

# NVBL Molecular Therapeutics

Marti Head  
Project Lead

**SLAC**

 Sandia  
National  
Laboratories

 **Los Alamos**  
NATIONAL LABORATORY  
EST. 1943

  
**Pacific Northwest**  
NATIONAL LABORATORY

  
**BROOKHAVEN**  
NATIONAL LABORATORY

  
**Argonne**  
NATIONAL  
LABORATORY

  
**BERKELEY LAB**

 Lawrence  
Livermore  
National  
Laboratory

 **OAK RIDGE**  
National Laboratory

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



Chemical, biological, and analytical sciences

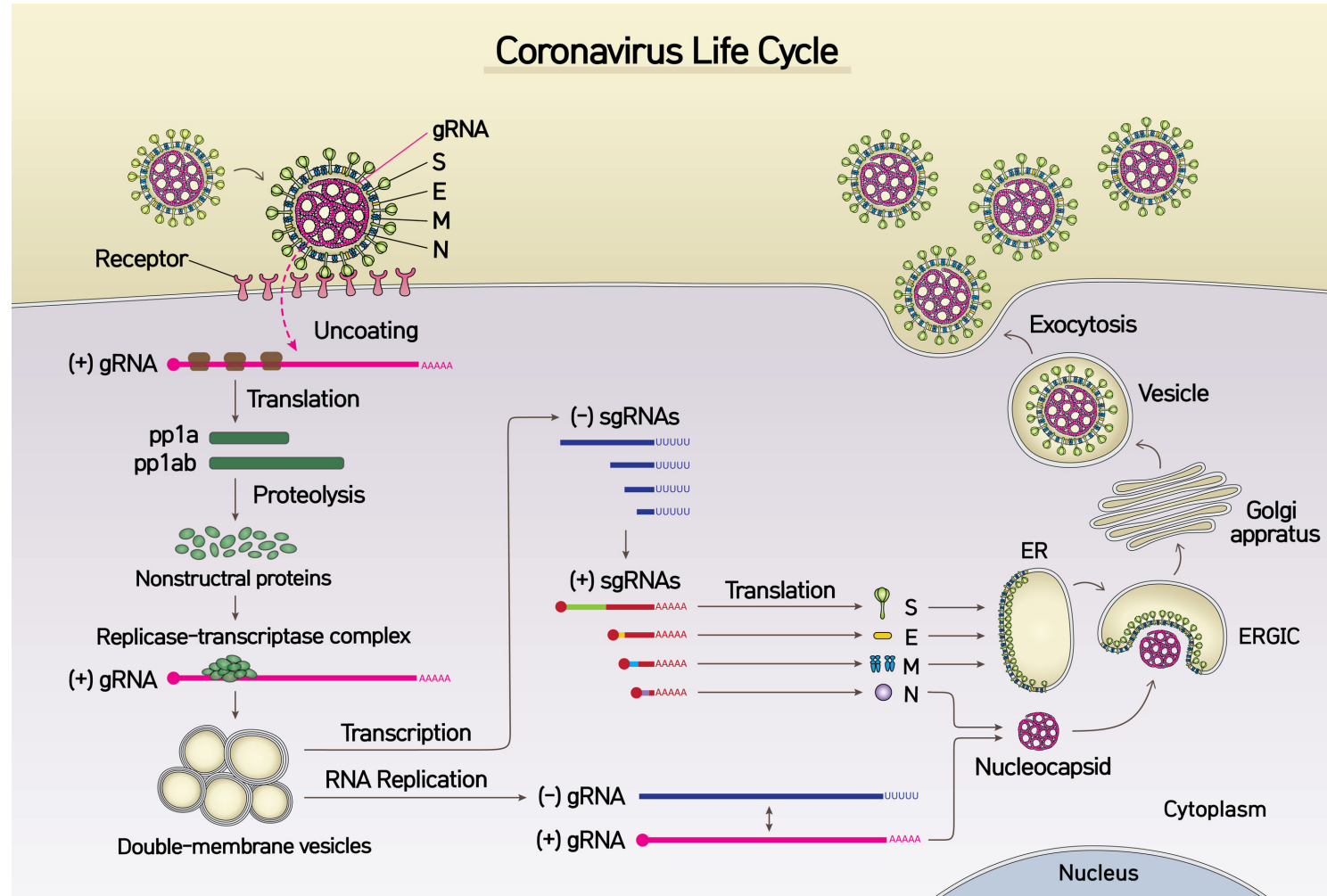


High performance computing

Light and neutron sources

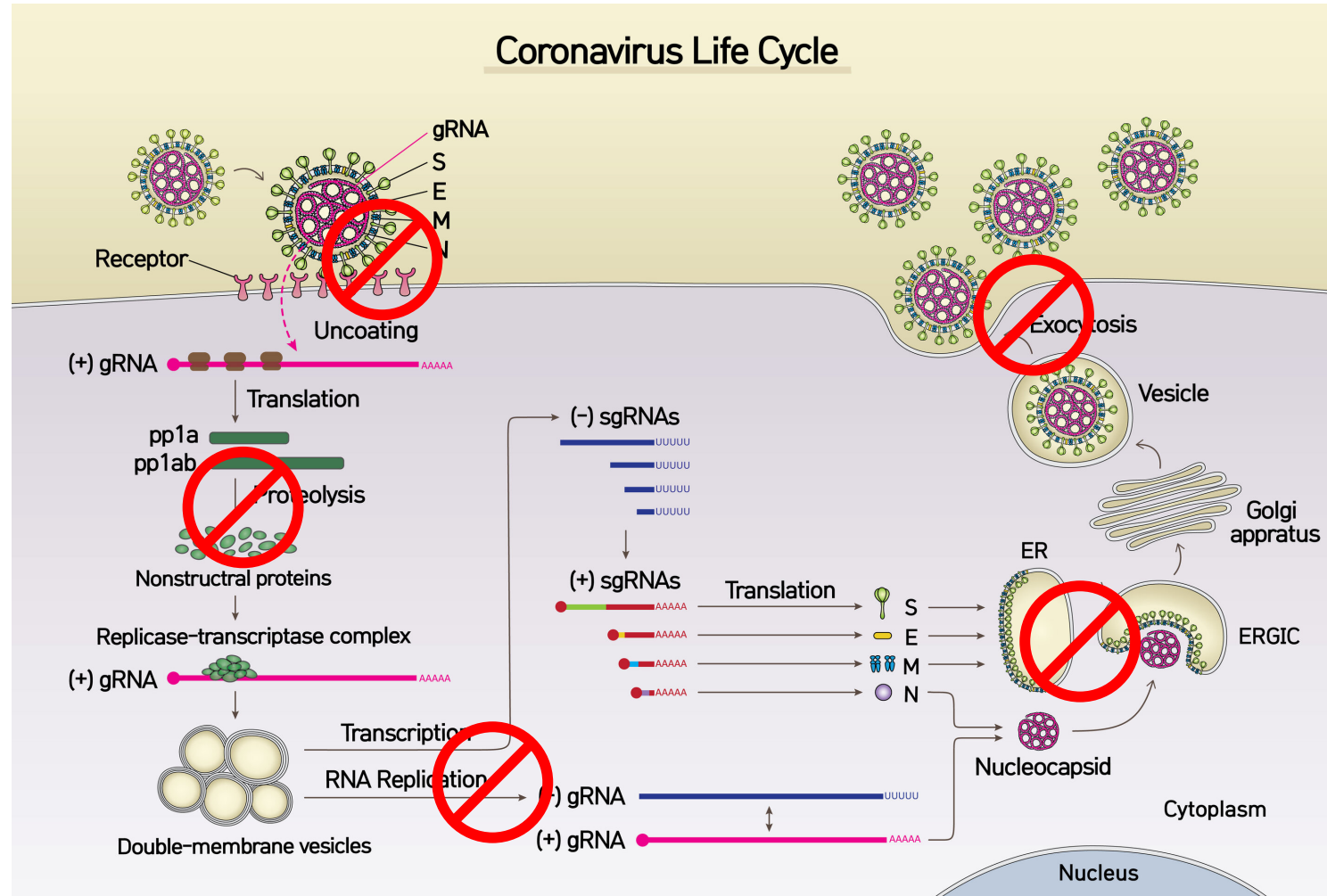


... to identify experimentally validated leads for targets across the entire coronavirus life cycle



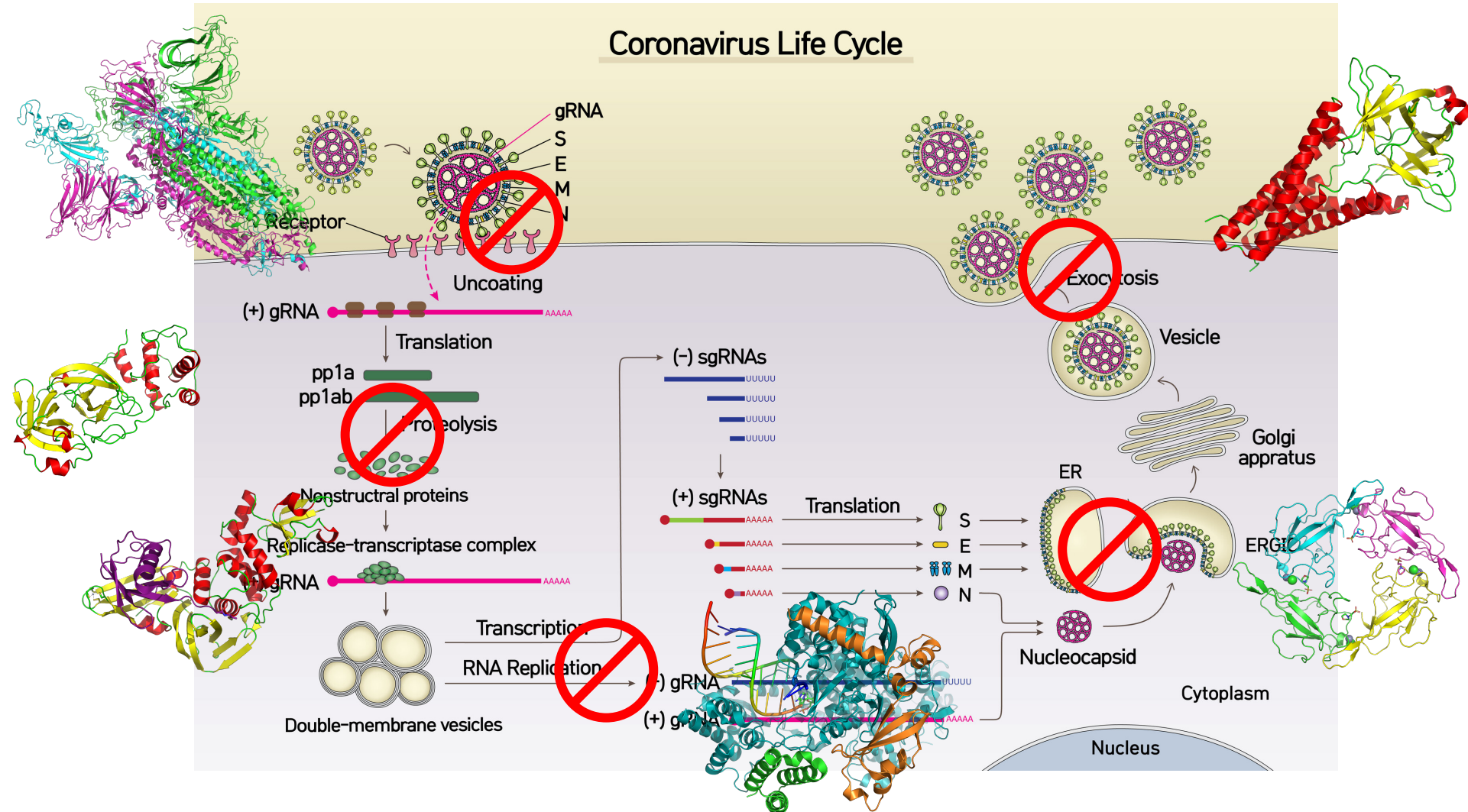


... to identify experimentally validated leads for targets across the entire coronavirus life cycle

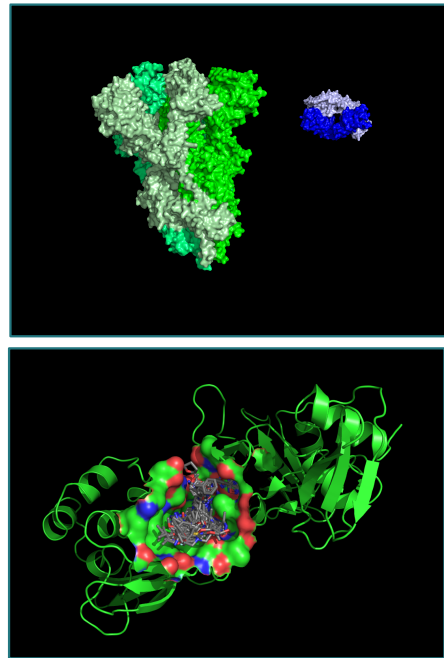




... to identify experimentally validated leads for targets across the entire coronavirus life cycle

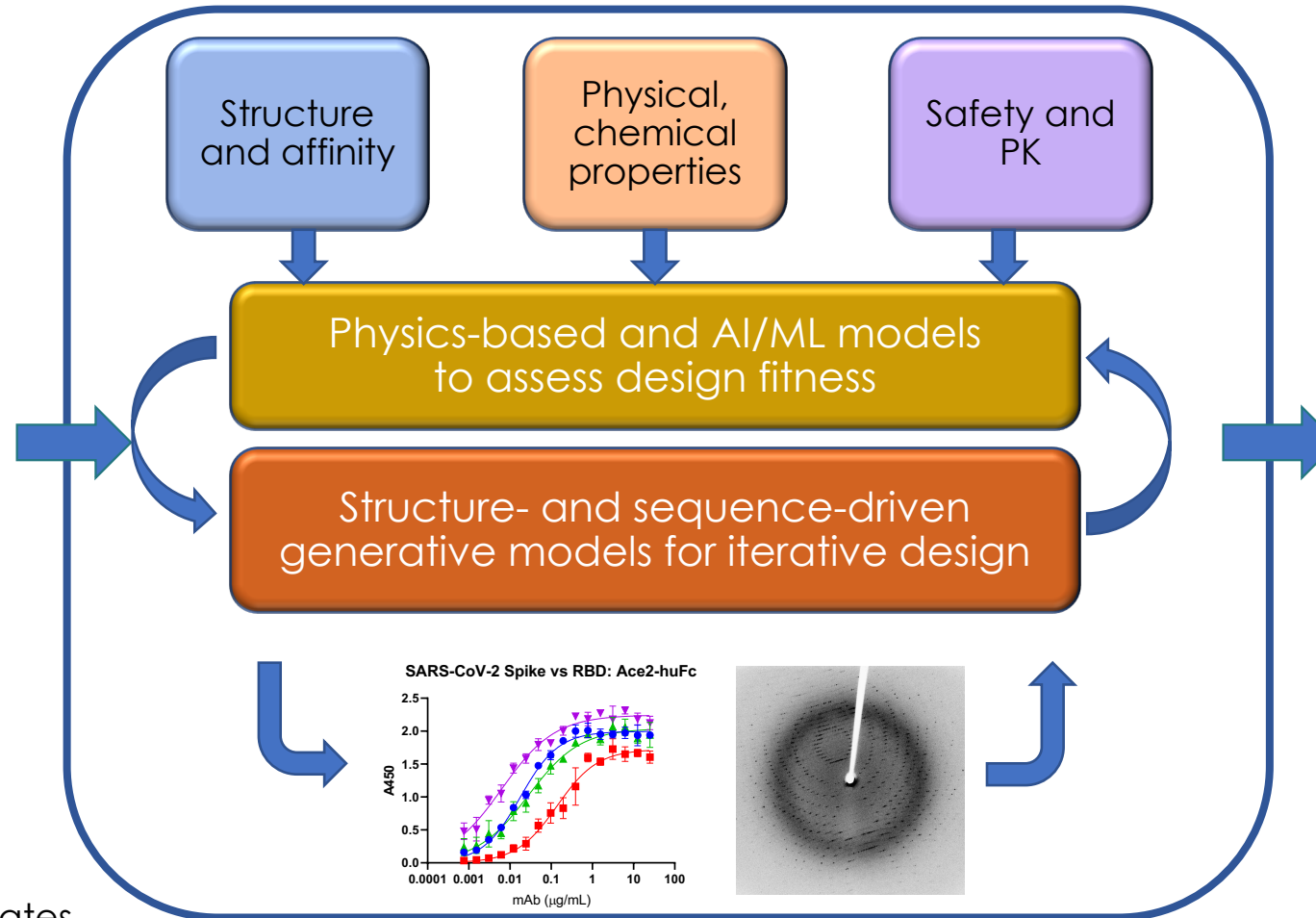


# Computational and experimental design platforms

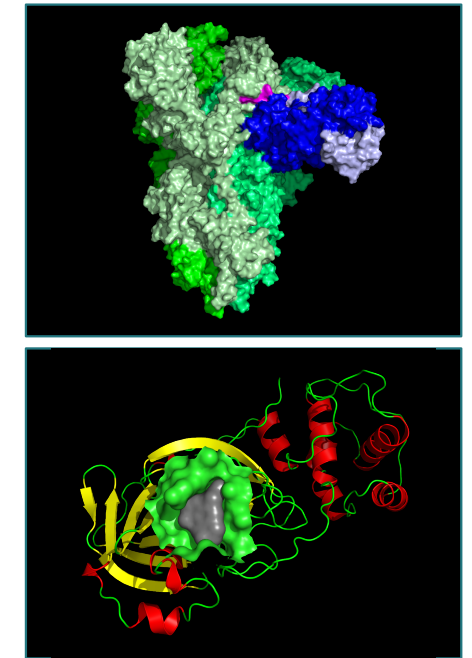


## Starting points

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



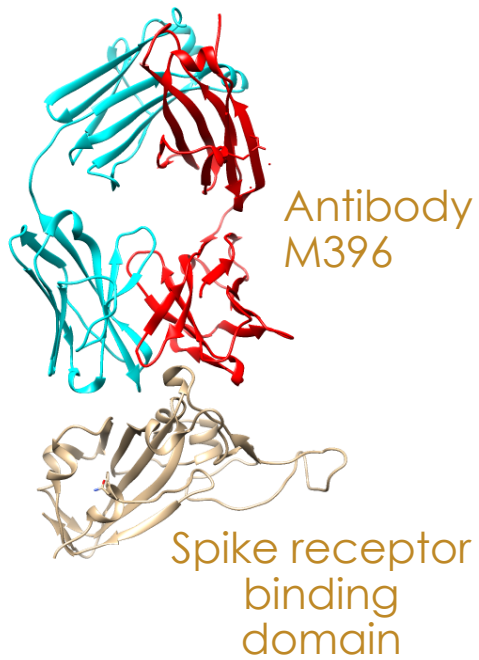
Platform capability build funded over time through DOE, LDRD, DARPA, DoD, and other funding sources



## Outputs

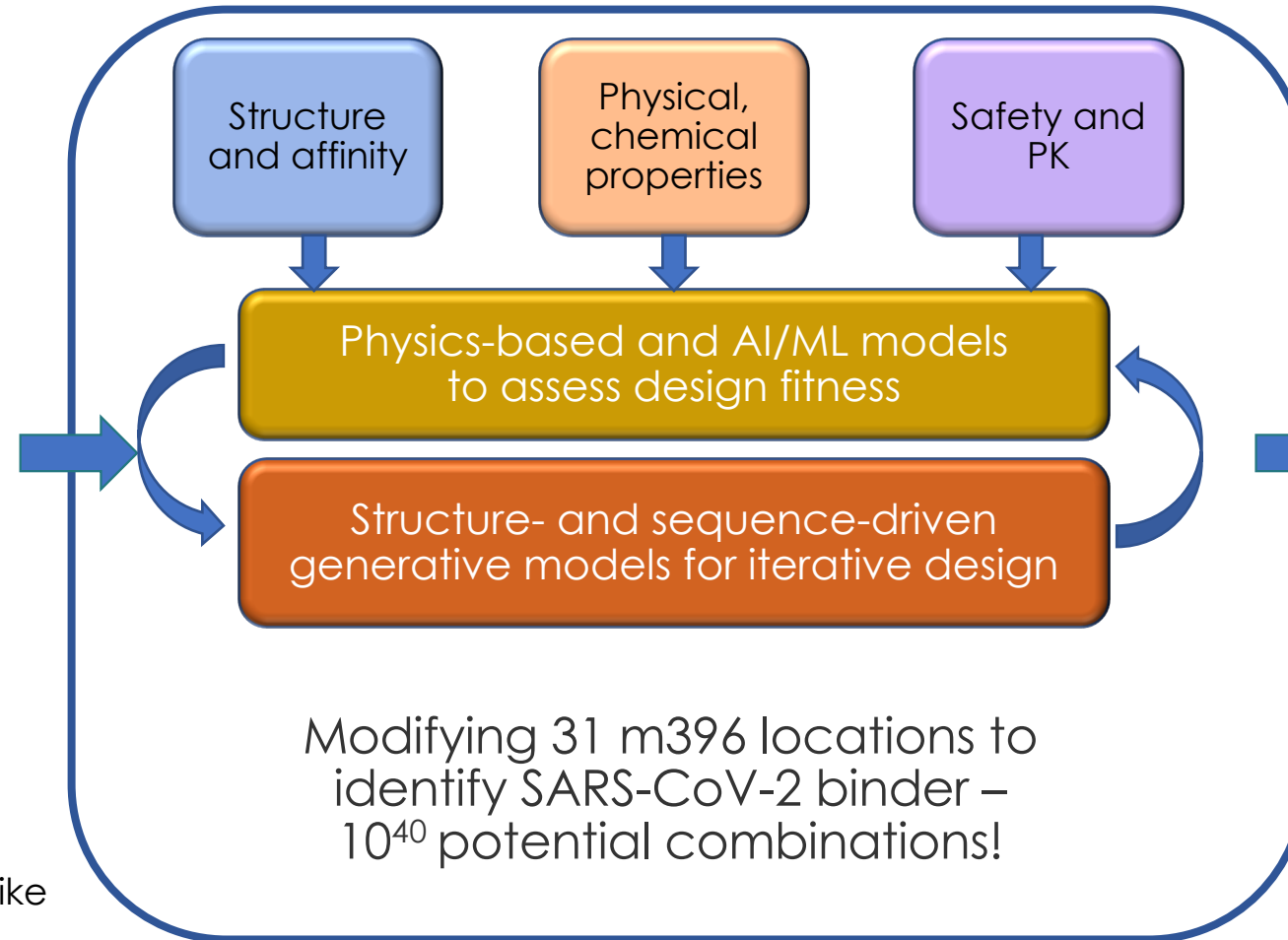
- Designs with probability of:
- Desired activity
  - Desired biological effect
  - Good physical and safety parameters

# Computational Design of Therapeutic Antibodies

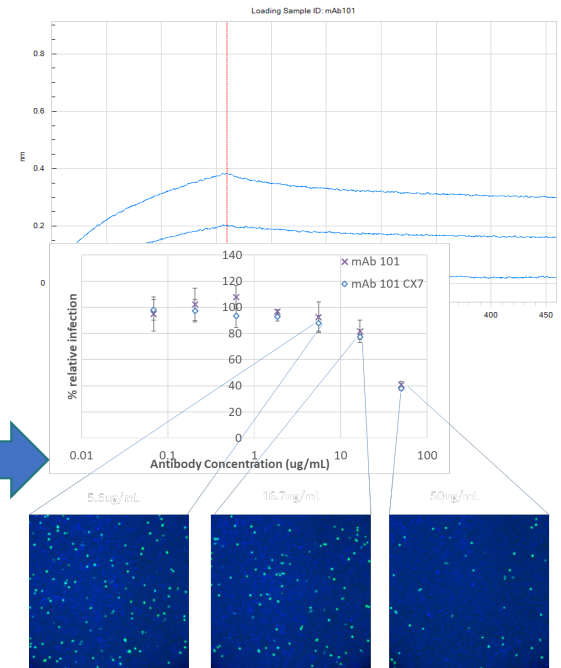


## Design starting point

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



Funded by NVBL and DARPA



## Design output

Experimentally validated designed antibody:

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





# Computational Docking for SARS-CoV-2 Proteins

Nsp1	91.1%	Suppresses 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	100.3%	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 Nsp16 methyltransferase activity	★
Nsp11	92.3%	Short peptide	★
Nsp12	98.3%	RNA polymerase	★
Nsp13	100.3%	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 phosphoprotein, binds to RNA genome	★
Orf9b	84.7%	Type I IFN antagonist	★
Orf9c	78.1%		★
Orf10	--		★

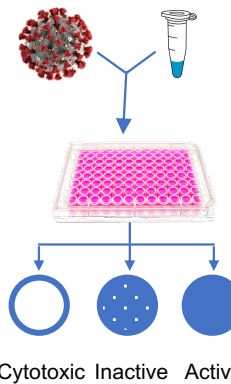
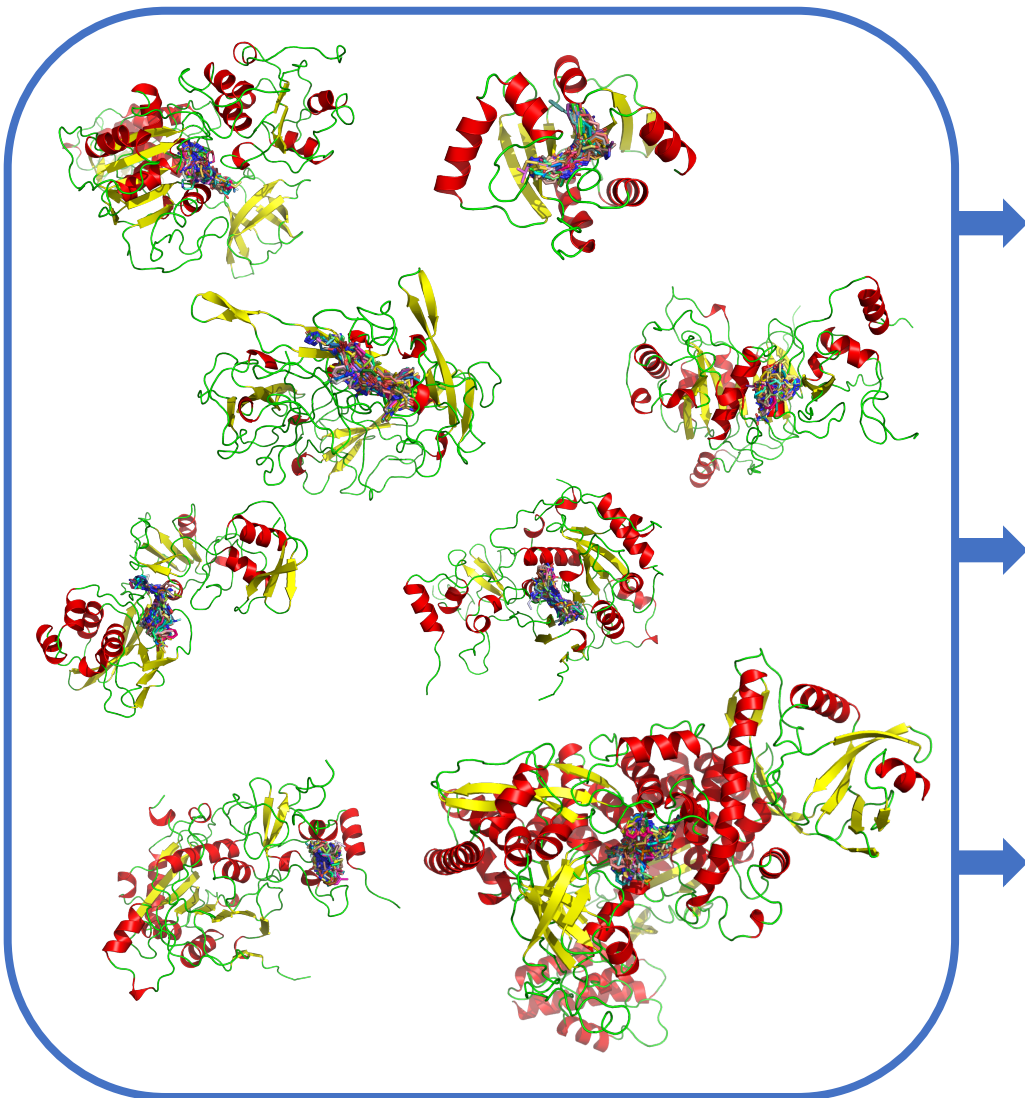
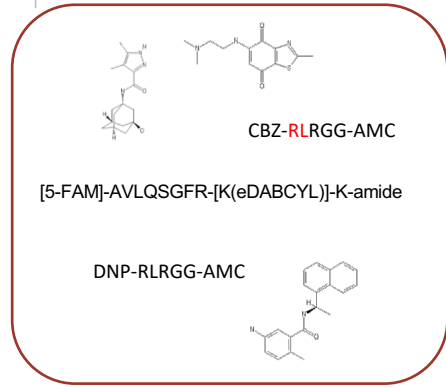
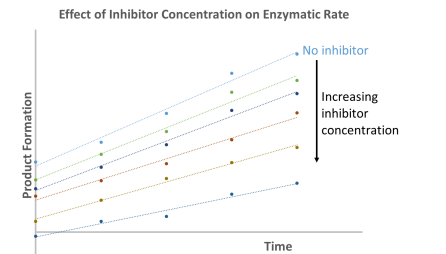
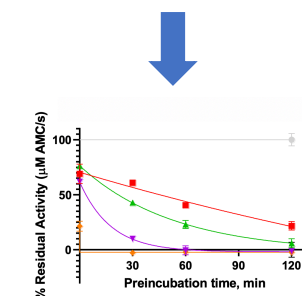
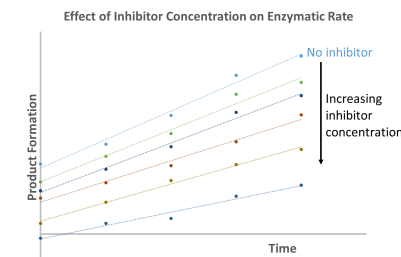
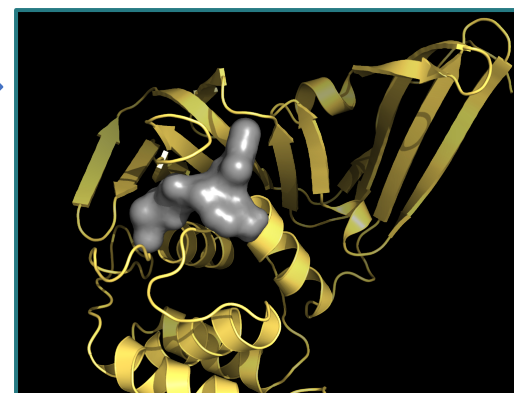
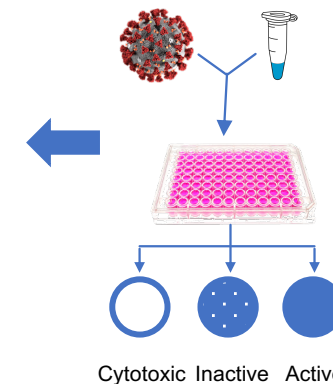
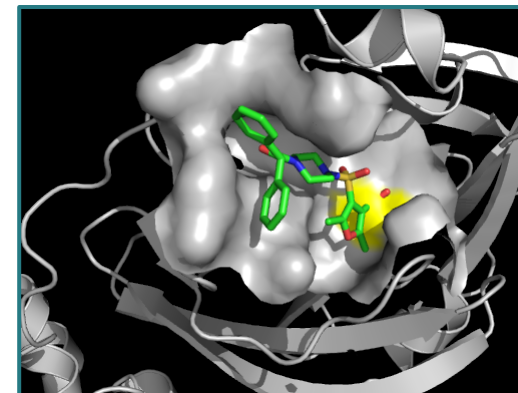
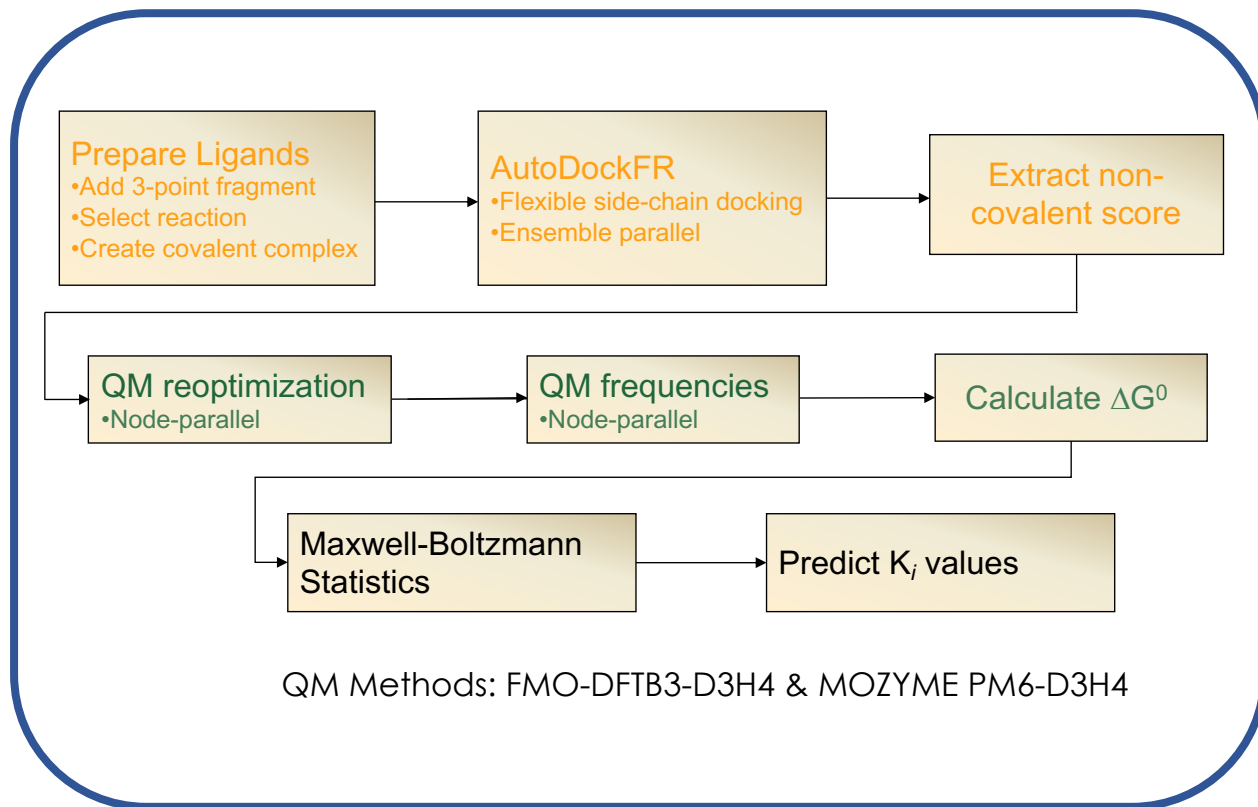


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8026	MDL3-408985644	ADSP_8902_A_1_H	-11.90502	0.23384	0.01127
8111	MDL3-408985644	ADSP_8902_A_1_H	-11.90502	0.23384	0.01127
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# SARS-CoV-2 Proteases Require a Special Workflow



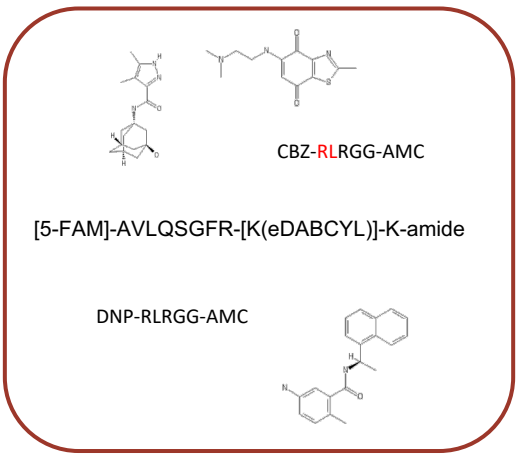
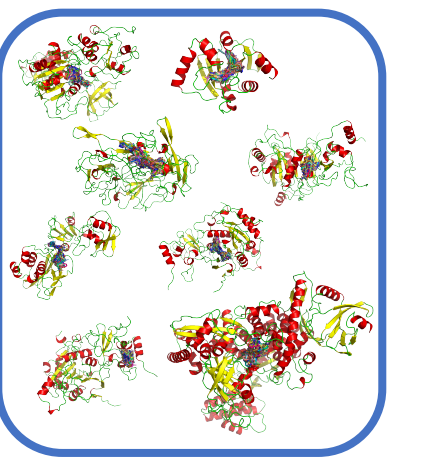
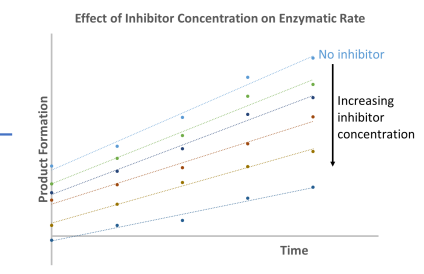
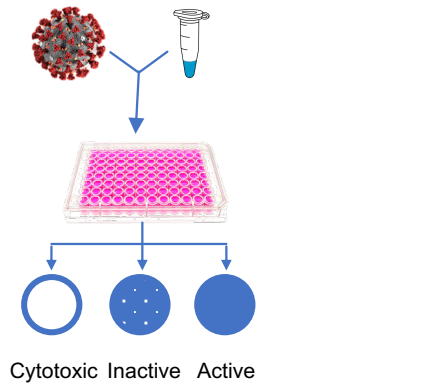


Nsp1	91.1%	Suppresses host antiviral response	★
Nsp2	82.9%		★
Nsp3	85.5%	Nsp3-Nsp4-Nsp6 complex involved in viral replication	★
Nsp4	90.8%	Nsp3-Nsp4-Nsp6 complex involved in viral replication	★
Nsp5	98.7%	Main protease (3C-like)	★
Nsp6	94.8%	Nsp3-Nsp4-Nsp6 complex involved in viral replication	★
Nsp7	100%	Nsp7-Nsp8 complex is part of RNA polymerase	★
Nsp8	99.2%	Nsp7-Nsp8 complex is part of RNA polymerase	★
Nsp9	98.2%	sRNA binding	★
Nsp10	99.3%	Essential for Nucleocapsid methyltransferase activity	★
Nsp11	92.8%	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%	Splice protein, mediates binding to AC22	★
Orf1a	85.1%	Activates the NLRP3 inflammasome	★
Orf1b	95.0%		★
E	96.1%	Envelope protein, involved in virus morphogenesis and assembly	★
M	95.4%	Membrane glycoprotein, predominant component of the envelope	★
Orf5	85.7%	Type 1fH antagonist	★
Orf7a	90.2%	Virus-induced apoptosis	★
Orf7b	84.1%		★
Orf8	45.3%		★
N	94.3%	Nucleocapsid phosphoprotein, binds to RNA genome	★
Orf9b	84.7%	Type 1fH antagonist	★
Orf1c	78.1%		★
Orf2a	-		★

# Dashboard Records

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

Team	Score Type	Score	Target	Ordered	Synthesized	SMILES	Product Link	Price
llnl	MM/GBSA	-87.875	protease	false	false	CNCC(O)=N[C@@H](CCCC(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)C)C)C(C)C	LINK	
llnl	MM/GBSA	-78.042	protease	true	false	Cc1cc2nc3c([O-])nc(=O)nc-3n[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@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(Cc2ccocnc2)CCN1C[C@@H](O)C[C@@H](Cc1ccc(O)cc1)C(O)=N[C@H]1c2ccc(O)cc2C[C@@H]1O	LINK	
llnl	MM/GBSA	-75.011002	protease	true	false	[O-]c4ccc(NCC5CCOC5)c([N+](=O)[O-])c4)c(1c4c[nH]c5[nH]ccc-5c4)c3)CC2=C(c2ccc(Cl)cc2)C1CC(C)N=C(O)	LINK	
llnl	MM/GBSA	-74.496002	protease	false	false	[C@@H]1C[C@@H]2CCCC[C@@H]2CN1C[C@@H](O)[C@H](Cc1cccc1)N=C(O)[C@H](CC(=N)O)NC(=O)c1ccc2ccc(O)cc2n1	LINK	
llnl	MM/GBSA	-72.046997	protease	true	false	CCCOC1ccc(S(=O)(=O)NH2)CC[C@@H]2CCCN2Ccc1-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](Cc1ccc(O)cc1)N=C(O)[C@@H](C)[NH3+])C(O)=N[C@@H](Cc1c[nH]c2ccc(O)cc1)C(O)=N[C@H](Cc1cccc1)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](Cc1cccc1)N=C(O)[C@H](CC(=N)O)NC(=O)c1ccc2ccc(O)cc2n1	LINK	
llnl	MM/GBSA	-70.692001	protease	false	false	C[C@@H](C)C[C@@H]1O[C@H](C(=O)O)[C@@H](O)[C@H](O)[C@H]1O)Nc1cc2[nH](-c3ccc(Cl)cc3)c3ccc(O)cc3[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]3O)[C@H](O)[C@@H](O)[C@@H](O)[C@@H]2O)[C@H](O)[C@@H](O)[C@@H]1O	LINK	



# NVBL Molecular Therapeutics Team

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# 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