Analysis of coronavirus helicases and CACHE Challenge #2 on finding hits for SARS-CoV-2 nsp13

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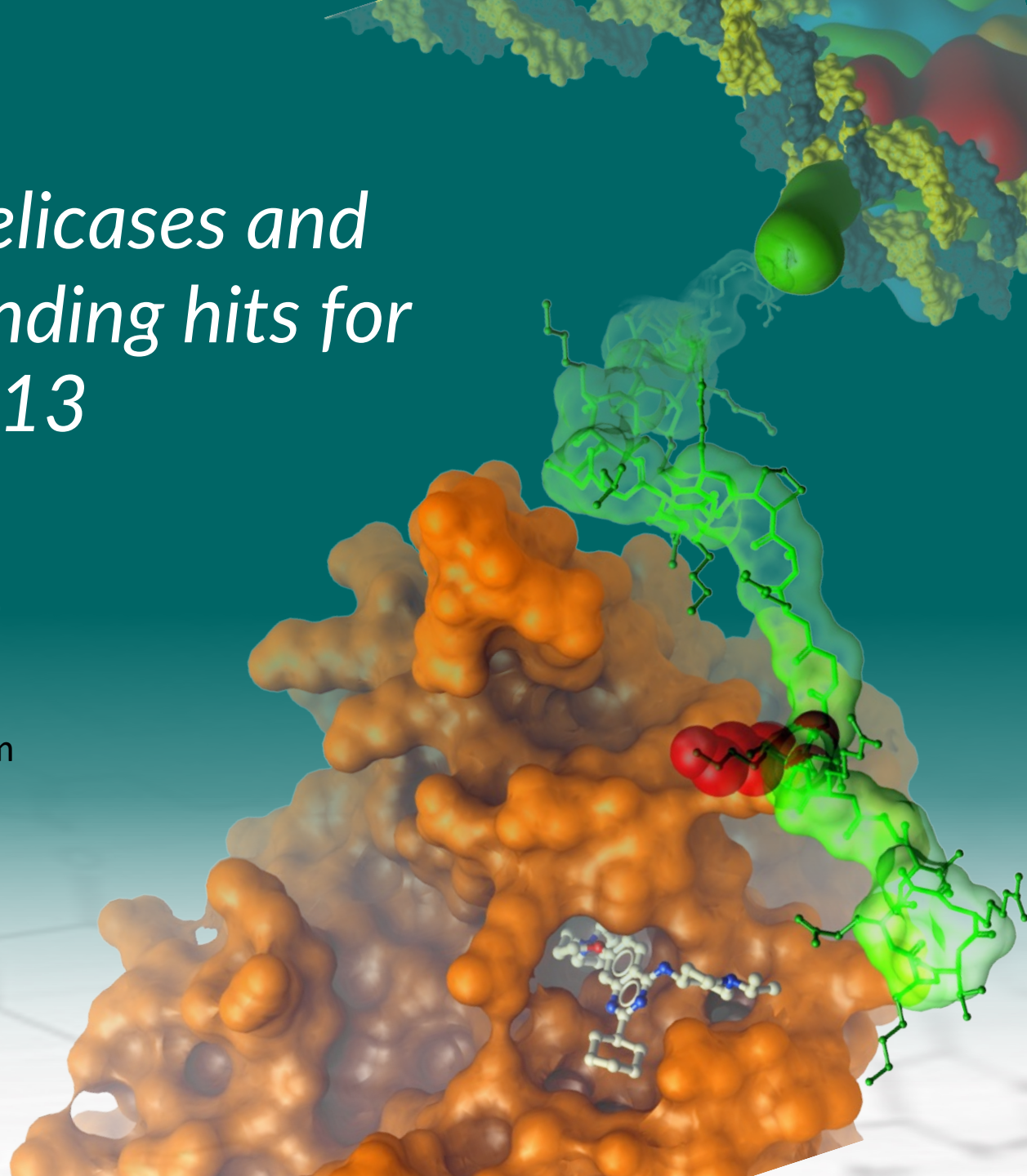
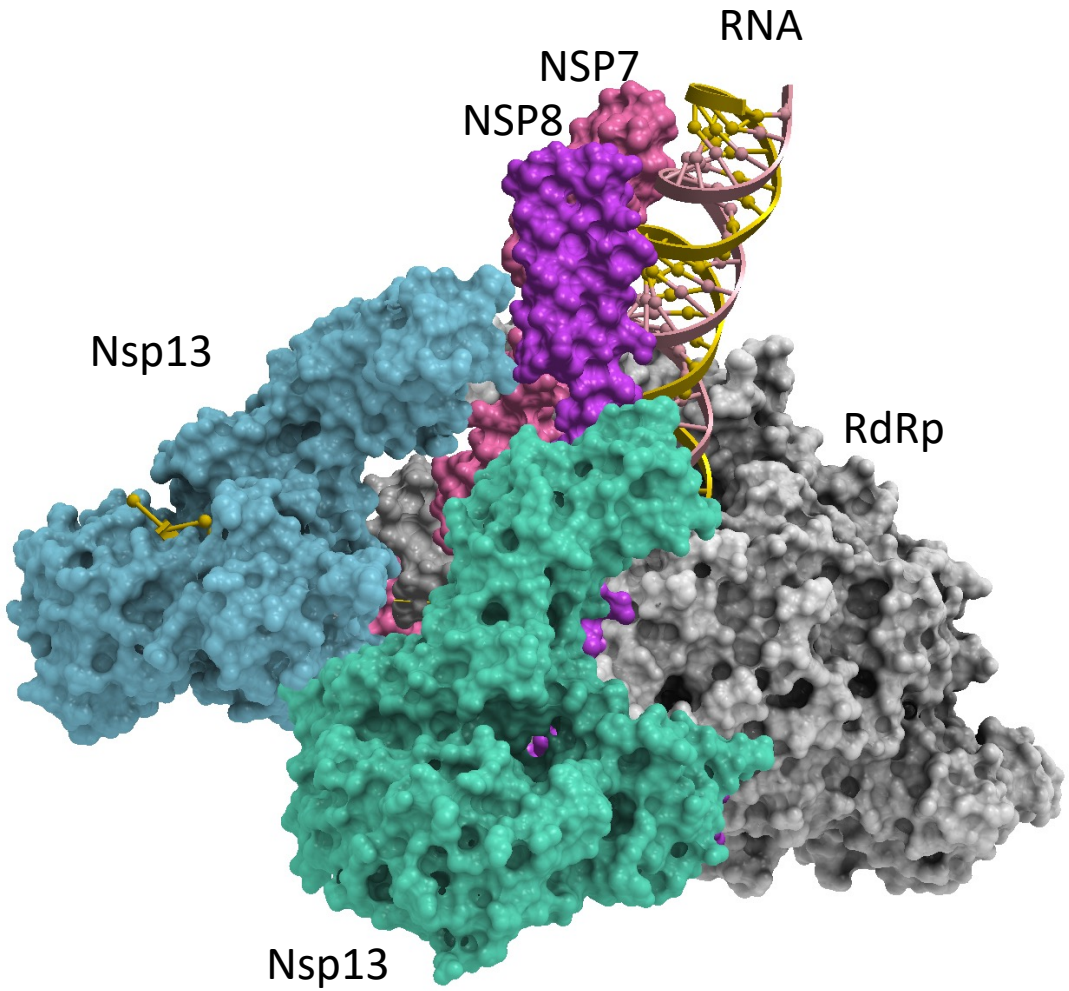
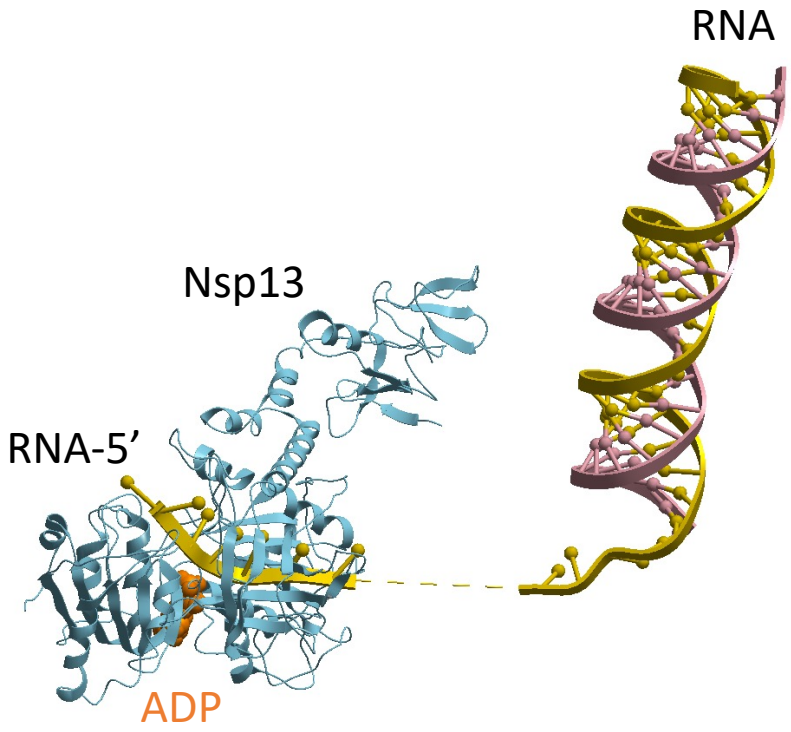


Nsp13 is an Integrated Component of the Replication Transcription Complex

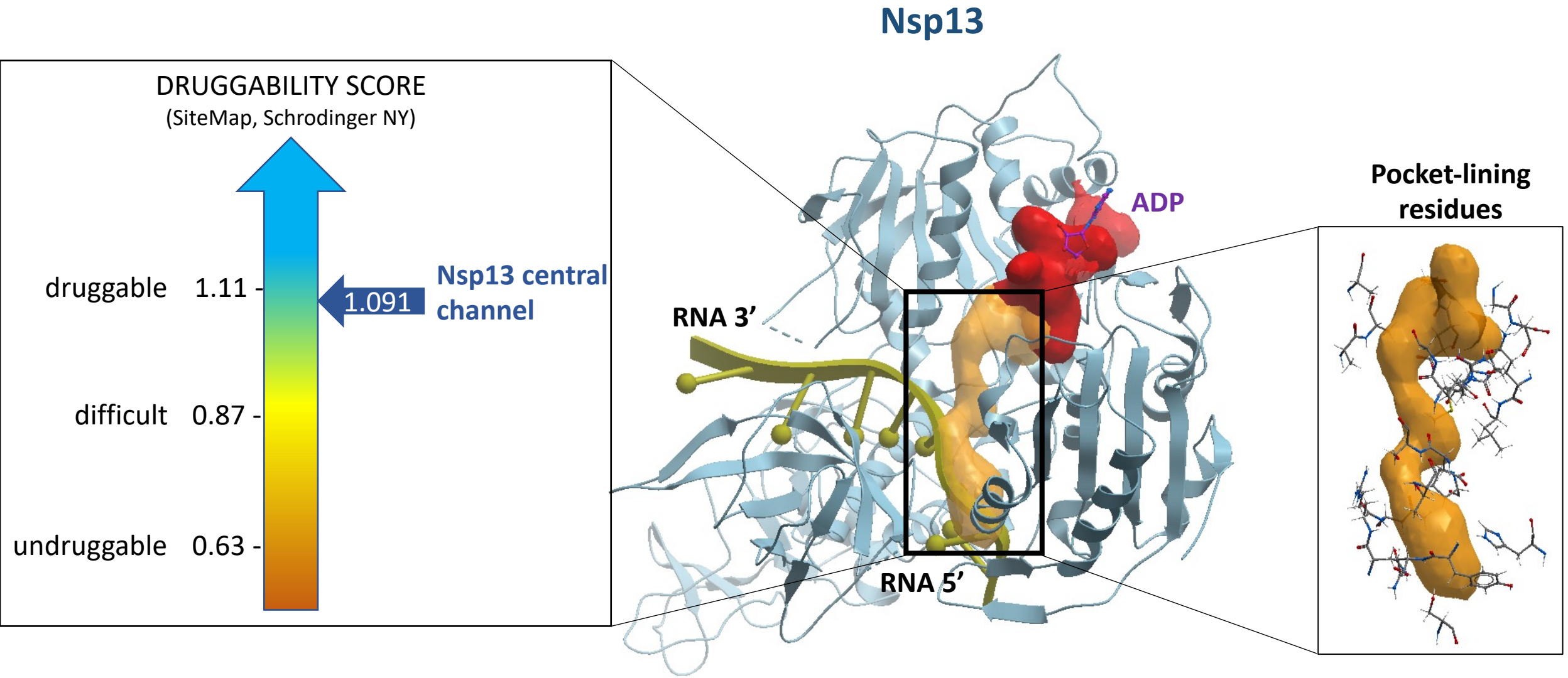


PDB: 7RDY



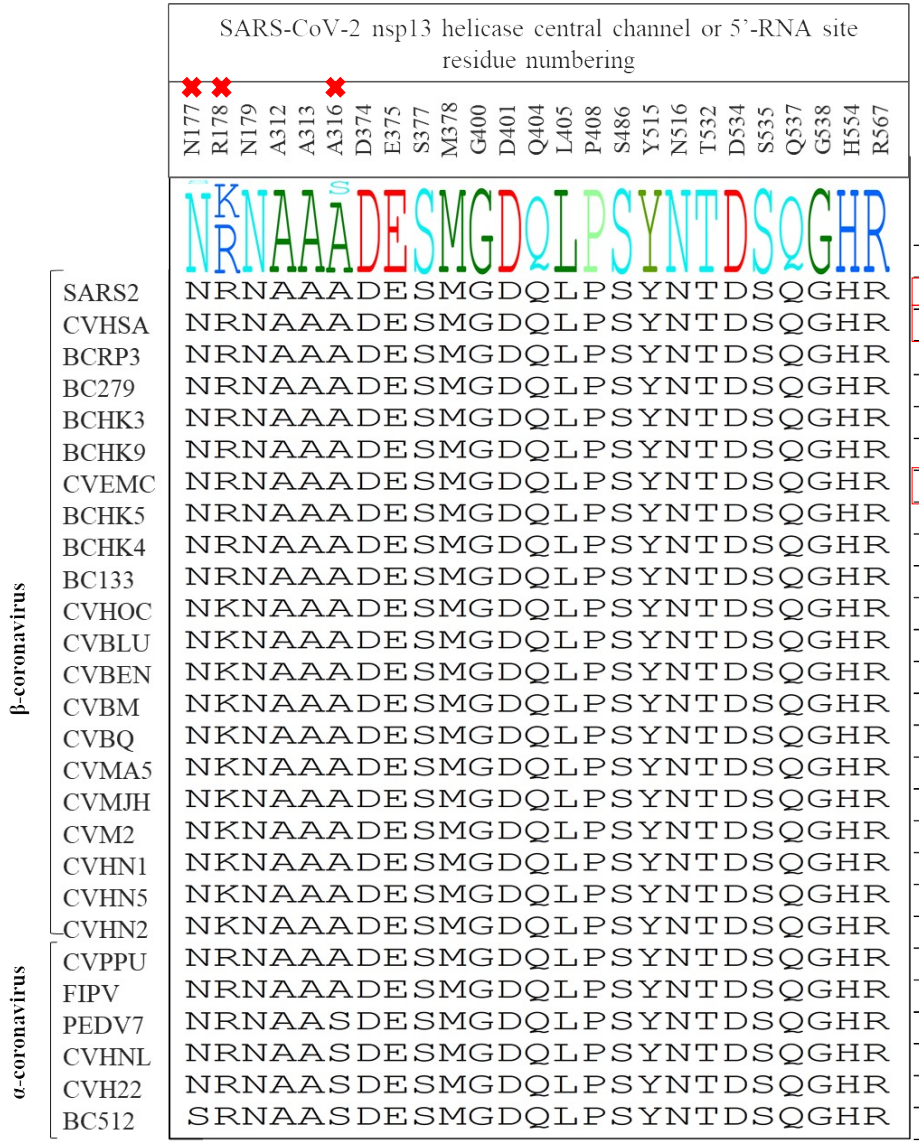
Chen et al. (2022) Nat Struct Mol Biol

RNA Occupies a Druggable Central Channel of Nsp13



Yazdani et al. (2021) J. Proteom Res.

Residues Lining the Central Channel of Nsp13 Are Highly Conserved in Coronavirus

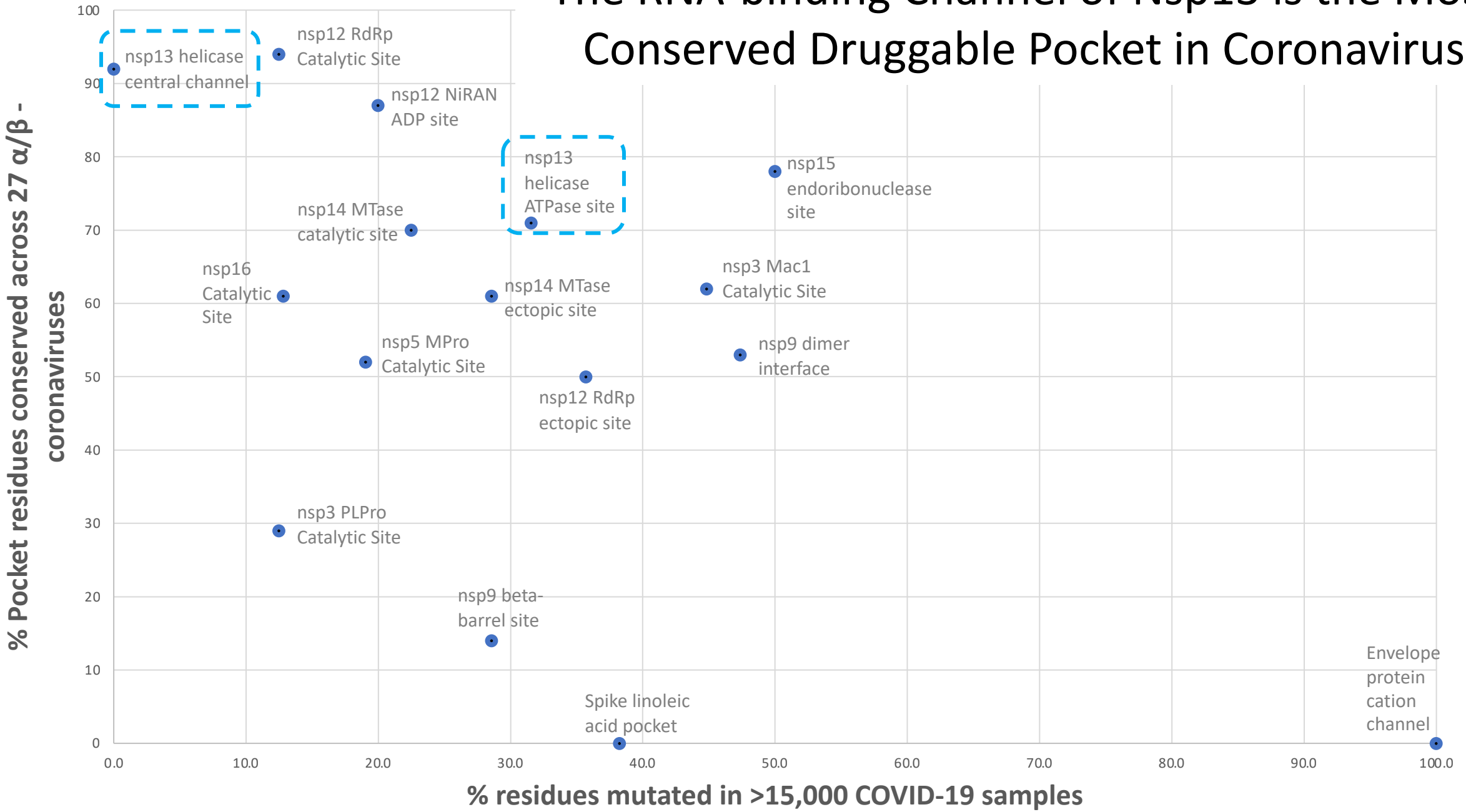


Organism
Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)
Severe acute respiratory syndrome coronavirus (SARS-CoV)
Bat coronavirus Rp3/2004 (BtCoV/Rp3/2004) (SARS-like coronavirus Rp3)
Bat coronavirus 279/2005 (BtCoV) (BtCoV/279/2005)
Bat coronavirus HKU3 (BtCoV) (SARS-like coronavirus HKU3)
Bat coronavirus HKU9 (BtCoV) (BtCoV/HKU9)
Middle East respiratory syndrome-related coronavirus (Human coronavirus EMC)
Bat coronavirus HKU5 (BtCoV) (BtCoV/HKU5/2004)
Bat coronavirus HKU4 (BtCoV) (BtCoV/HKU4/2004)
Bat coronavirus 133/2005 (BtCoV) (BtCoV/133/2005)
Human coronavirus OC43 (HCoV-OC43)
Bovine coronavirus (strain 98TXSF-110-LUN) (BCoV-LUN) (BCV)
Bovine coronavirus (strain 98TXSF-110-ENT) (BCoV-ENT) (BCV)
Bovine coronavirus (strain Mebus) (BCoV) (BCV)
Bovine coronavirus (strain Quebec) (BCoV) (BCV)
Murine coronavirus (strain A59) (MHV-A59) (Murine hepatitis virus)
Murine coronavirus (strain JHM) (MHV-JHM) (Murine hepatitis virus)
Murine coronavirus (strain 2) (MHV-2) (Murine hepatitis virus)
Human coronavirus HKU1 (isolate N1) (HCoV-HKU1)
Human coronavirus HKU1 (isolate N5) (HCoV-HKU1)
Human coronavirus HKU1 (isolate N2) (HCoV-HKU1)
Porcine transmissible gastroenteritis coronavirus (TGEV)
Feline coronavirus (strain FIPV WSU-79/1146) (FCoV)
Porcine epidemic diarrhea virus (strain CV777) (PEDV)
Human coronavirus NL63 (HCoV-NL63)
Human coronavirus 229E (HCoV-229E)
Bat coronavirus 512/2005 (BtCoV) (BtCoV/512/2005)

✖ Non-identical residues

Yazdani et al. (2021) J. Proteom Res.

The RNA-binding Channel of Nsp13 is the Most Conserved Druggable Pocket in Coronavirus



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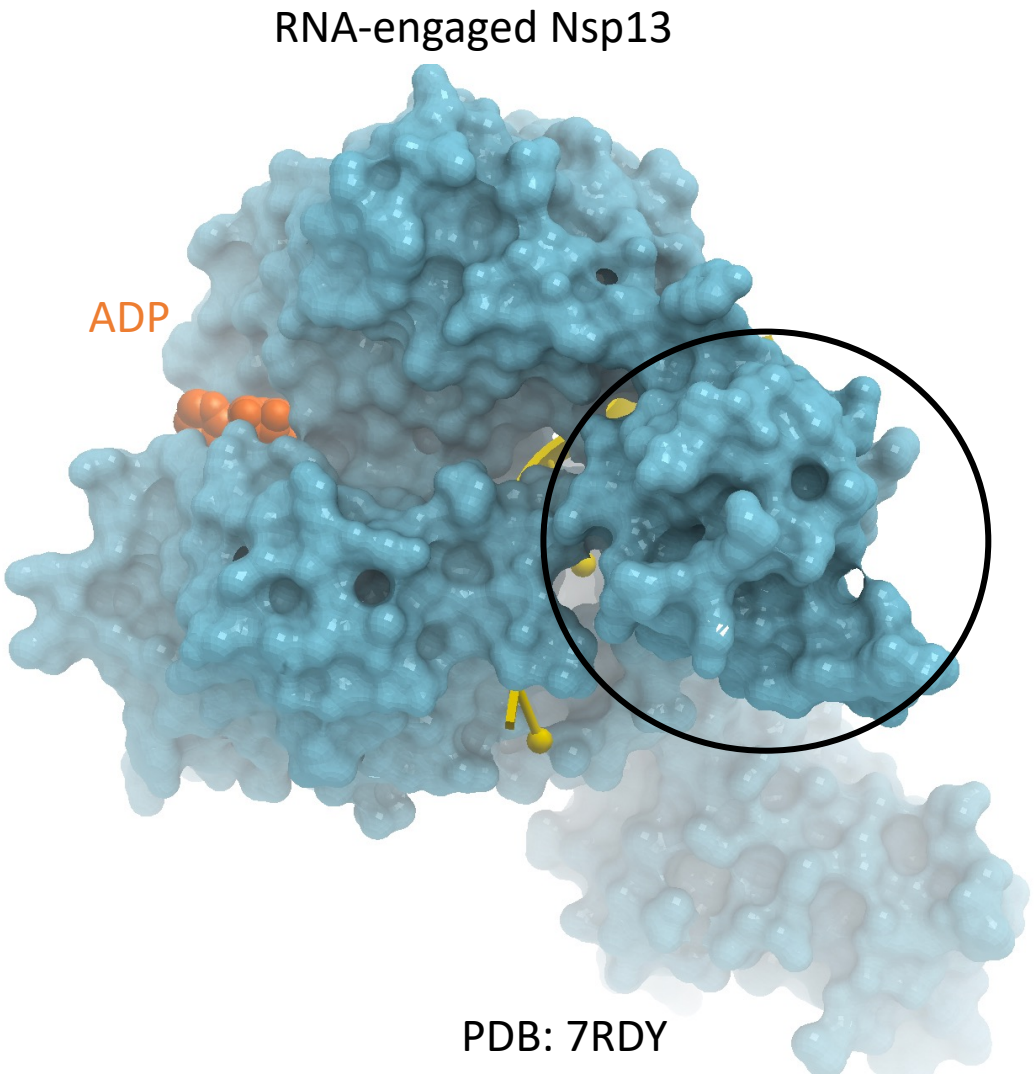
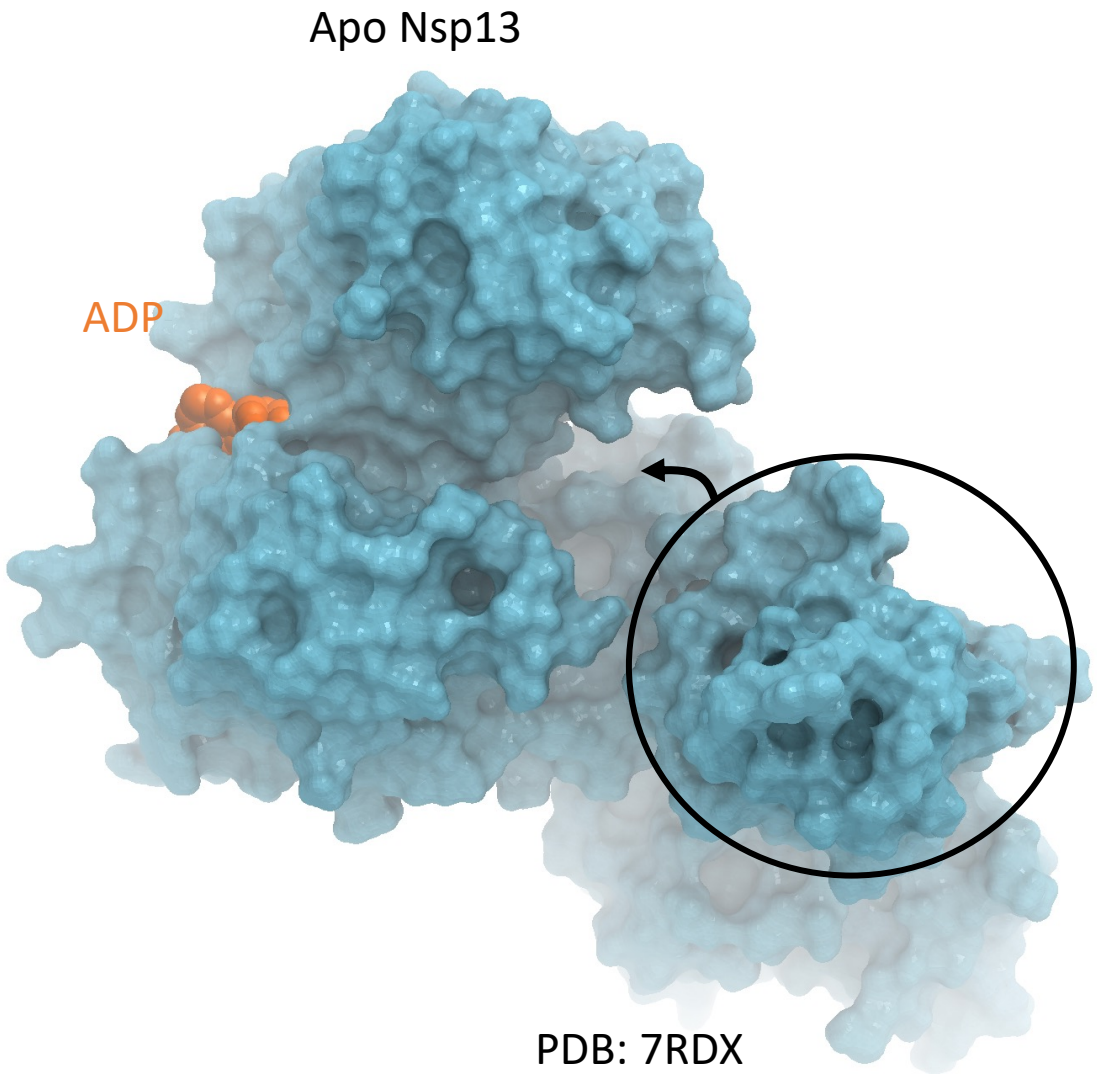
RNA Engagement is Associated with a Massive Conformational Rearrangement at the Nsp13 Central Channel





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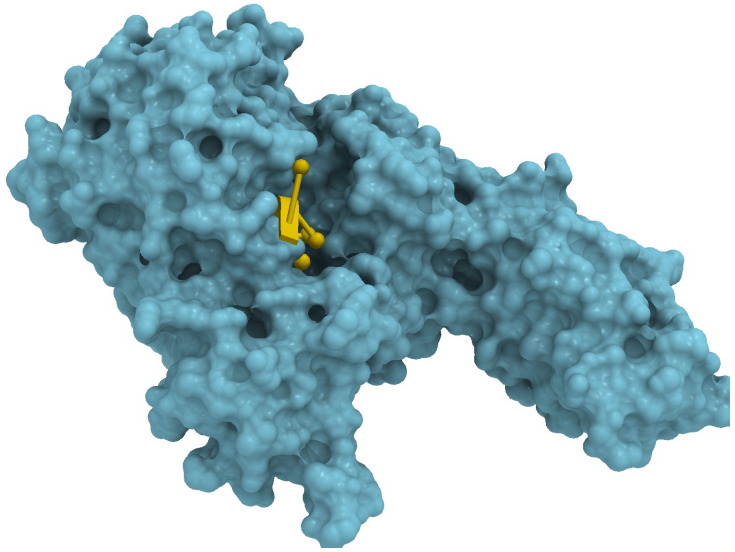
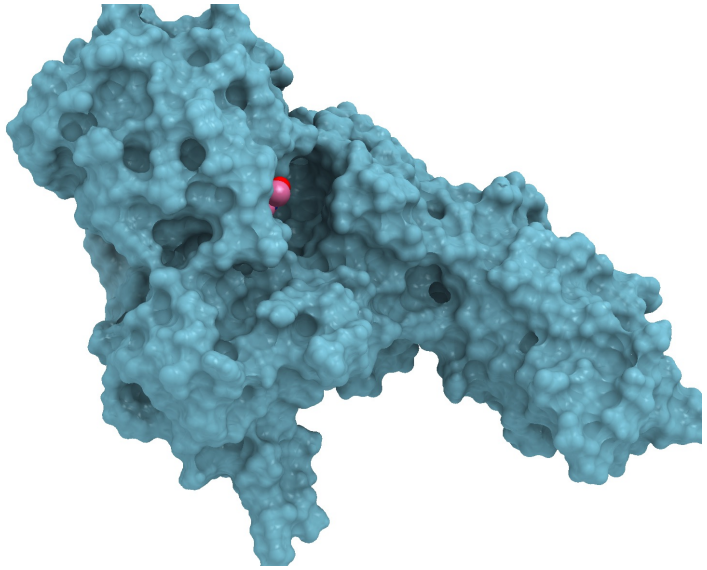
Fragment-Bound Nsp13 Conformation is Close to the RNA-Engaged State

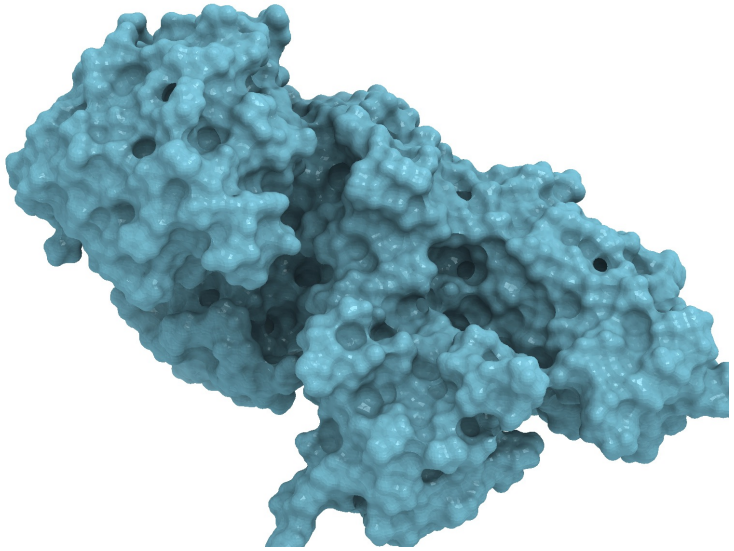
RNA-bound



Fragment-bound

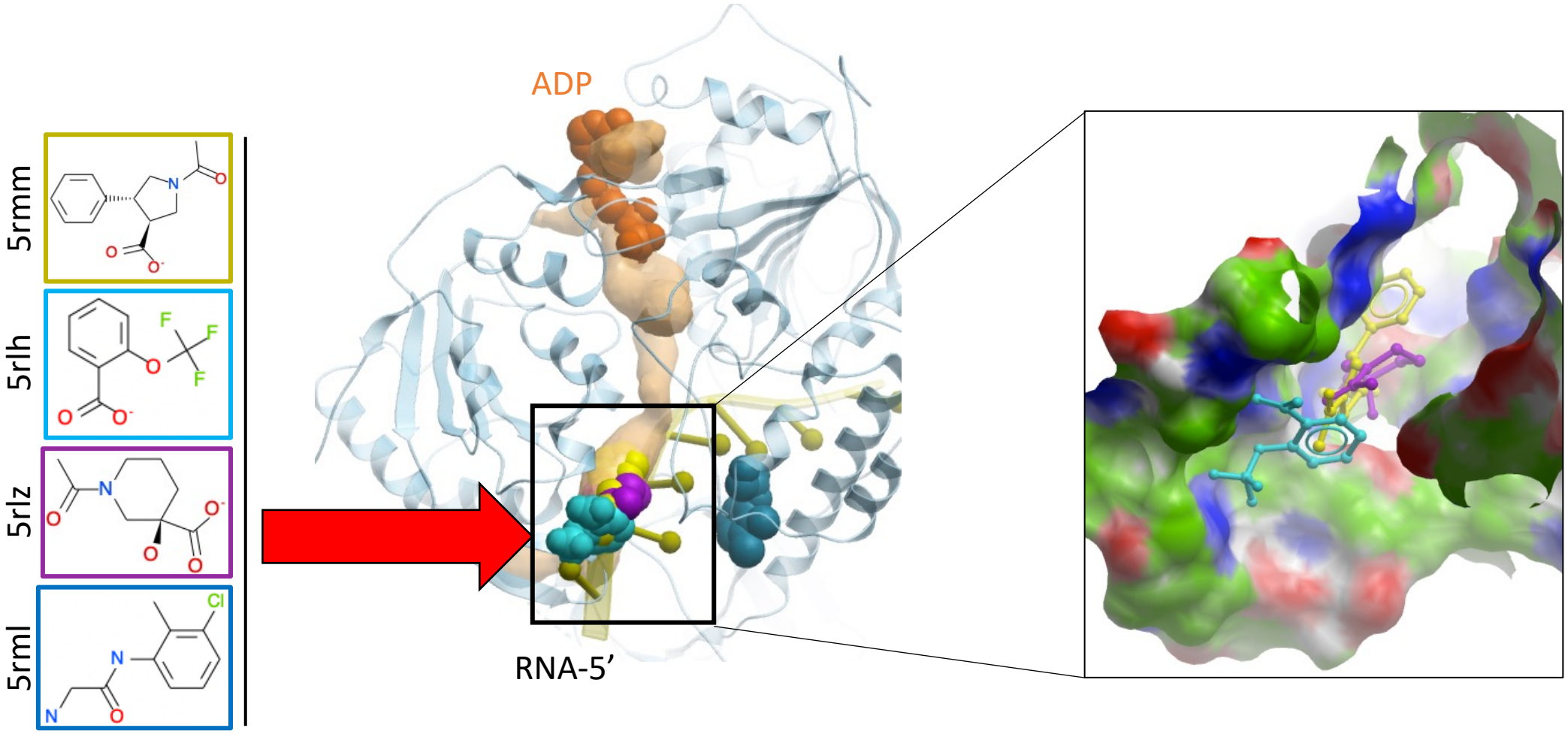


Apo



Newman et al. (2021) Nat. Commun.

Fragments in the PDB May be a Starting Point for Inhibitor Design



Newman et al. (2021) Nat. Commun.

CACHE Challenge #2: Asking Participants to Predict Ligands Targeting the RNA-Binding Channel of Nsp13

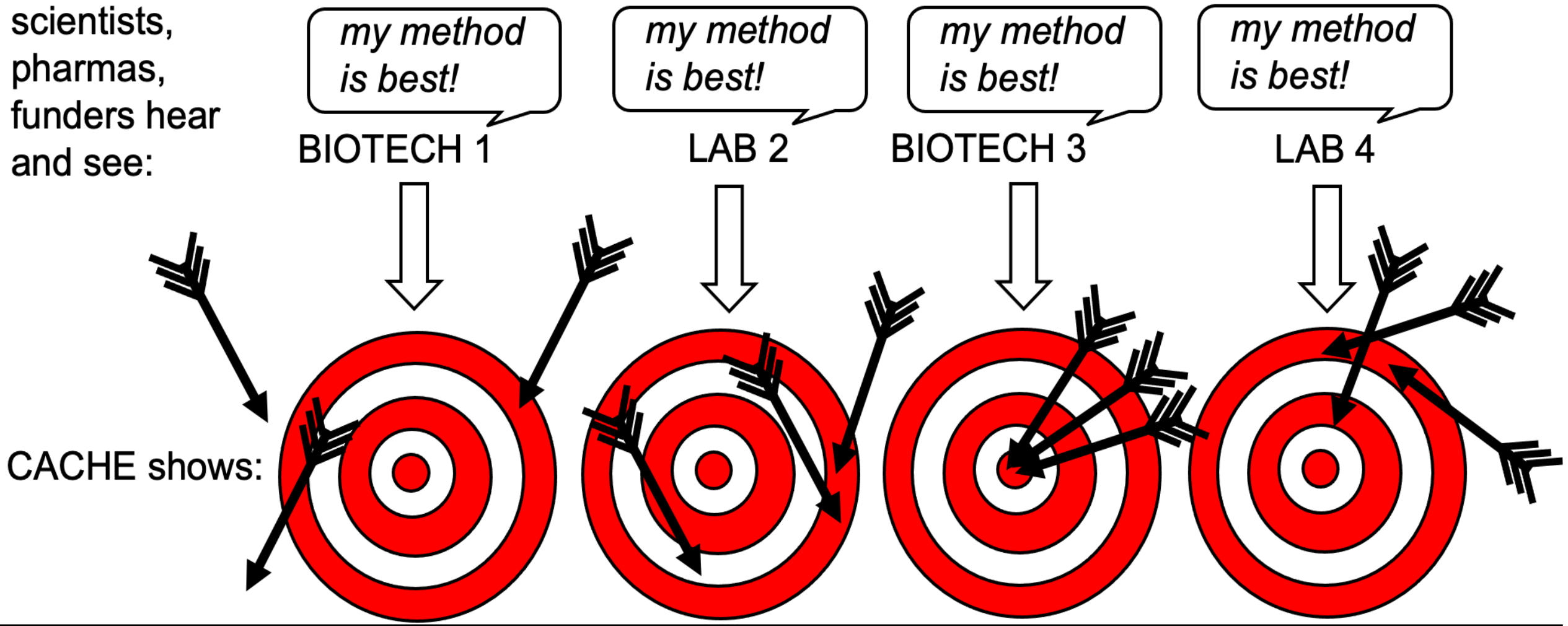
CACHE is modelled after the protein structure prediction challenge CASP

CACHE is a benchmarking initiative to reveal the most efficient computational methods for hit finding and to guide future technological improvement

CACHE Is a Prospective Hit Finding Competition

- Participants use their computational method to predict up to 100 hits that are ordered and tested experimentally by CACHE
- All data is publicly released without restriction on use at the end of each competition

CACHE Reveals the State-of-The-Art to Scientists, Pharmas, Funders

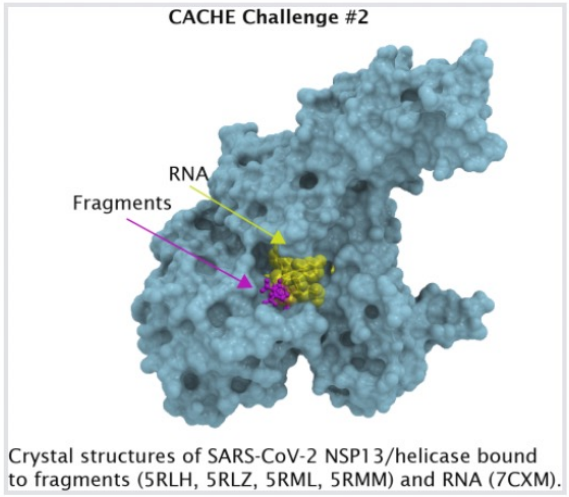


WWW.CACHE-CHALLENGE.ORG

CACHE CHALLENGE

CRITICAL ASSESSMENT OF COMPUTATIONAL HIT-FINDING EXPERIMENTS

CHALLENGE #2



Crystal structures of SARS-CoV-2 NSP13/helicase bound to fragments (5RLH, 5RLZ, 5RML, 5RMM) and RNA (7CXM).

FINDING LIGANDS TARGETING THE CONSERVED RNA BINDING SITE OF SARS-COV-2 NSP13

The second CACHE Challenge target is the NSP13 helicase of SARS-CoV-2.

Participants are asked to find hits for the RNA-binding site of NSP13. Read more under Details below.

Challenge #2: RNA Binding Site of SARS-CoV-2 NSP13

41 Applications, including multiple leaders in the field

US	11
UK	5
China	4
Canada	3
Germany	3
Korea	3
Brazil	2
Denmark	1
India	1
Ireland	1
Italy	1
Japan	1
Malaysia	1
So. Africa	1
Switzerl.	1
Taiwan	1
Ukraine	1

Academia	28
Biotech	7
Electronics giant	1
Government	2
Internet giant	1
Pharma	1
Independent	1

CACHE Attracted a Diverse Team of Computational Chemistry and AI Experts to Work on Nsp13

Publications from the 25 selected participants to CACHE #2

JOURNAL	papers since 2020
Any	367
Journal of Chemical Information and Modeling	27
Journal of Medicinal Chemistry	11
Drug Discovery Today	10
Molecules	9
Advances in Neural Information Processing Systems	8
Scientific Reports	8
PLoS Computational Biology	7
Journal of Chemical Theory and Computation	7
European Journal of Medicinal Chemistry	6
Journal of Chemical Physics	6
Nature	5
Science	5

Drug-it is One of the 25 Participants of CACHE #2. Will Crowd-Sourcing do Better than the Experts?

https://fold.it/drugit

fold it Game Community About Download Log in Sign up

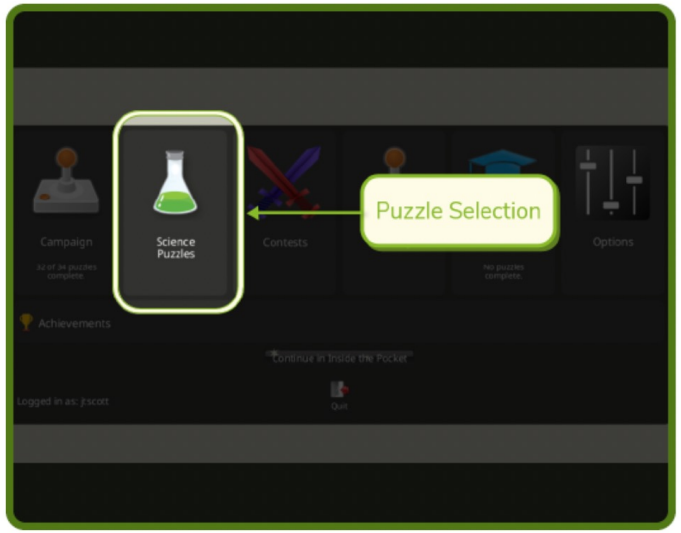
Download the Game!

Current Small Molecule Drug Design Puzzle

- SARS-CoV-2 helicase CACHE Challenge: Round 3

Finding the Small Molecule Puzzles

- Once the game is running you will be asked to play online or offline.
- Select **Play Online** and sign in.
- Select **Science Puzzles.**
- The current Small Molecule Drug Design Puzzles will automatically appear in your puzzle selection menu shown below:



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CACHE (Critical Assessment of Computational Hit-finding Experiments): A public-private partnership benchmarking initiative to enable the development of computational methods for hit-finding

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Nsp13

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CACHE Experimental Platform

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