NVBL Molecular Therapeutics

Marti Head
Project Lead

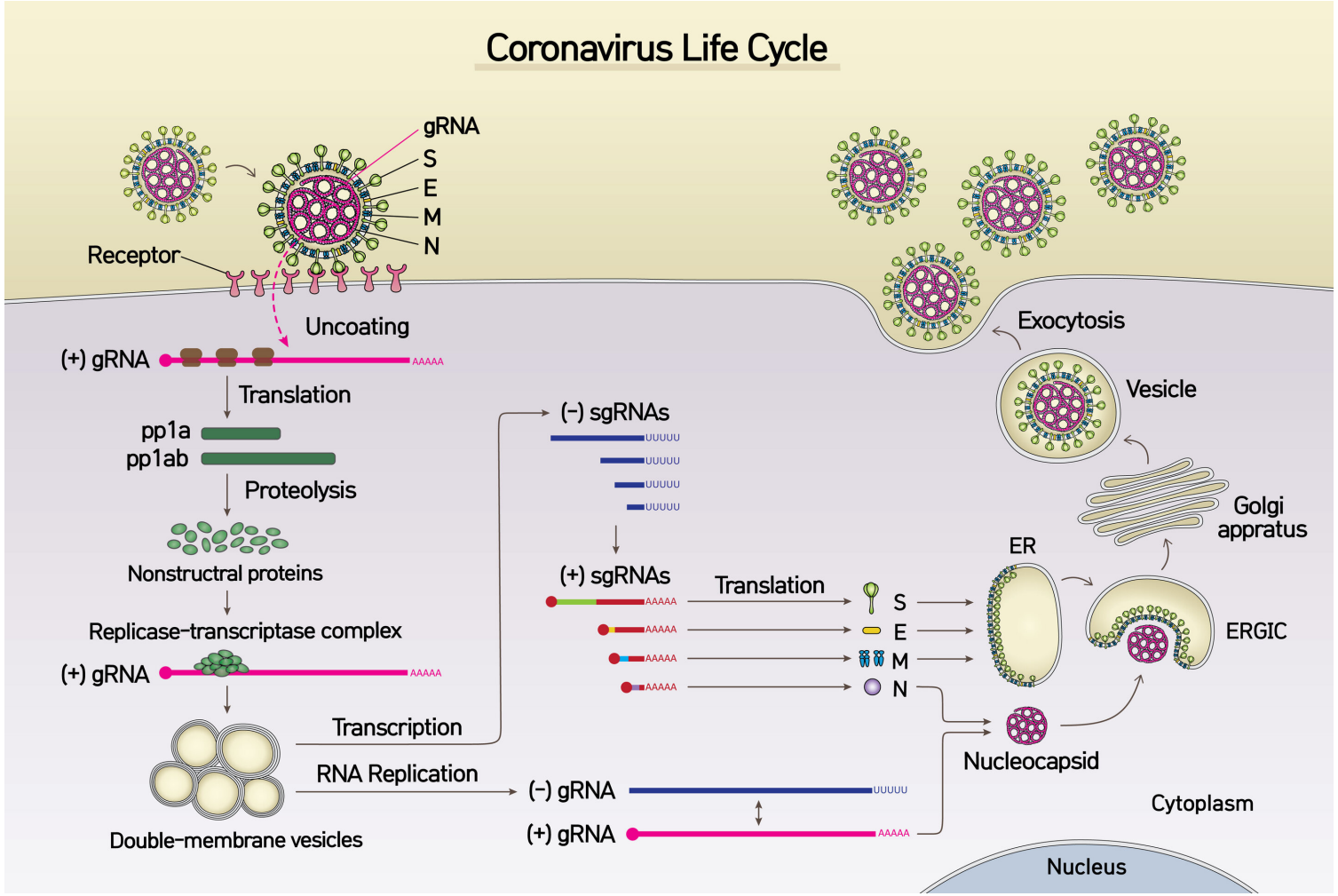
Goal: Leverage the world-leading capabilities of the Department of Energy National Labs…

Chemical, biological, and analytical sciences

High performance computing

Light and neutron sources

… to identify experimentally validated leads for targets across the entire coronavirus life cycle



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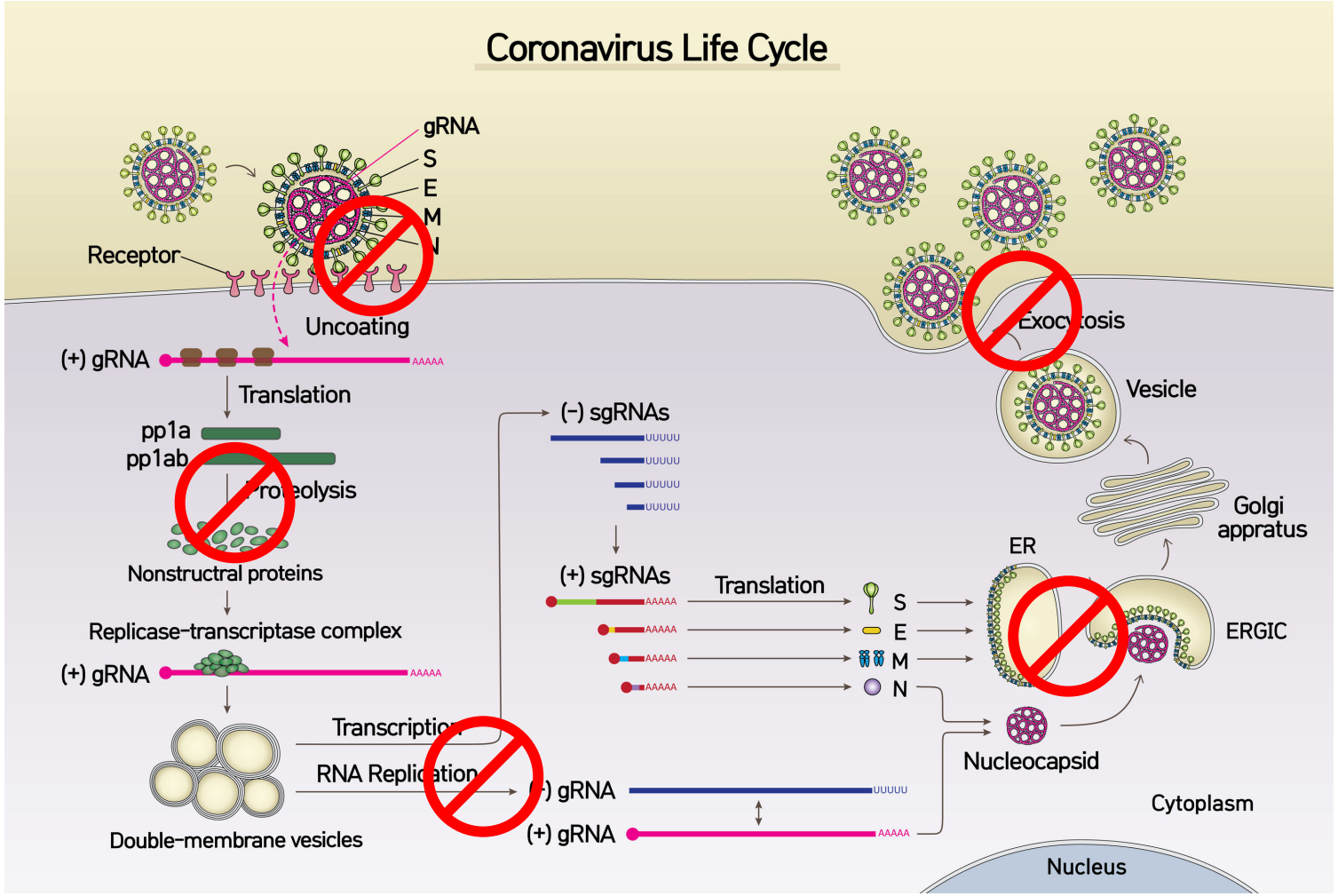

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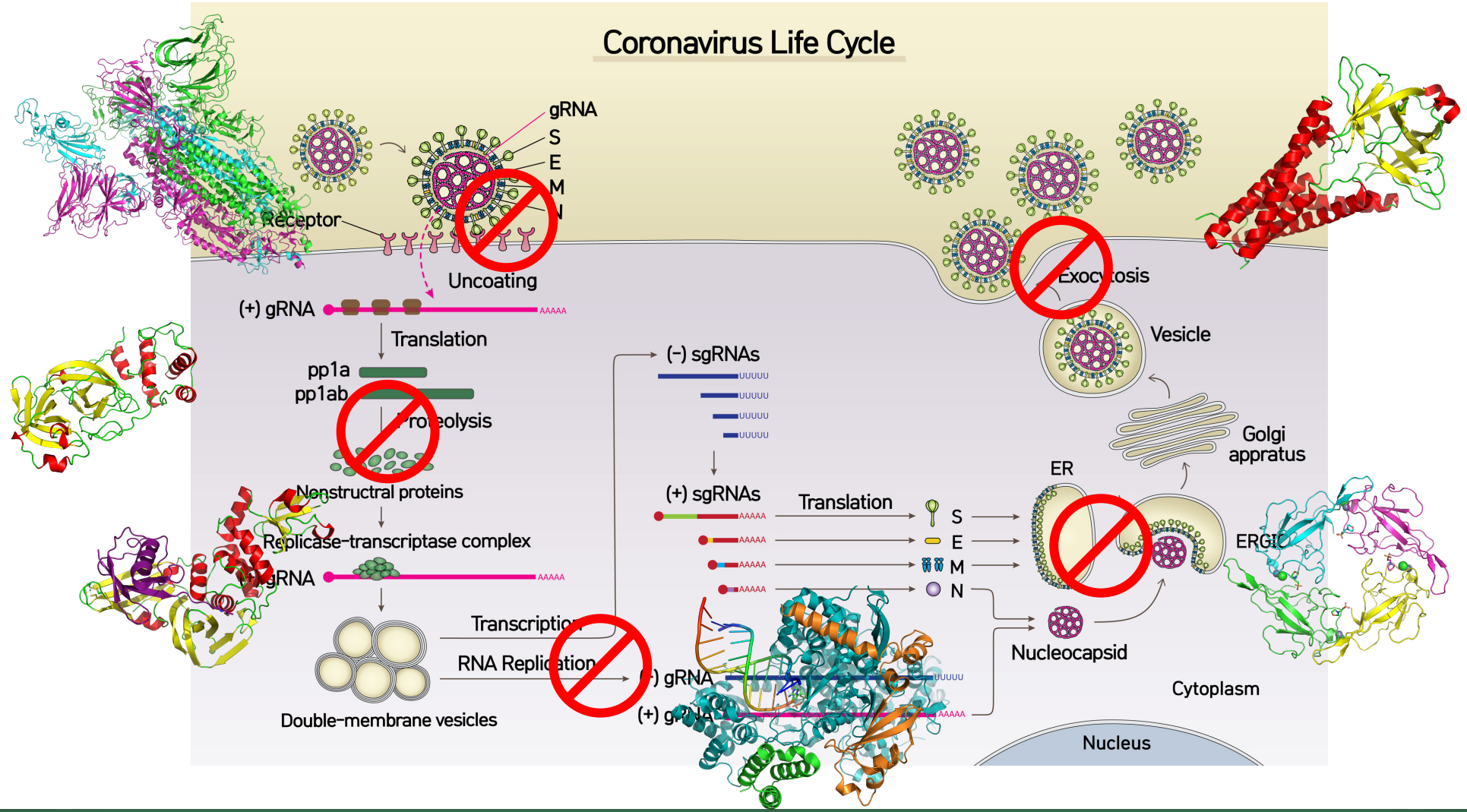
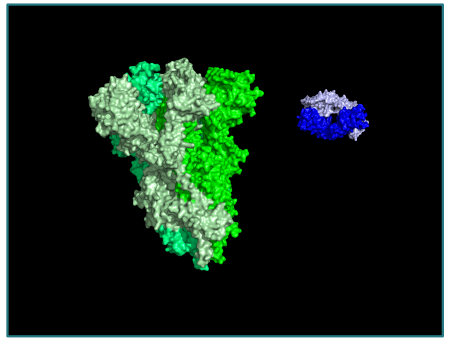
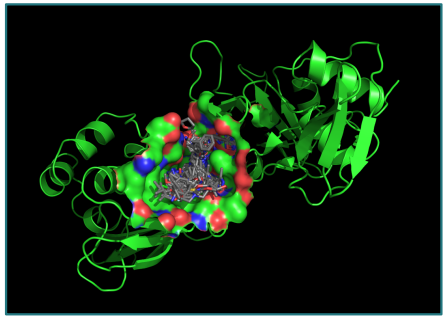


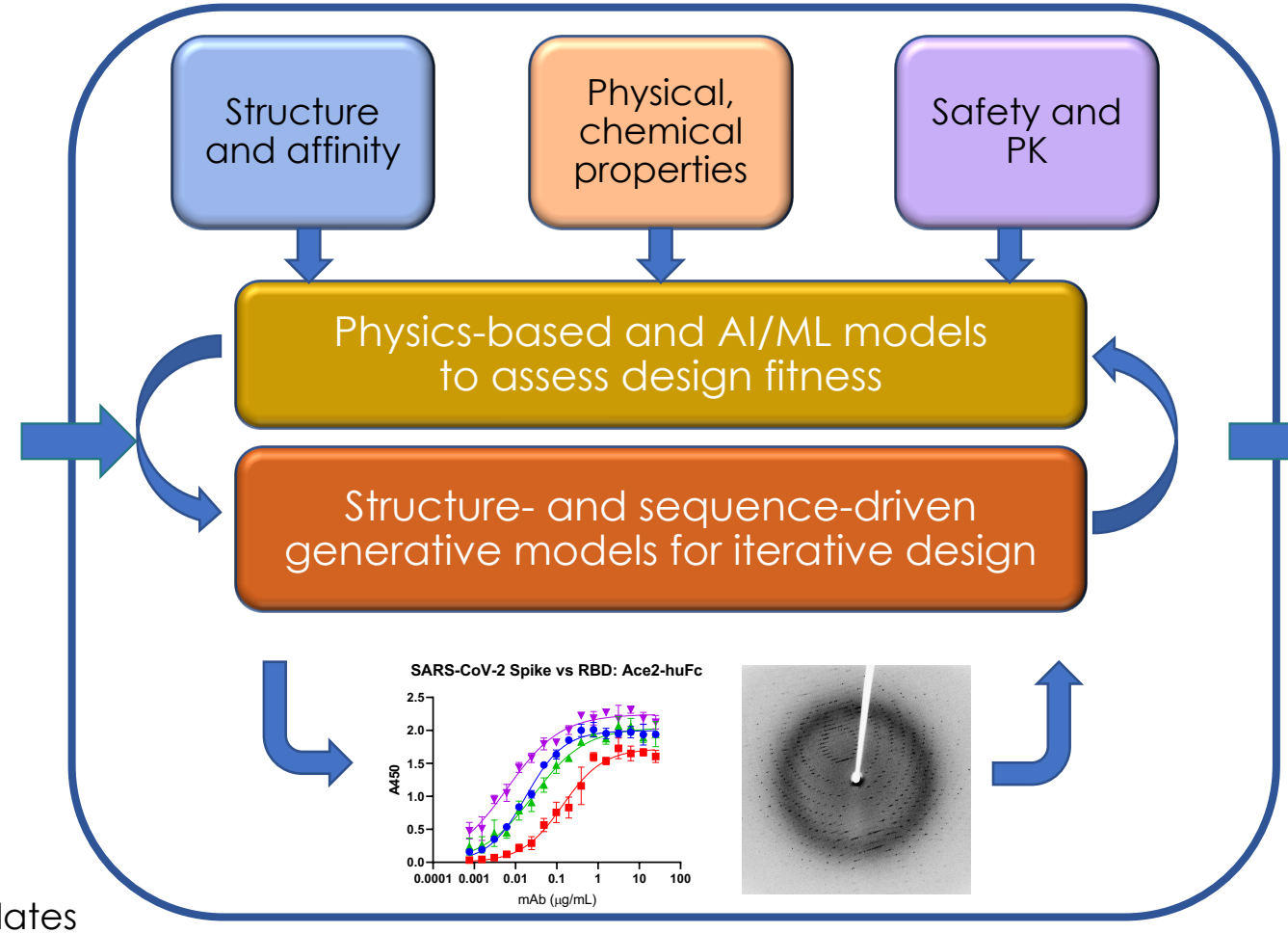
Computational and experimental design platforms



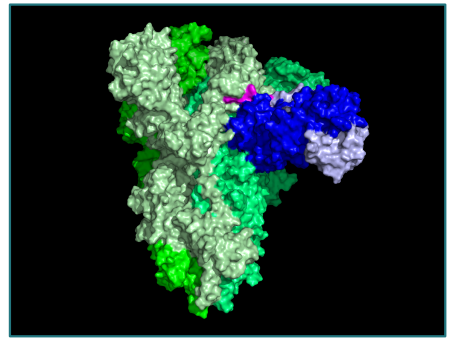


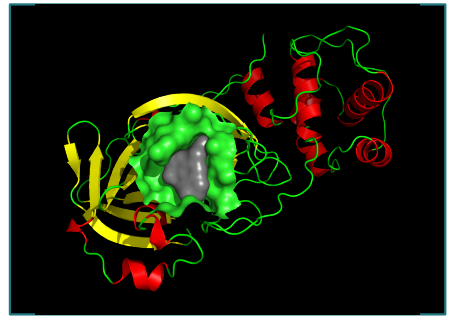
Starting points

- Crystal structures and structural models
- Multiple antibody templates
- Databases of purchasable small molecules



Platform capability build funded over time through DOE, LDRD, DARPA, DoD, and other funding sources



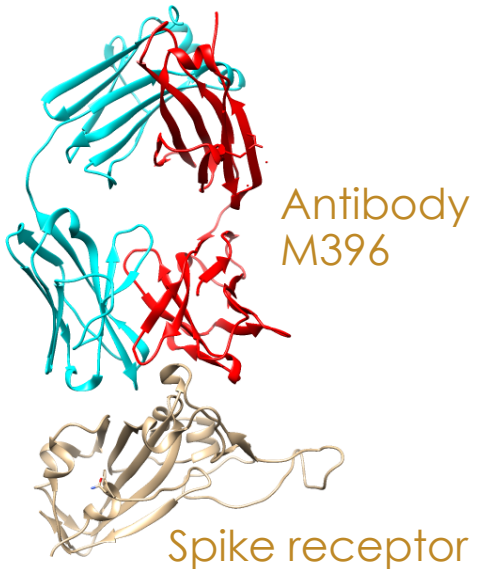


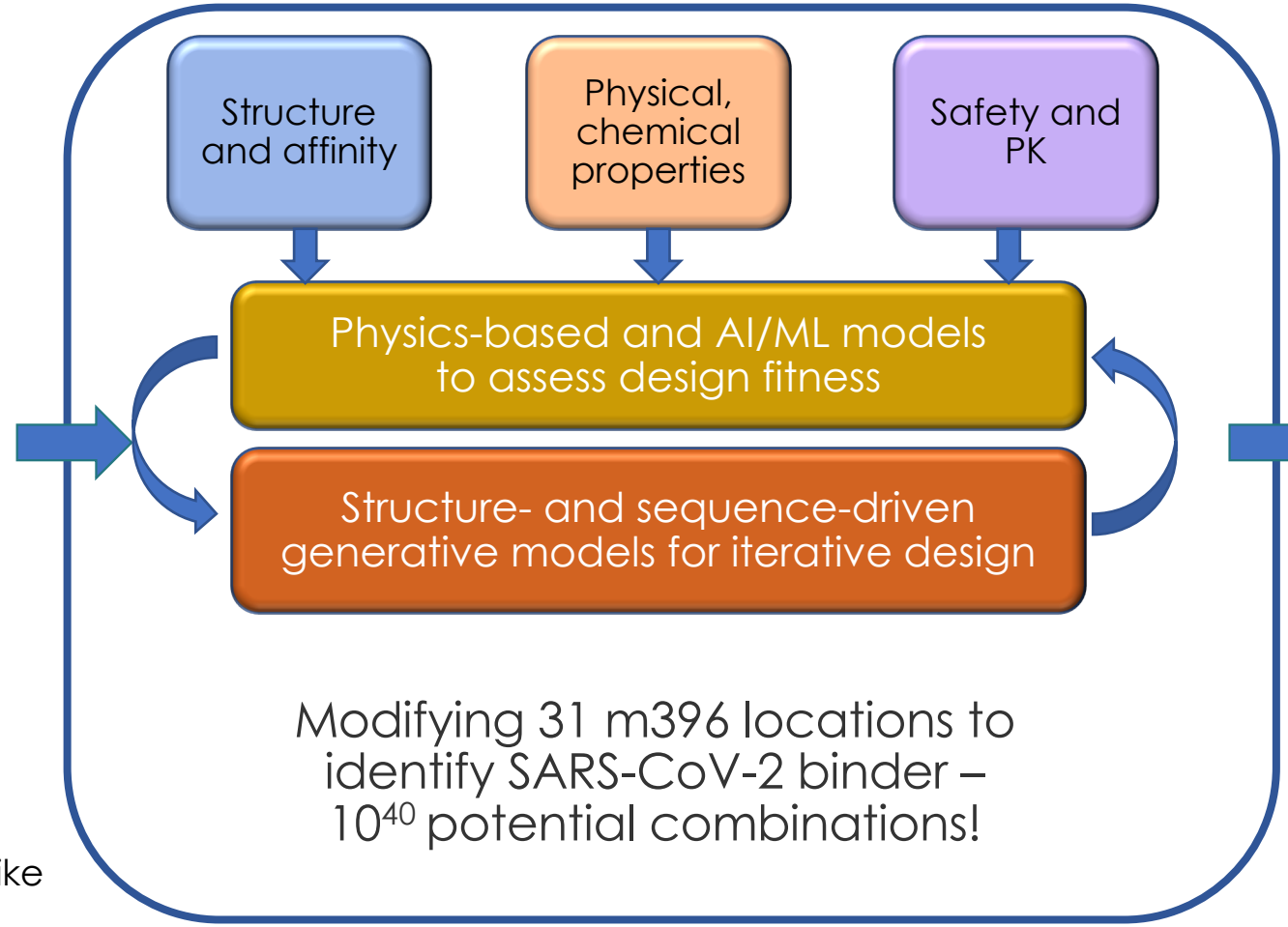
Outputs

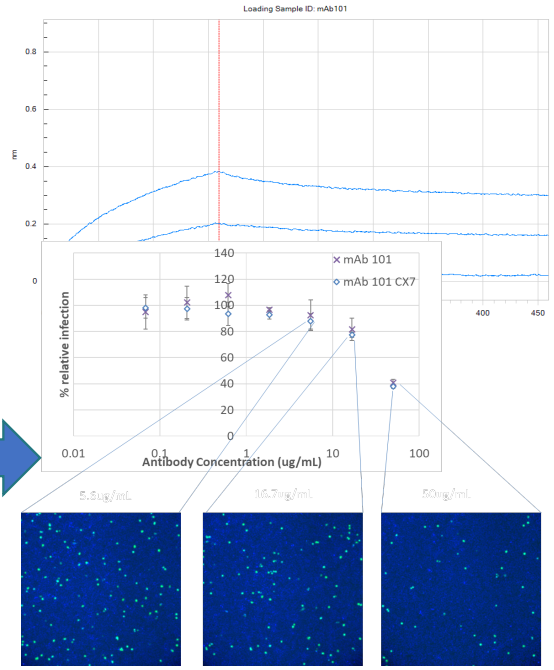
Designs with probability of:

- Desired activity
- Desired biological effect
- Good physical and safety parameters

Computational Design of Therapeutic Antibodies







Design starting point

- m396, a neutralizing antibody against the spike protein of SARS-CoV-1 that does not bind spike from SARS-CoV-2

Design output

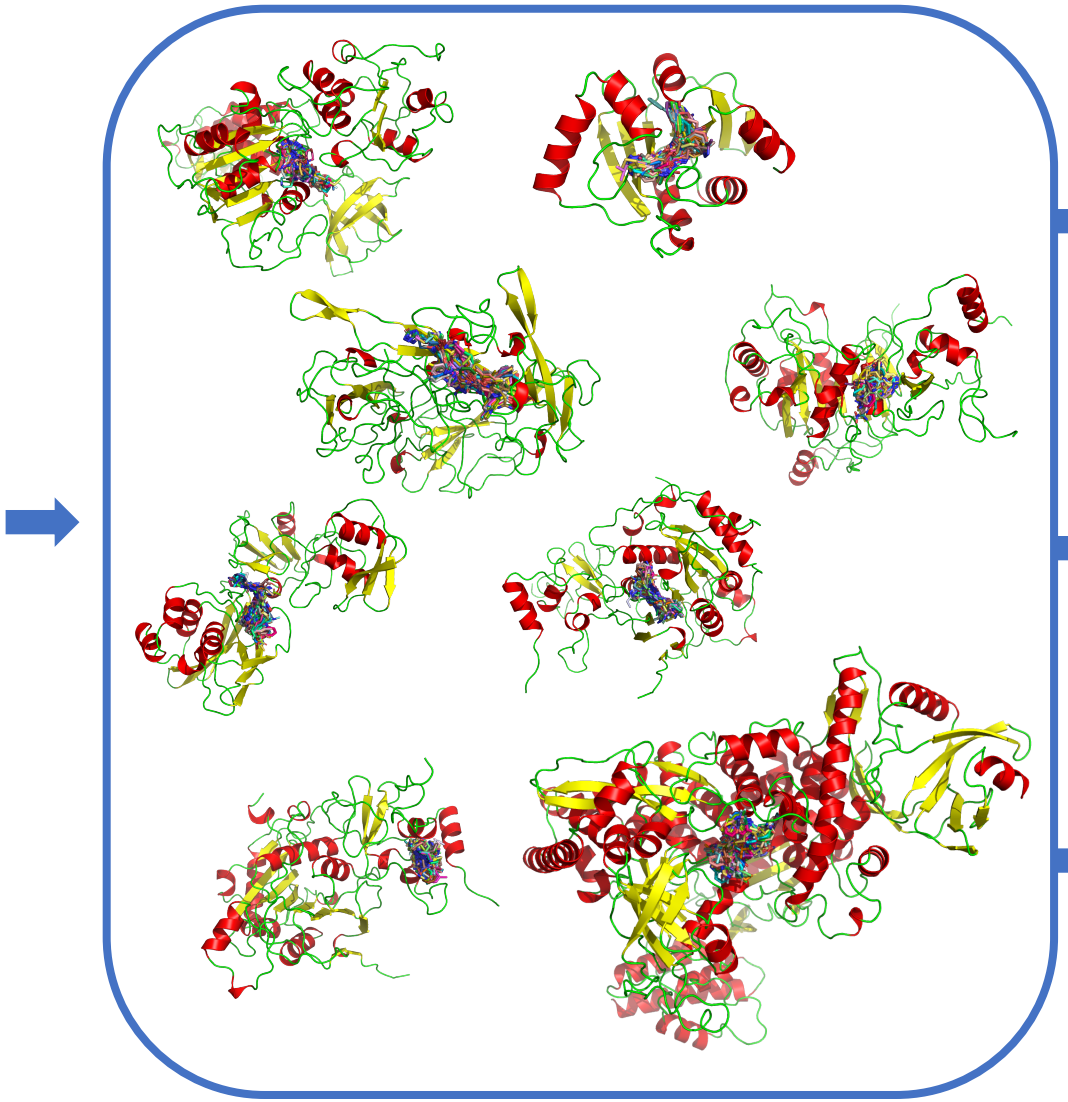
Experimentally validated designed antibody:

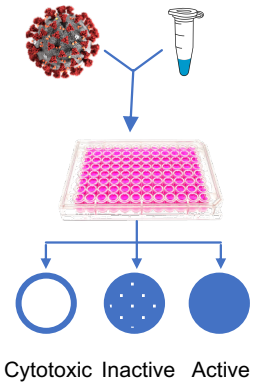
- Binds to spike protein
- Neutralizes VSV-SARS-CoV-2 pseudovirus

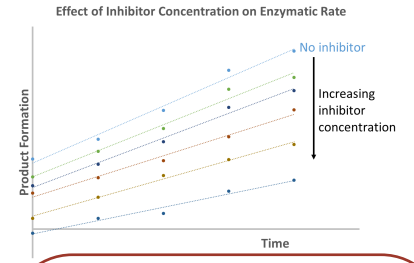
Funded by NVBL and DARPA

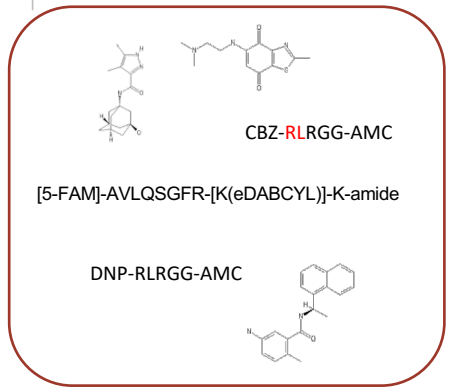
Computational Docking for SARS-CoV-2 Proteins

Nsp1	91.1%	Supresses host antiviral response	★
Nsp2	82.9%		
Nsp3	86.5%	Nsp3-Nsp4-Nsp6 complex involved in viral replication	★ ★
Nsp4	90.8%	Nsp3-Nsp4-Nsp6 complex involved in viral replication	
Nsp5	98.7%	Main protease (3C-like)	★ ★
Nsp6	94.8%	Nsp3-Nsp4-Nsp6 complex involved in viral replication	
Nsp7	100.%	Nsp7-Nsp8 complex is part of RNA polymerase	★ ★
Nsp8	99.0%	Nsp7-Nsp8 complex is part of RNA polymerase	★ ★
Nsp9	98.2%	ssRNA binding	
Nsp10	99.3%	Essential for Nso16 methyltransferase activity	★ ★
Nsp11	92.3%	Short peptide	
Nsp12	98.3%	RNA polymerase	★
Nsp13	100.%	Helicase/triphosphatase	★
Nsp14	98.7%	3'-5 exonuclease	
Nsp15	95.7%	Uridine-specific endoribonuclease	★ ★
Nsp16	98.0%	RNA-cap methyltransferase	★
S	87.0%	Spike protein, mediates binding to ACE2	
Orf3a	85.1%	Activates the NLRP3 inflammasome	★
Orf3b	95.0%		
E	96.1%	Envelope protein, involved in virus morphogenesis and assembly	★
M	96.4%	Membrane glycoprotein, predominant component of the envelope	★
Orf6	85.7%	Type I IFN antagonist	
Orf7a	90.2%	Virus-induced apoptosis	★ ★
Orf7b	84.1%		
Orf8	45.3%		
N	94.3%	Nucleocapsid phophoprotein, binds to RNA genome	★ ★
Orf9b	84.7%	Type ! IFN antagonist	
Orf9c	78.1%		
Orf10	--		









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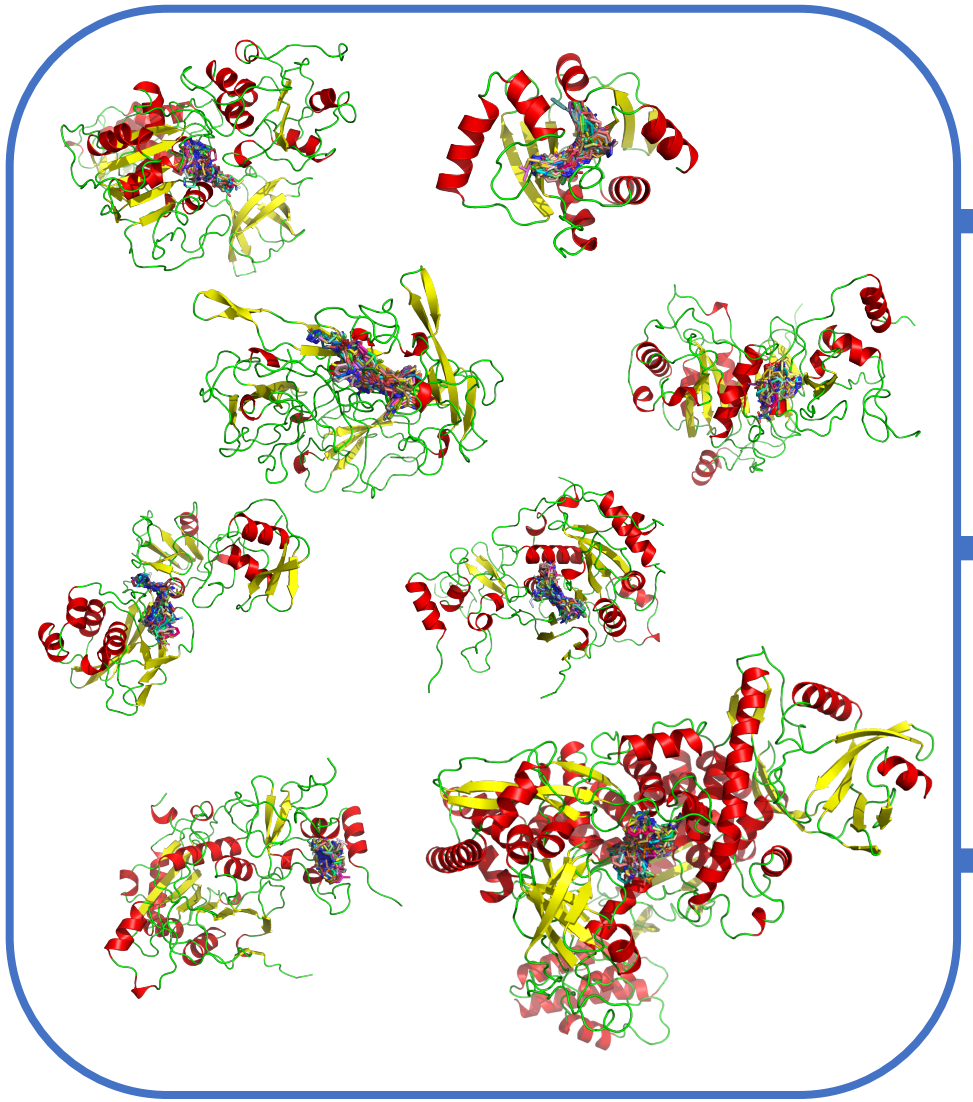
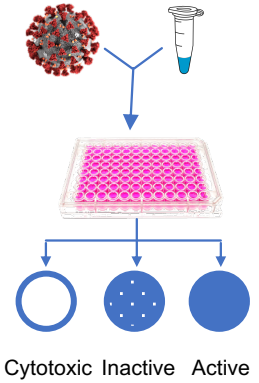
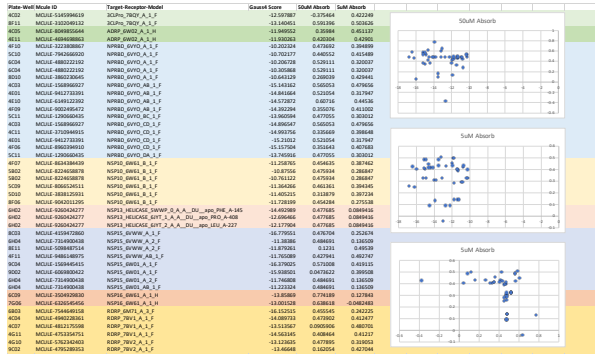
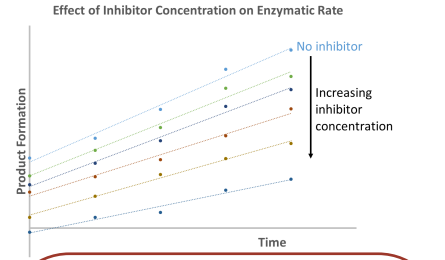
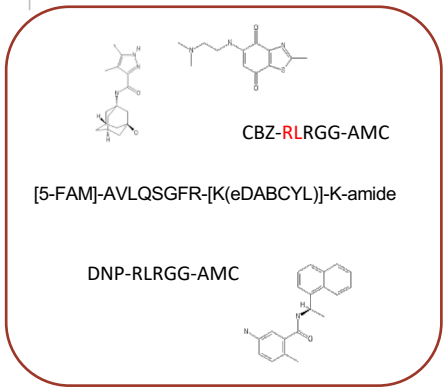










SARS-CoV-2 Proteases Require a Special Workflow

Prepare Ligands
- Add 3-point fragment
- Select reaction
- Create covalent complex

AutoDockFR
- Flexible side-chain docking
- Ensemble parallel

Extract non-covalent score

QM reoptimization
- Node-parallel

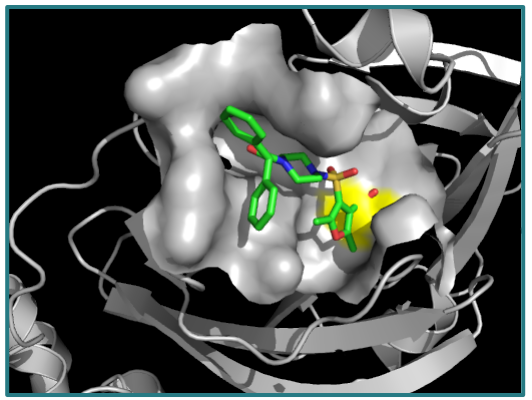
QM frequencies
- Node-parallel

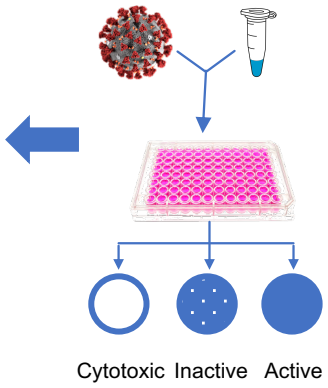
Calculate ΔG^0

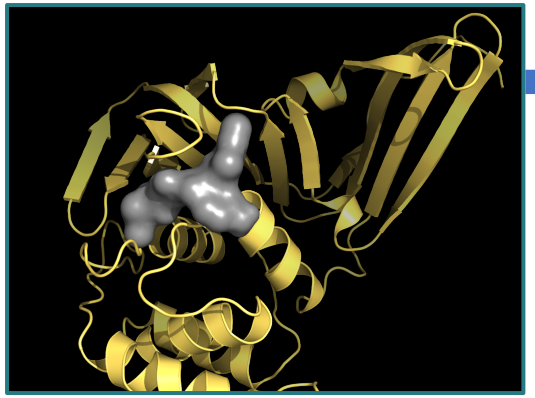
Maxwell-Boltzmann Statistics

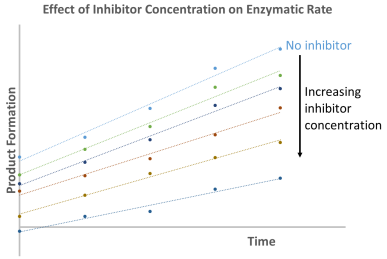
Predict K_i values

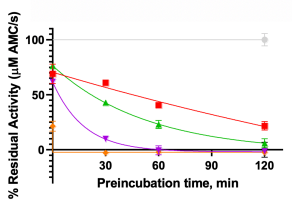
QM Methods: FMO-DFTB3-D3H4 & MOZYME PM6-D3H4

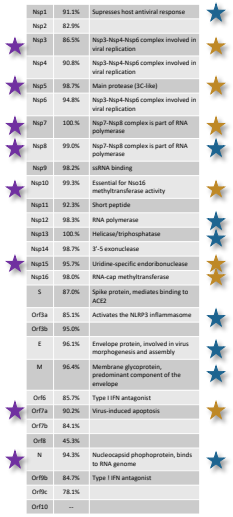












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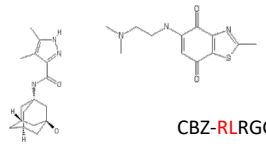
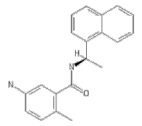


CBZ-RLRGG-AMC

[5-FAM]-AVLQSGFR-[K(eDABCYL)]-K-amide

DNP-RLRGG-AMC

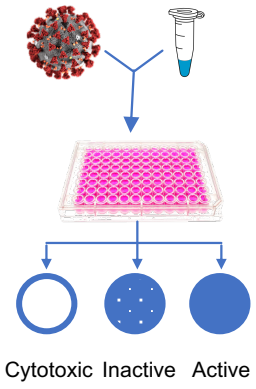


Dashboard Records

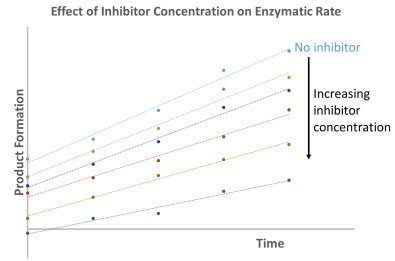
Target SPIKE PROTEASE Team ARGONNE LLNL Score Type VINA FUSION MM/GBSA

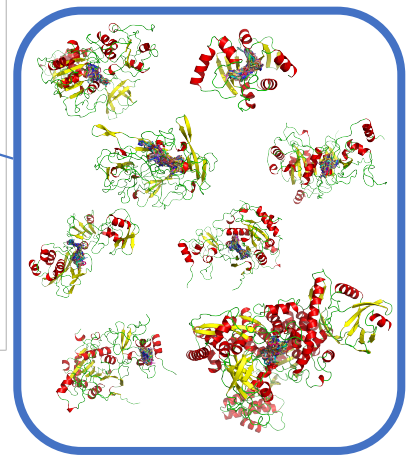
Search

Team	Score Type	Score	Target	Ordered	Synthesized	SMILES	Product Link	Price
llnl	MM/GBSA	-87.875	protease	false	false	CNCC(O)=N[C@@H](CCCNC(N)=[NH2+])C(O)=N[C@H](C(O)=N[C@@H](Cc1ccc(O)cc1)C(O)=N[C@H](C(O)=N[C@@H](Cc1cnc[nH]1)C(=O)N1CCC[C@H]1C(O)=N[C@@H](C)C(=O)O)C(C)C)C(C)C	LINK	
llnl	MM/GBSA	-78.042	protease	true	false	Cc1cc2nc3c([O-])nc(=O)nc-3n(C[C@H](O)[C@H](O)[C@H](O)COP(=O)([O-])OP(=O)([O-])OC[C@H]3O[C@@H]([n+]4c[nH]c5c(N)ncnc54)[C@H](O)[C@@H]3O)c2cc1C	LINK	
llnl	MM/GBSA	-78.042	protease	true	false	Cc1cc2nc3c([O-])nc(=O)nc-3n(C[C@H](O)[C@H](O)[C@H](O)COP(=O)([O-])OP(=O)([O-])OC[C@H]3O[C@@H]([n+]4c[nH]c5c(N)ncnc54)[C@H](O)[C@@H]3O)c2cc1C	LINK	
llnl	MM/GBSA	-77.752998	protease	false	false	CC(C)(C)N=C(O)[C@@H]1CN(Cc2ccccc2)CCN1C[C@@H](O)C[C@@H](Cc1ccccc1)C(O)=N[C@H]1c2ccccc2C[C@H]1O	LINK	
llnl	MM/GBSA	-75.011002	protease	true	false	CC1(C)CCC(CN2CCN(c3ccc(C(O)=NS(=O)(=O)c4ccc(NCC5CCOCC5)c([N+](=O)[O-])c4)c(Oc4c[nH]c5[nH+]ccc-5c4)c3)CC2)=C(c2ccc(Cl)cc2)C1	LINK	
llnl	MM/GBSA	-74.496002	protease	false	false	CC(C)(C)N=C(O)[C@@H]1C[C@H]2CCCC[C@@H]2CN1C[C@@H](O)[C@H](Cc1ccccc1)N=C(O)[C@H](CC(=N)O)NC(=O)c1ccc2ccccc2n1	LINK	
llnl	MM/GBSA	-72.046997	protease	true	false	CCCOc1ccc(S(=O)(=O)[NH2+]CC[C@@H]2CCCN2C)cc1-c1nc2c(CCC)nn(C)c2c(=O)[nH]1	LINK	
llnl	MM/GBSA	-71.747002	protease	true	false	C[C@H](N=C(O)[C@@H](Cc1ccc2ccccc2c1)N=C(O)[C@@H](C)[NH3+])C(O)=N[C@@H](Cc1c[nH]c2ccccc12)C(O)=N[C@H](Cc1ccccc1)C(O)=N[C@@H](CCCC[NH3+])C(=N)O	LINK	
llnl	MM/GBSA	-71.466003	protease	true	false	CC(C)(C)N=C(O)[C@@H]1C[C@@H]2CCCC[C@@H]2CN1C[C@@H](O)[C@H](Cc1ccccc1)N=C(O)[C@H](CC(=N)O)NC(=O)c1ccc2ccccc2n1	LINK	
llnl	MM/GBSA	-70.692001	protease	false	false	C[C@@H](CO[C@@H]1O[C@H](C(=O)[O-])[C@@H](O)[C@H](O)[C@H]1O)Nc1cc2[n+](-c3ccc(Cl)cc3)c3ccccc3[nH]c-2cc1=Nc1ccc(Cl)cc1	LINK	
llnl	MM/GBSA	-70.529999	protease	false	false	OC[C@H]1O[C@H](OC[C@H]2O[C@H](O[C@@H]3[C@@H](CO)O[C@H](O)[C@H](O)[C@H]3O)[C@H](O)[C@@H](O)[C@@H]2O[C@H]2O[C@H](CO)[C@@H](O)[C@H](O)[C@H]2O)	LINK	



Cytotoxic Inactive Active





NVBL Molecular Therapeutics Team

Ai Kagawa
Aidan Epstein
Alexander Partin
Alexander Batyuk
Andria Rodrigues
Andy DeGiovanni
Arvind Ramanathan
Austin Clyde
Babak Andi
Ben Brown
Bobbie-Jo Webb-Robertson
Brooke Harmon
Carlos Gamboa
Carlos Simmerling
Chris Mungall
Chris Ellis
Chris Stanley
Connor Cooper
Cornelius Gati
Dan Jacobson
Dan Faissol
Derek Jones
Ed Lau
Elijah Hoffman
Emily Dietrich
Fangqiang Zhu
Felice Lightstone
Garry Buchko
Gyorgy Babnigg
Henrique Pereira
Hubertus Van Dam
Hugh O'Neill
Hyunseung Yoo
Ian Foster
Irimpan Mathews
Jason Mcdermott
Jerry Parks
Jha Shantenu
Jim Brase
Joe Schoeniger
Jonathan Allen
Joshua Ladau
Jurgen Schmidt
Justin Reese
Katrina Waters
Kelly Williams
Kenneth Sale
Kerstin Kleese Van Dam
Kevin Mcloughlin
Kris Kulp
Li Tan
Magda Franco
Marisa Torres
Mark Steven Hunter
Marti Head
Matt Coleman
Michael Kent
Mitch Doktycz
Naoki Horikoshi
Neeraj Kumar
Nick Fischer
Oscar Negrete
Paul Adams
Quan Van Vuong
Richard Keith
Rick Stevens
Robert Netzor
Ryan Chard
Ryszard Michalczyk
Sam Chen
Sean McCorkle
Sean McSweeney
Sergio Wong
Simone Raugei
Sindhu Bhowmik
Soichi Wakatsuki
Srinivas Iyer
Stephan Irle
Stephanie Galanie
Stewart He
Tom Brettin
Tom Desautels
Tony Ferreira
Uma Ganapathy
Vilmos Kertesz
Yihui (Ray) Ren
Yue Yang

Impacts of the Molecular Design Team

- The team formed quickly and applied their broad expertise to:
  - Solve new structures of viral proteins
  - Build multiple computational models
  - Use massive supercomputing resources to identify and design potential hits
  - Develop biochemical assays and use them to
    - Validate computational predictions
    - Experimentally characterize active hits
    - And feed data back into improving computational models
  - Obtain experimentally validated antibody and small-molecule hits
  - All in six months time!
- The team continues to refine experimental hits into therapeutic leads
- The DOE labs worked together to do things no single lab could do alone