cattle)	-43.6	-42.5	No naturally occurring infections[26]
Ophiophagus hannah (king cobra)	-39.5	-40.7 ± 1.2	No reported infection
Mus musculus (mouse)	-38.8	-39.4	Resistant to infection[28]

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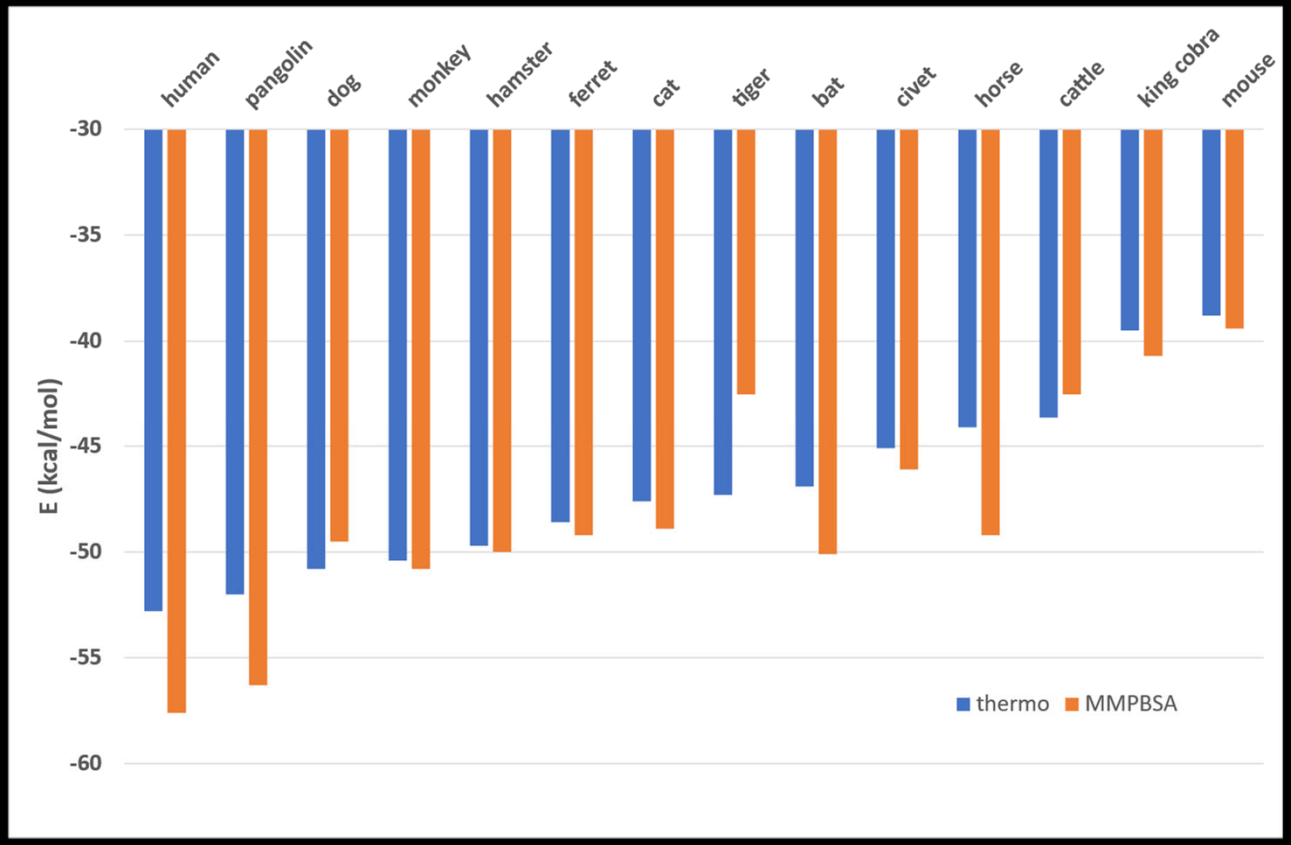
Spike–ACE2 binding free energies



Spike-pangolin ACE2 interactions

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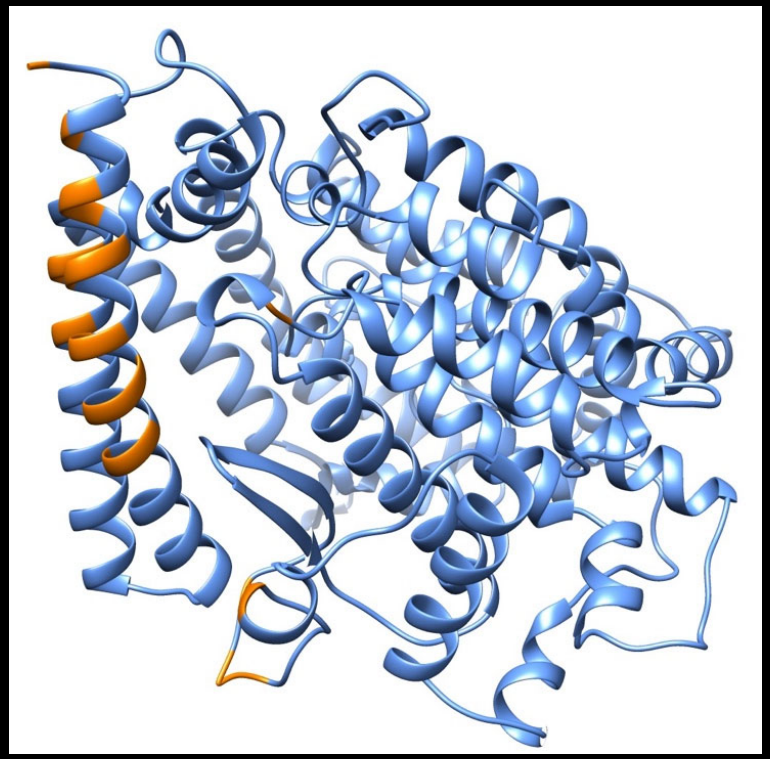
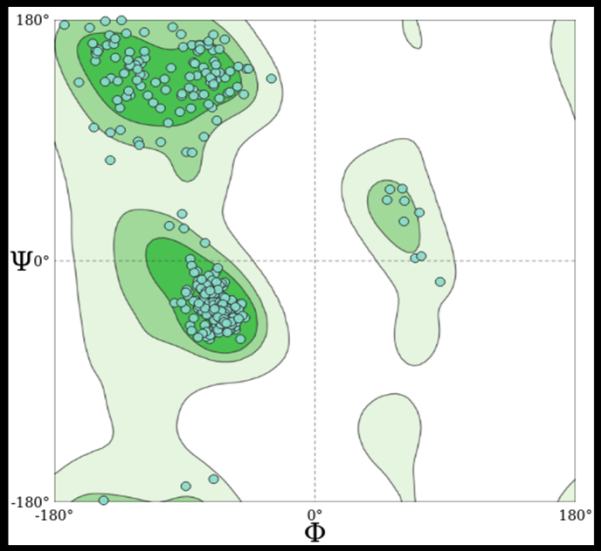
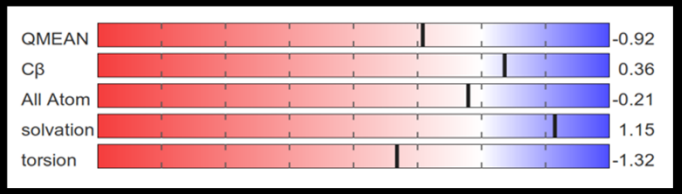
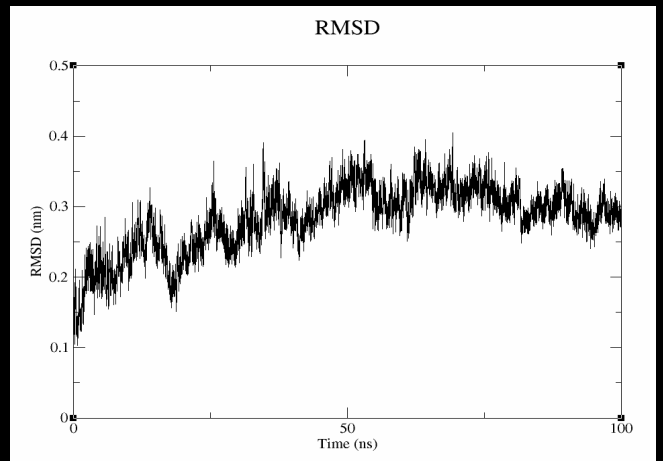
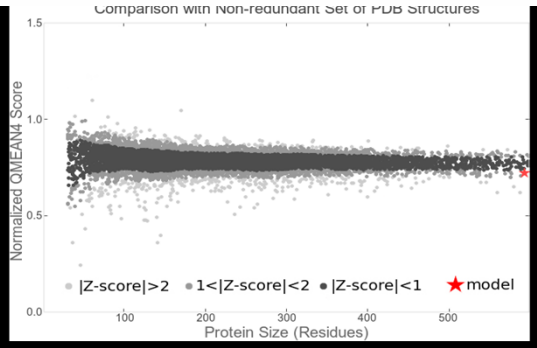






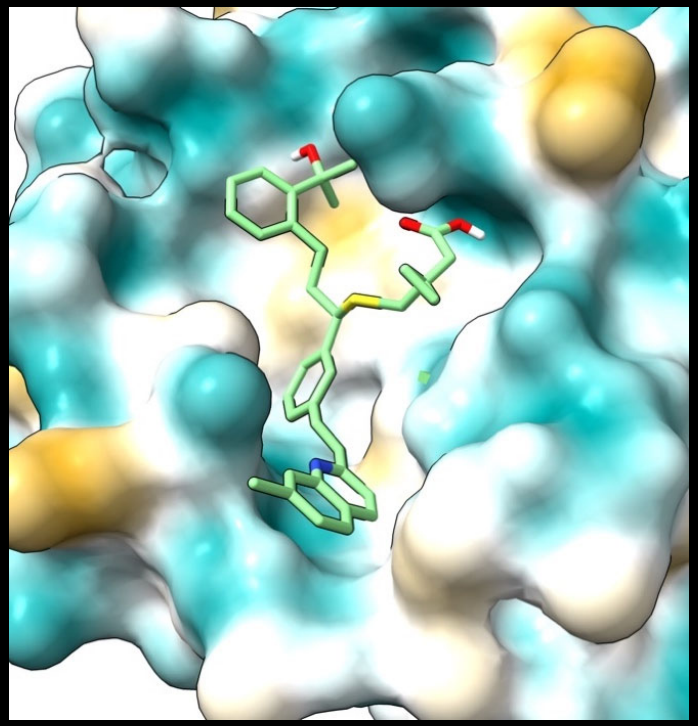




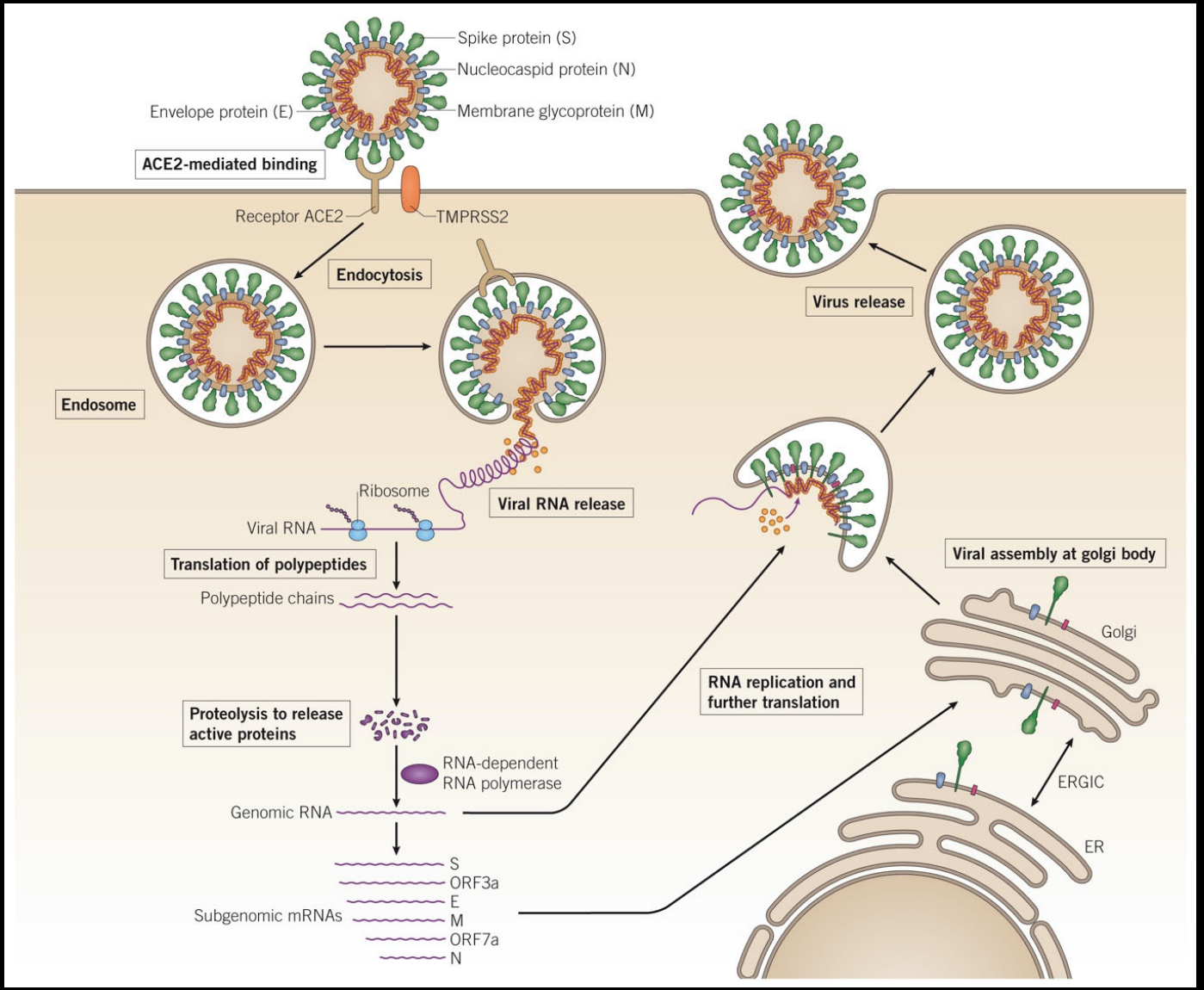
ACE2 RBD residues interacting with the S protein RBD from MD simulations of complexes

Species	Accession Number	Position															% common residues
		19	24	27	28	30	31	34	37	38	41	42	79	83	330	353	393	
Homo sapiens (human)	Q9BYF1	S	Q	T	F	D	K	H	E	D	Y	Q	L	Y	N	K	R	100
Macaca fascicularis (monkey)	A0A2K5X283	S	Q	T	F	D	K	H	E	D	Y	Q	L	Y	N	K	R	100
Rhinolophus sinicus (bat)	U5WHY8	S	E	M	F	D	K	T	E	D	H	Q	L	Y	N	K	R	75
Mustela putorius furo (ferret)	Q2WG88	D	L	T	F	E	K	T	E	E	Y	Q	-	Y	N	K	R	69
Manis javanica (pangolin)	XP_017505752.1	-	E	T	F	E	K	S	E	E	Y	Q	I	Y	N	K	R	63
Ophiophagus Hannah (snake)	ETE61880.1	Q	V	K	F	E	Q	A	-	D	Y	N	N	F	N	L	R	38

Computational repurposing of existing drugs to treat COVID-19



SARS-CoV-2 infection and replication cycle



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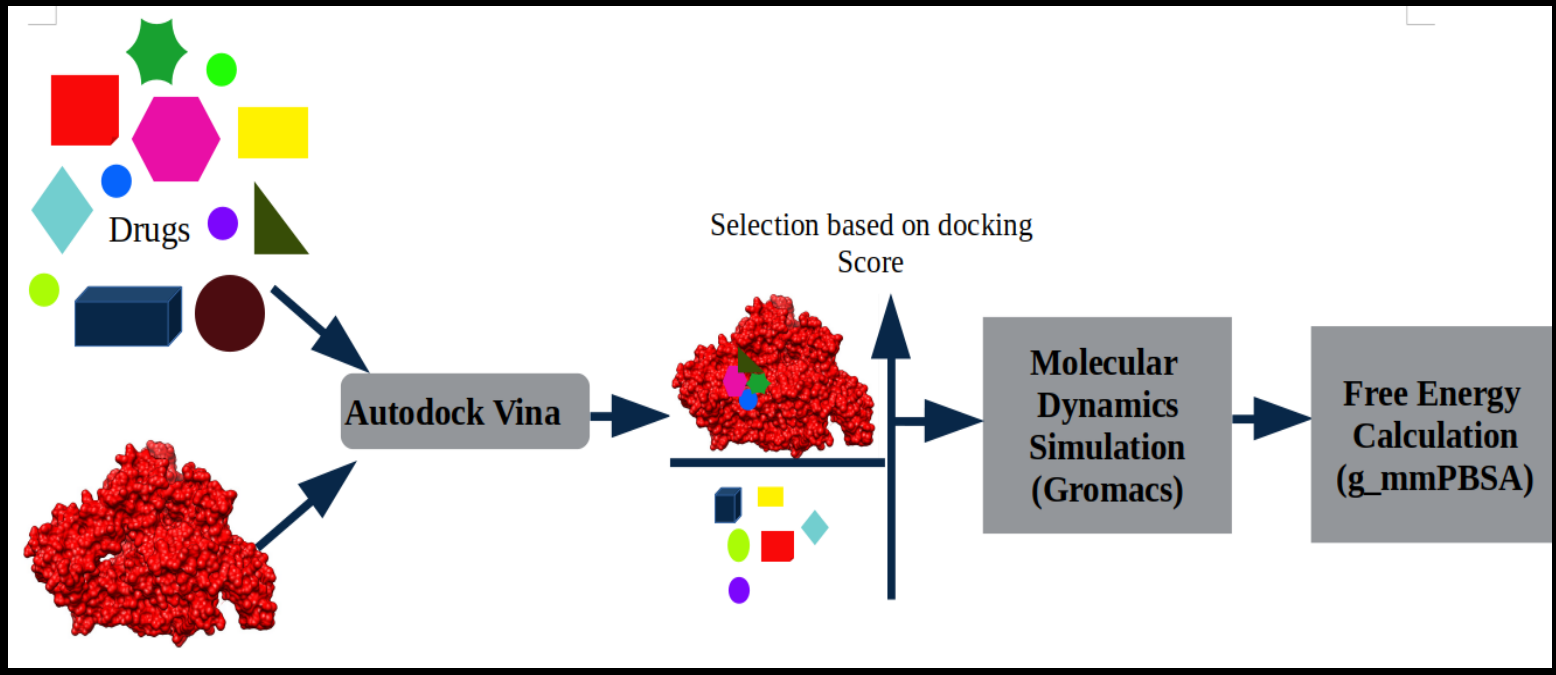
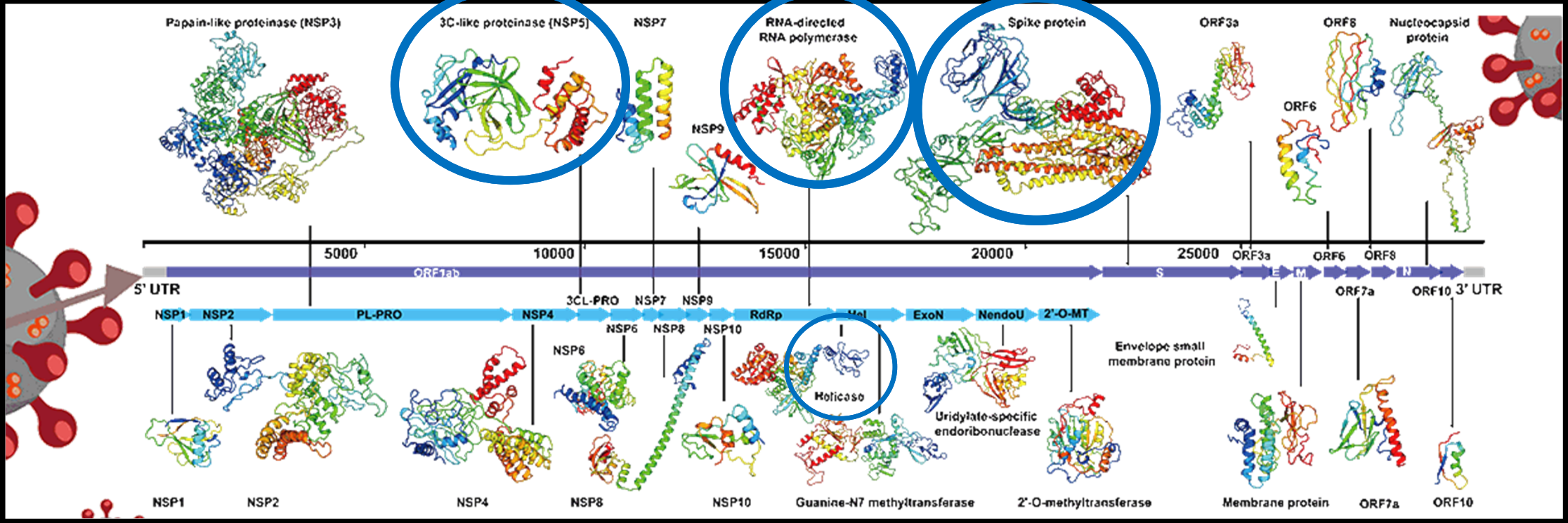
Computational screening of pathogen target proteins



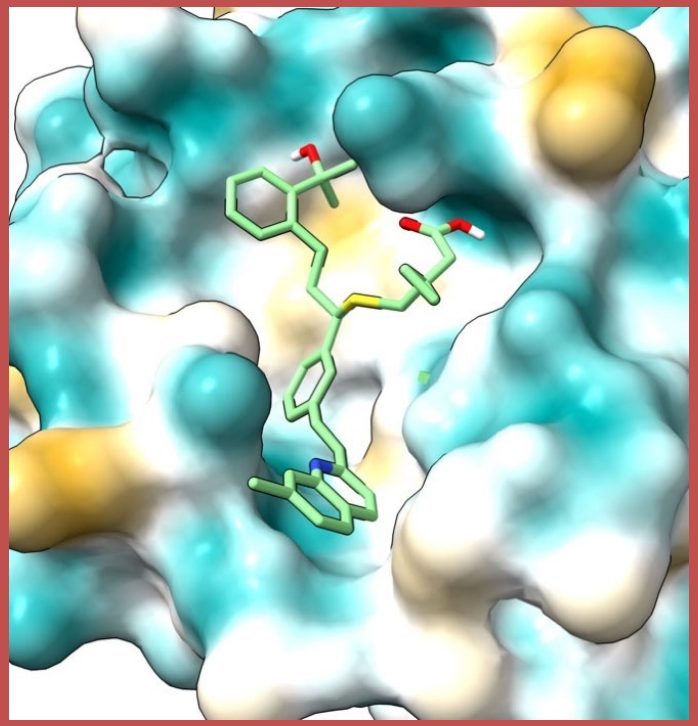
Pilani, et al., *Rational repurposing of drugs, clinical trials candidates, and natural products for SARS-Cov-2 therapy,* in Frontiers of COVID-19: Scientific and Clinical Perspectives of the Novel SARS-CoV-2, Sasan Adibi, Abbas Rajabifard, Shariful Islam, Alireza Ahmadvand (eds.), Springer Nature 2021.

Drug targets – SARS-CoV-2 nonstructural proteins (nsps)



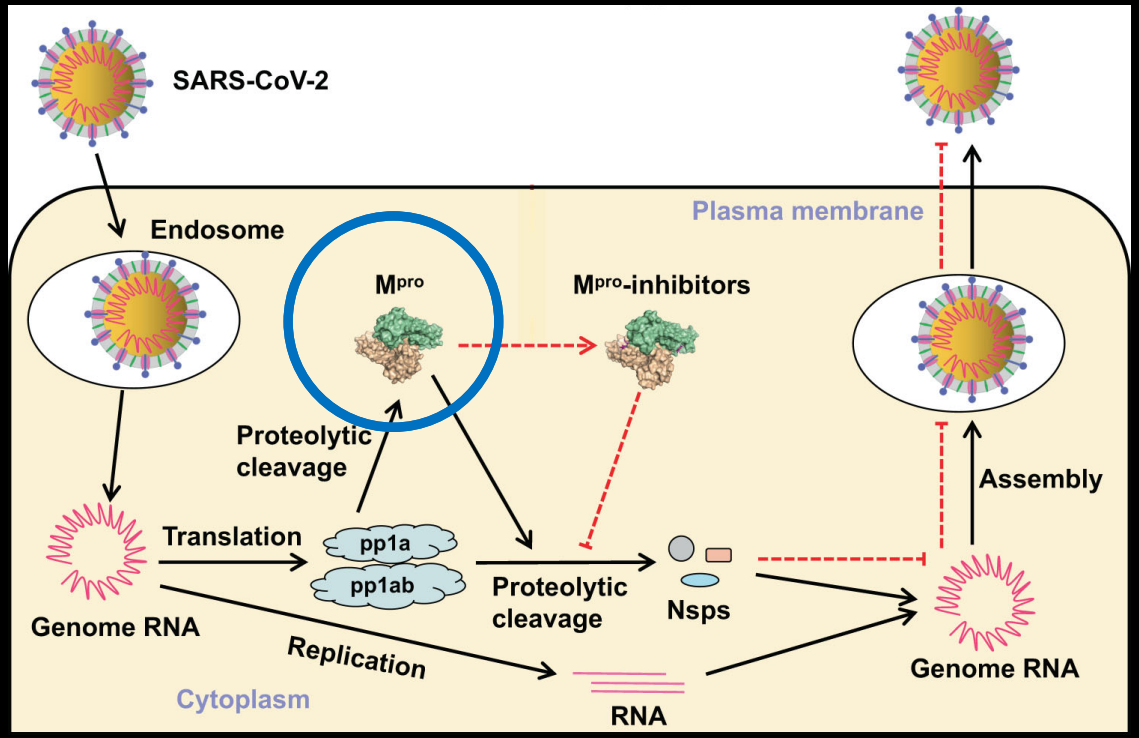
Zhang Lab, UMich

Repurposed drugs against the main protease (M^{pro}, nsp5)



Mode of action of M^{pro} inhibitors

M^{pro}, (3C-like protease) cleaves a peptide bond between a glutamine at position P1 and a small amino acid (serine, alanine, or glycine) at position P1'. The SARS coronavirus 3CLpro self-cleaves the TSAVLQ-SGFRK-NH2 and SGVTFQ-GKFKK peptides.
The protease is essential for processing of the coronavirus replicase polyprotein. It is the main protease in coronaviruses, cleaving the coronavirus polyprotein at 11 conserved sites.



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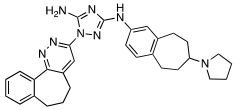
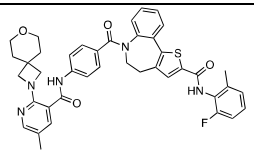
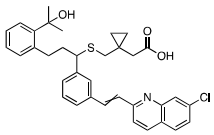
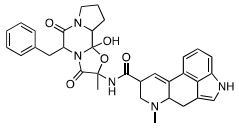
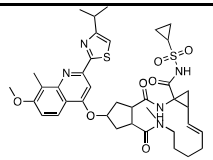
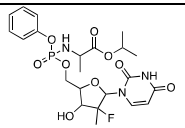
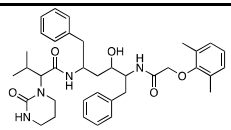
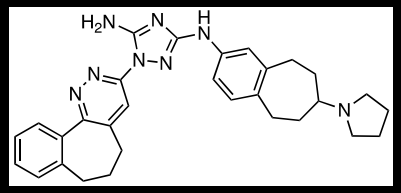
Selected top hits from M^{pro}

ID	Structure	Description	ΔG_{MMPBSA} (ΔG_{bind}) (kcal/mol)
C3809489 Bemcentinib		Inhibitor of the kinase domain of AXL receptor.	-34.7±2.6 (-30.7)
C4291143 PC786		Respiratory syncytial virus (RSV) L protein polymerase inhibitor.	-33.1±0.3 (-29.2)
C787 Montelukast		Leukotriene receptor antagonist used with cortico-steroids for asthma therapy.	-32.7±0.2 (-20.6)
C442 Ergotamine		Alpha-1 selective adrenergic agonist used in migraine treatment.	-31.5±0.3 (-28.7)
D06290 Simeprevir		Hepatitis C virus (HCV) NS3/4A protease inhibitor.	-31.4±0.2 (-29.2)
D08934 Sofosbuvir		Nucleotide prodrug and HCV NS5B polymerase inhibitor	-31.0±0.5 (-22.8)
D01601 Lopinavir		Antiretroviral protease inhibitor for treatment of HIV-1	-30.7±0.3 (-20.4)

Computational Repurposing of Drugs and Natural Products
tential COVID-19 Therapies, Front. Mol. Biosci. 2022, 9, 781039.

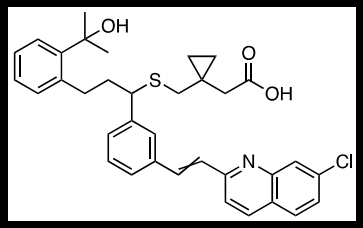
Experimental validation of top 10 hit repurposed drugs

Bemcentinib



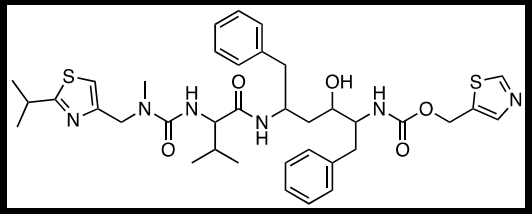
Phase 2 clinical trial, ED_{50} 0.1 (Huh7.5), 0.47 (Vero), 2.1 (Calu3) μM, predicted 2'-O-methyltransferase nsp16/nsp10 complex binding.

Montelukast



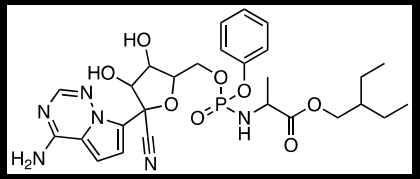
Significant reduction in SARS-CoV-2 infection in elderly asthmatic patients treated with MK.[65] Several predicted M^{pro} binding studies.

Ritonavir



In vitro EC_{50} 5.73 μM, Multiple single agent and combination human trials. In vitro EC_{50} 26.63 μM. Predicted M^{pro} binding

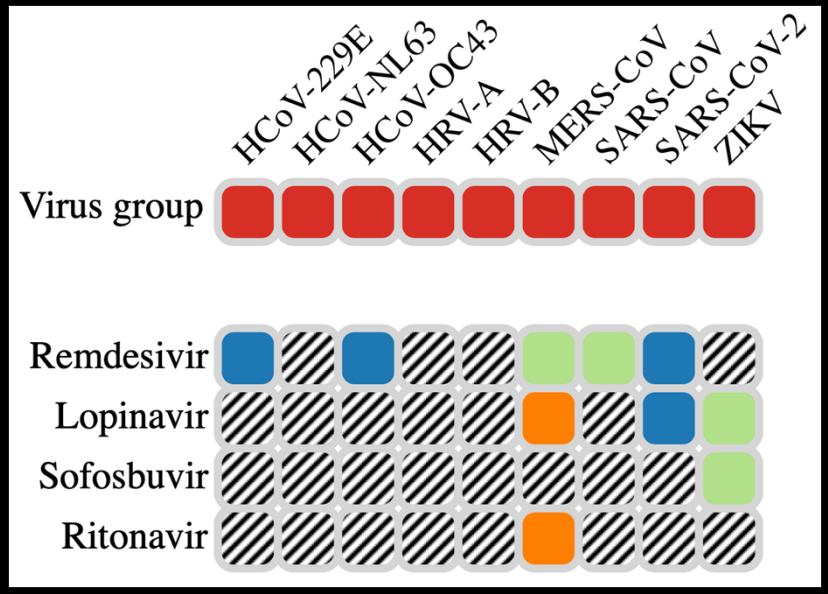
Remdesivir

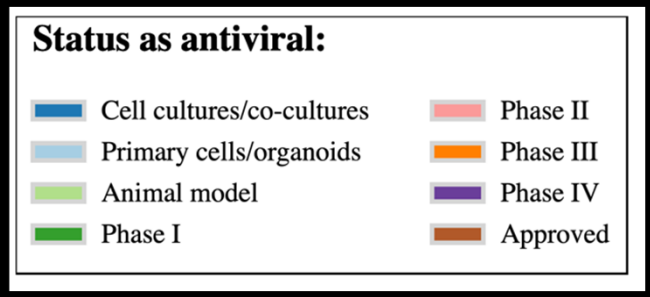


Multiple human trials, in vitro EC_{50} 23.15 μM, predicted M^{pro} and RdRp binding

30% of 87 top predicted repurposing hits have experimental validation by 2022

Known antiviral activity of hits





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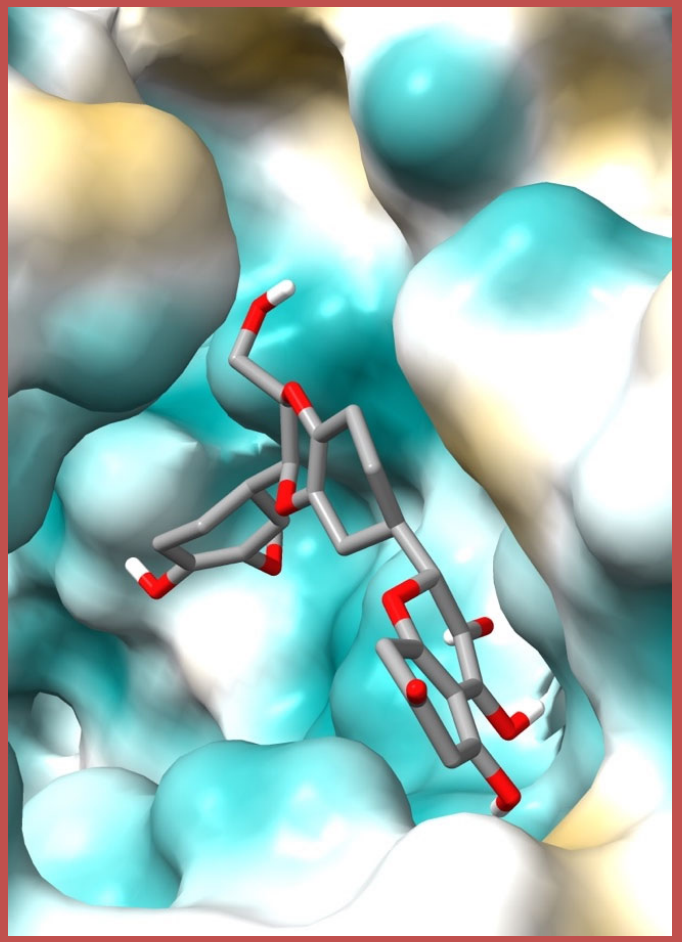
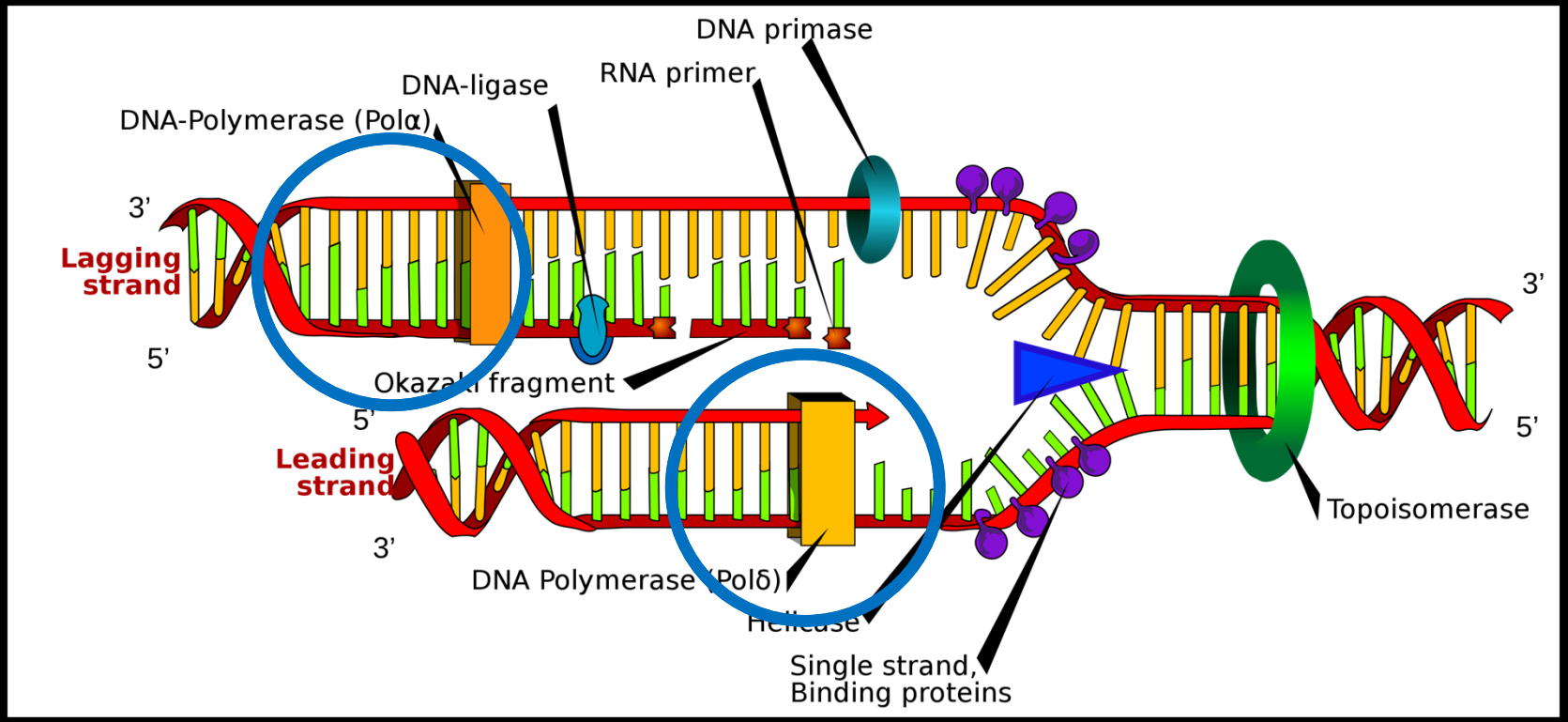
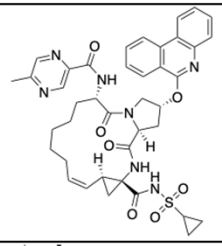
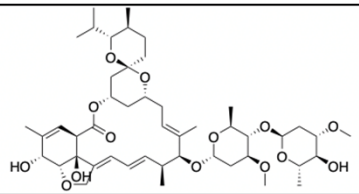
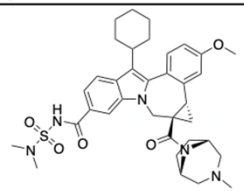
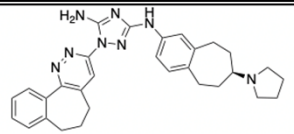
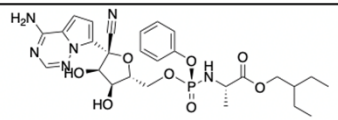
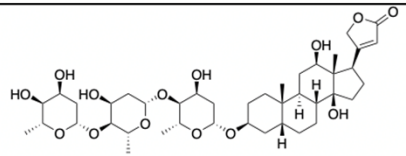
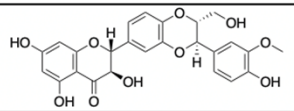
Repurposed drugs against the RNA-dependent RNA polymerase (RdRP, nsp7)



RNA/DNA polymerases



Selected top hits from RdRP computational screen

Database ID C=ChemBL D=Drugbank	Drug Name	Structure	ΔG_{MMPBSA} (ΔG_{thermo}) kcal/mol
C 3391662	Paritaprevir (antiviral)		-54.3 (-67.5)
C 1200633	Ivermectin (anti-parasitic)		-54.1 (-69.7)
C 3126842	Beclabuvir (antiviral)		-53.5 (-66.4)
C 3809489	Bemcentinib (anticancer)		-46.1 (-62.5)
D 14761	Remdesivir (antiviral)		-44.6 (-56.8)
C 1751	Digoxin (cardiac drug)		-41.2 (-54.4)
D 09298	Silibinin (chemo-protectant		-40.2 (-57.2)

Piplani, S.; Singh, P.; Petrovsky, N.; Winkler, D.A. Computational screening of repurposed drugs and natural products against SARS-CoV-2 RNA-dependent RNA polymerase as potential COVID-19 therapies, Mol. Biomed. 2021, 2, 28.

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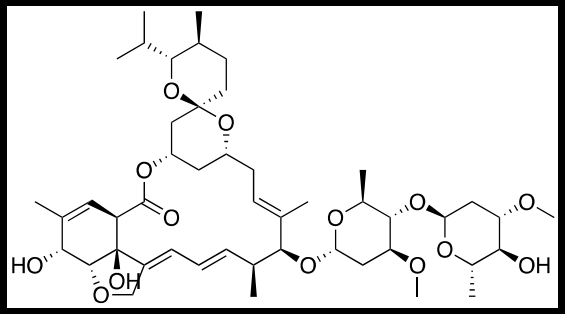
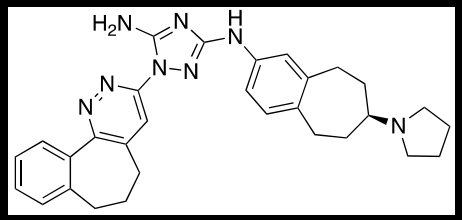
Experimental validation of top 10 hit repurposed drugs

Ivermectin



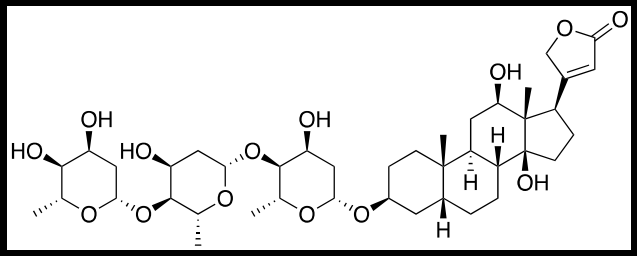
IC_{50} of 2.2 - 2.8 μM in monkey kidney cells.

Bemcentinib



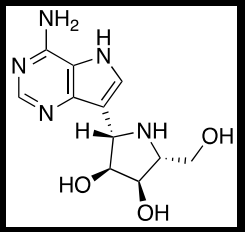
10-40% protection at 50μM in Vero cells. IC^{50} 100nM and CC_{50} 4.7μM in Huh7.5 cells, IC_{50} of 470nM and CC_{50} of 1.6μM in Vero cells, investigational treatment for COVID-19, predicted to bind to Mpro.

Digoxin



Predicted RdRP inhibitor,15 IC_{50} = 0.043 μM and CC_{50} >10μM in Vero cells

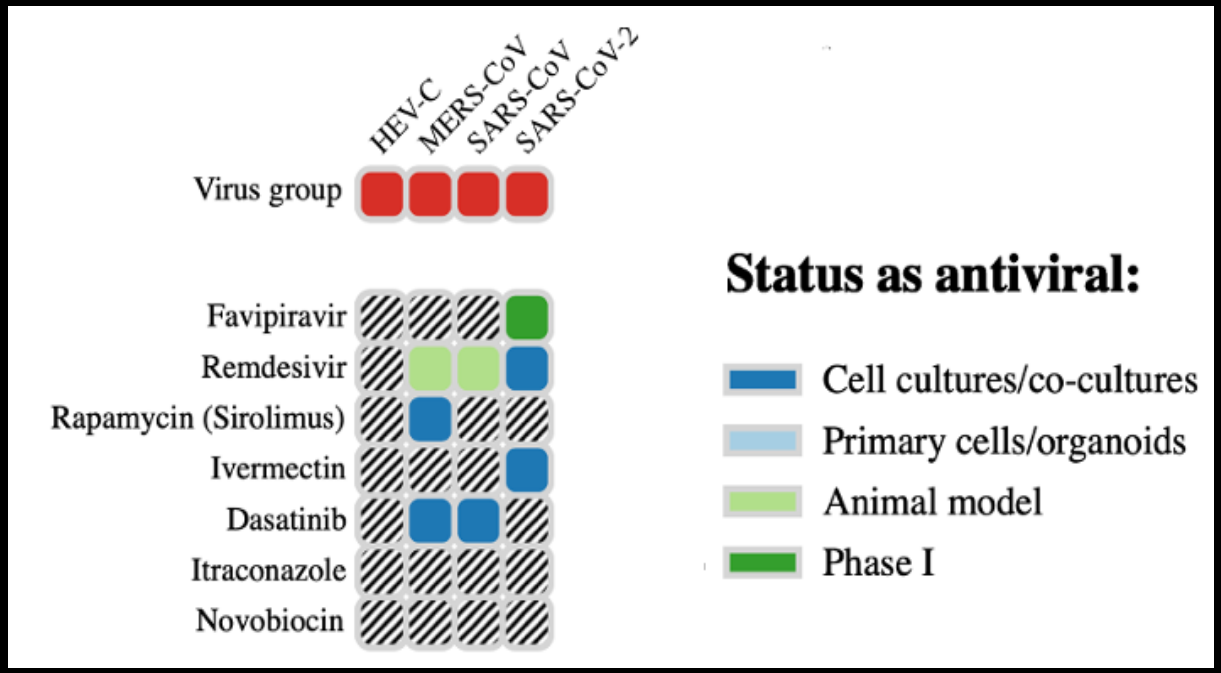
Galidesvir



Clinical trials for COVID-19 and RdRP inhibitor

>30% of 80 top predicted repurposing hits have experimental validation at 2021

Known antiviral activity of hits



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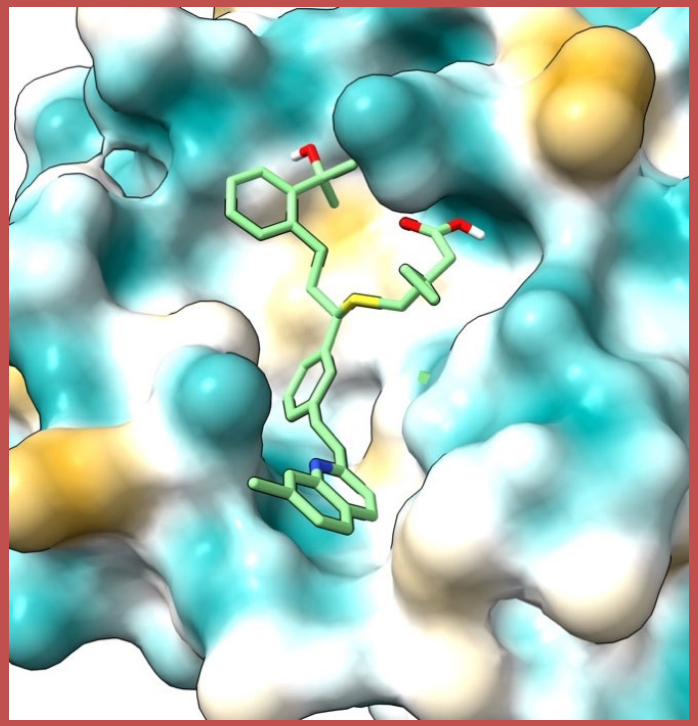
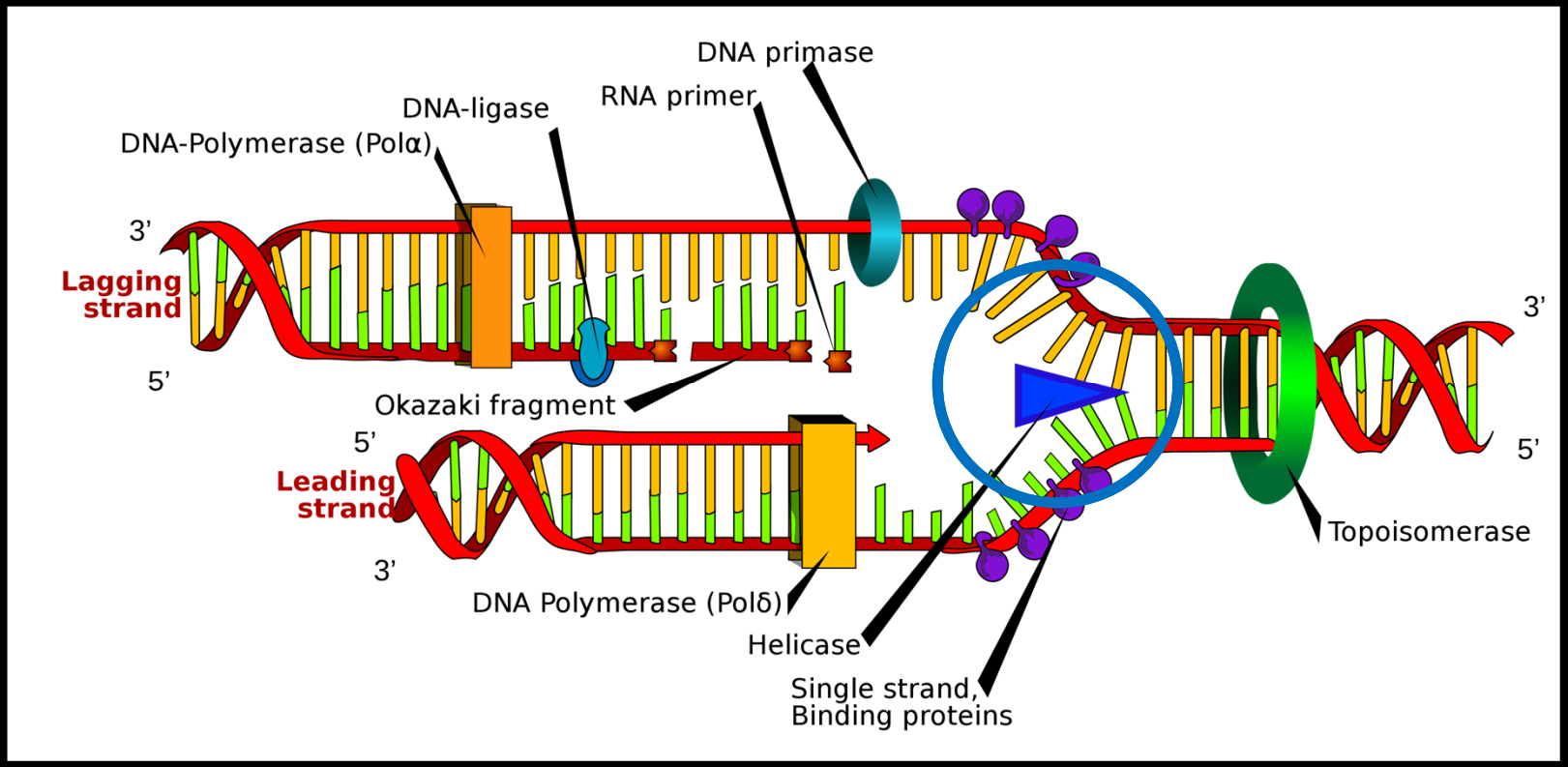
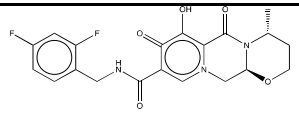
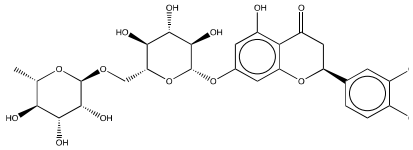
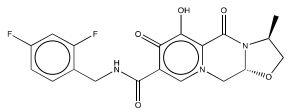
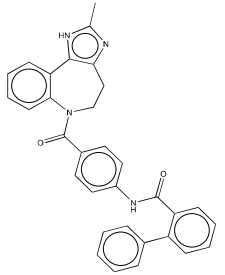
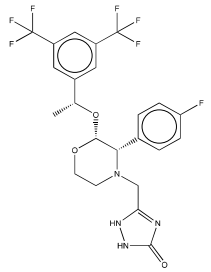
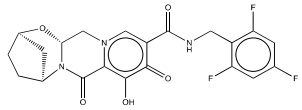
Repurposed drugs against the helicase (nsp12)



RNA/DNA helicases

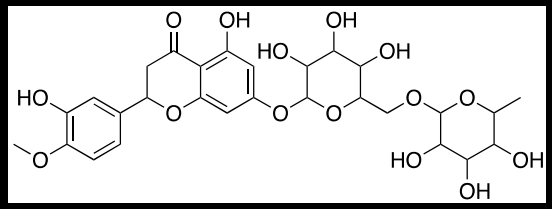


Selected top 10 hits from helicase c

Database ID	Drug Name	Structure	ΔG_{MMPBSA} kcal/mol	ΔG_{thermo} kcal/mol
DB08930	Dolutegravir (antiretroviral)		-42.2	-45.9
DB04703	Hesperidin (citrus flavanone glycoside)		-41.2	-39.6
DB11751	Cabotegravir (antiviral integrase inhibitor)		-40.8	-42.3
DB00872	Conivaptan (vasopressin inhibitor)		-40.2	-39.7
DB00673	Aprepitant (NK1 antagonist)		-40.1	-45.6
DB11799	Bictegravir (antiviral		-39.8	-41.2

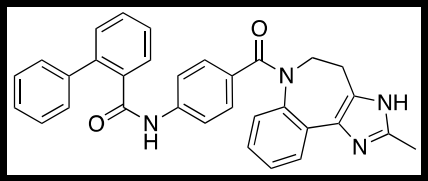
Experimental validation of top 10 hit repurposed drugs

Hesperidin (citrus flavanone glycoside)



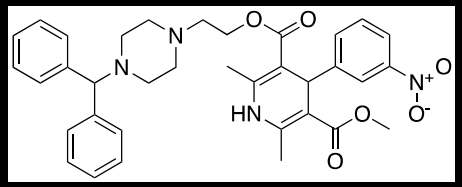
SARS-Cov-2 Mpro inhibition IC_{50} = 8.3 μM

Conivaptan (vasopressin inhibitor)



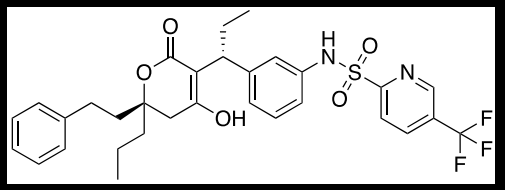
SARS-CoV-2 EC_{50} 10μM CC_{50} 13μM in HEK-293T cells.3 EC_{50} = 12.2 μM against HCoV-OC43

Manidipine (anti-hypertensive)



IC_{50} 10μM in SARS-CoV-2 Mpro; 14μM in PLpro. SARS-CoV-2 EC_{50} = 15±1 μM in plaque reduction assay. Mpro IC_{50} = 4.8 μM. SARS-CoV-2 activity in HUH7 cells (IC_{50}=2μM) and Vero cells (IC_{50}=7.5μM).

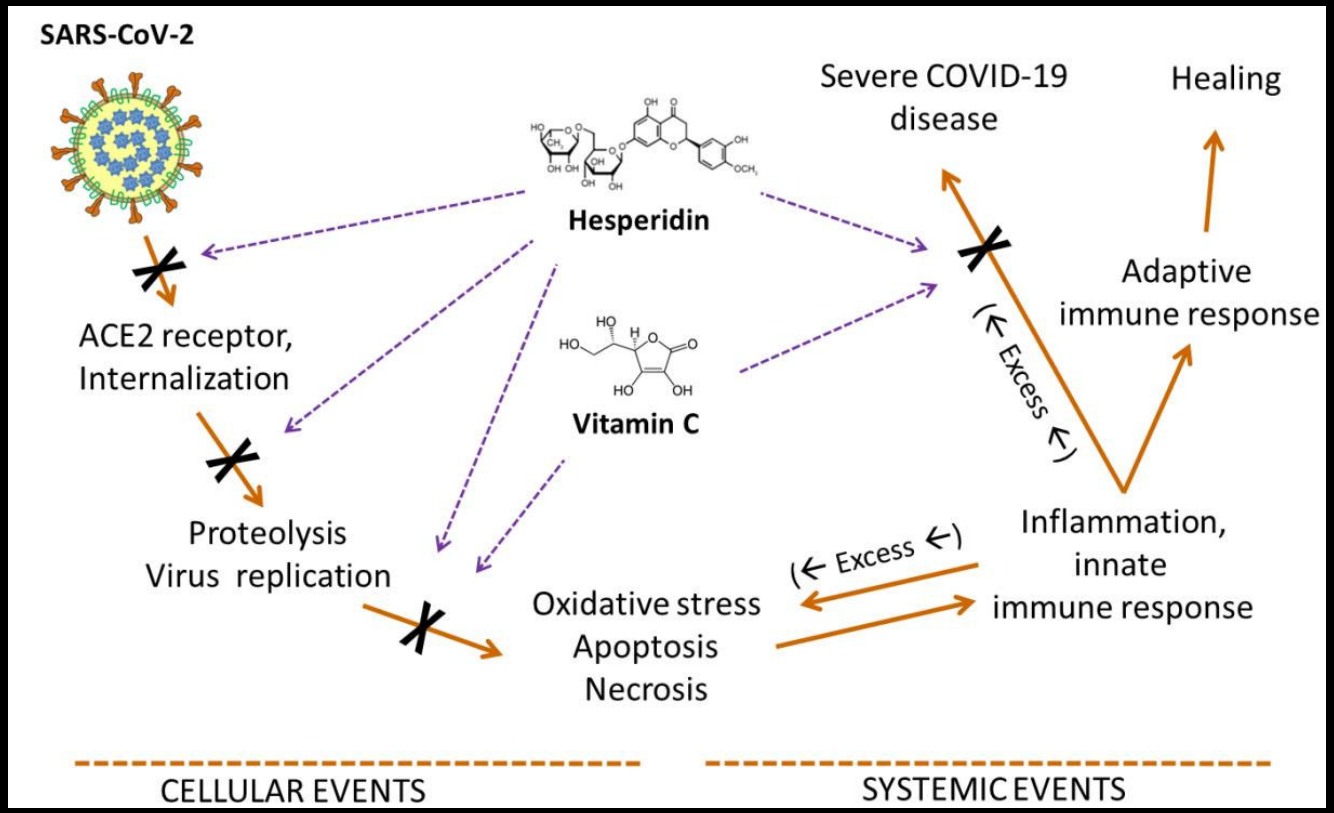
Tipranavir (antiviral protease inhibitor)



Inhibits replication of SARS-CoV-2 in VeroE6 cells, but low SI (EC_{50} = 13 μM, CC_{50} = 77 μM, SI = 6).

~30% of 87 top predicted repurposing hits have experimental validation at 2021

Hesperidin MoA



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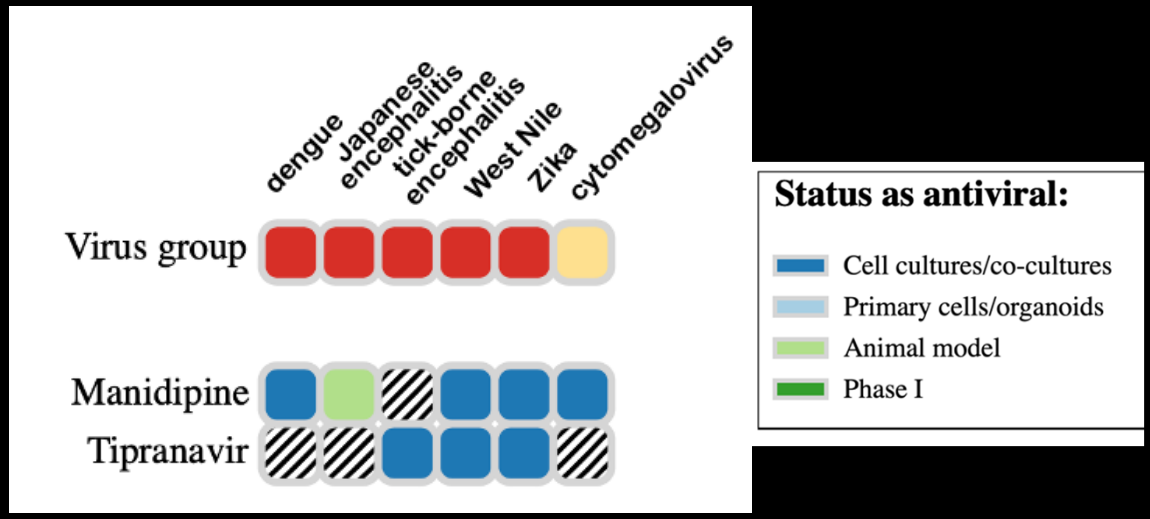
Known antiviral activity of hits



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Summary

- **We have shown how state of the art computational methods can predict the binding affinities of the SARS-CoV-2 spike for the ACE2 receptor protein in diverse species**
- Binding affinities of species broadly consistent with observed animal susceptibilities
- Surprisingly, of all animals assessed, the **susceptibility of human ACE2 is the highest**, with pangolin being lower and bat much lower.
- There are two main ways this could occur: –
  - from bat virus to an intermediate animal to humans. Despite extensive searches, no intermediate animal has yet been found
  - accidental escape from a virology lab. WHO considers this unlikely but cannot be excluded
- We have also identified 80-100 repurposing candidates for each of three molecular targets: the main protease, the RNA-dependent RNA polymerase, and the helicase
- Subsequent experimental validation shows that at least 30% of tested compounds show activity against the respective target or the virus or both in vitro.
- Our computational protocol is **useful** for identifying new or repurposed drug candidates

Acknowledgements

- **Oracle Cloud systems for their generous grant of supercomputing time**
- Peter Winn and Dennis Ward from Oracle Cloud Systems for invaluable support in setting up and running the modelling, docking and MD calculations
- **Vaxine Pty Ltd for generous financial support of the project**
- Sakshi Piplani and Puneet Singh (Flinders University and Vaxine Pty Ltd) for setting up, running and analysis of docking and MD calculations
- Prof. Nikolai Petrovsky (Flinders, Vaxine) for leading the project and securing support
- **Dr. Harinda Rajapaksha (La Trobe, now Oracle) for invaluable support in algorithm development and optimization and critical analysis of research outcomes**





Selected recent publications

- Pilani, et al, *Rational repurposing of drugs, clinical trials candidates, and natural products for SARS-CoV-2 therapy*, in Frontiers of COVID-19: Scientific and Clinical Aspects of the Novel Coronavirus 2019, Adibi, Rajabifard, Islam, Ahmadvand (eds.), **Springer Nature** 2022. p 471.
- Winkler, D.A., *Computational repurposing of drugs for viral diseases and current and future pandemics*, **J. Math. Chem**. 2024.
- Winkler, D.A. Exploiting advances in automation and AI to find drugs for neglected tropical diseases**, Pharm. Sci**., 2023, 29, 252.
- Piplani, et al. *Identifying SARS-CoV-2 drugs binding to the spike fatty acid binding pocket using in silico docking and molecular dynamics*, **Int. J. Mol. Sci**., 2023, 24, 4192.
- Piplani et al. *Potential COVID-19 therapies from computational repurposing of drugs and natural products against the SARS-CoV-2 helicase*, **Int. J. Mol. Sci**. 2022 23, 7704.
- Piplani et al. *Computational Repurposing of Drugs and Natural Products Against SARS-CoV-2 Main Protease (Mpro) as Potential COVID-19 Therapies*, Front. **Mol. Biosci**. 2022, 9, 781039.
- Muratov, et al. *A critical overview of computational approaches employed for COVID-19 drug discovery*. **Chem. Soc. Rev**., 2021, 50, 9121.
- Piplani, et al. *Computational screening of repurposed drugs and natural products against SARS-CoV-2 RNA-dependent RNA polymerase as potential COVID-19 therapies*, **Mol. Biomed**. 2021, 2, 28.
- Piplani, et al. *In silico comparison of SARS-CoV-2 virus spike protein-ACE2 binding affinities across species; significance for animal susceptibility and viral origin*, **Nat. Sci Rep**., 2021, 11, 13063.
- Winkler, D.A. *Artificial intelligence and machine learning for discovery of drugs for neglected tropical diseases*, **Front. Chem**. 2021, 9, 39,
- Zhang, et al. *Opening the black box of neural networks: methods for interpreting neural network models in clinical applications*. **Ann. Transl. Med.** 2018. 6(11), 2016.
- Wijffels, et al. *Binding inhibitors of the bacterial sliding clamp by design***, J. Med. Chem**. 2011; 54 (13): 4831-4838.

Thank you –

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