

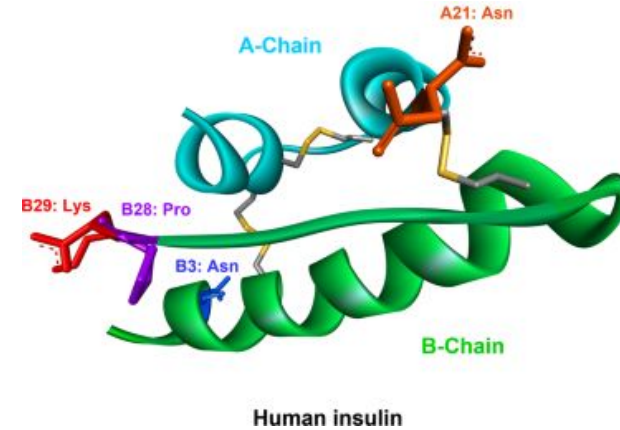
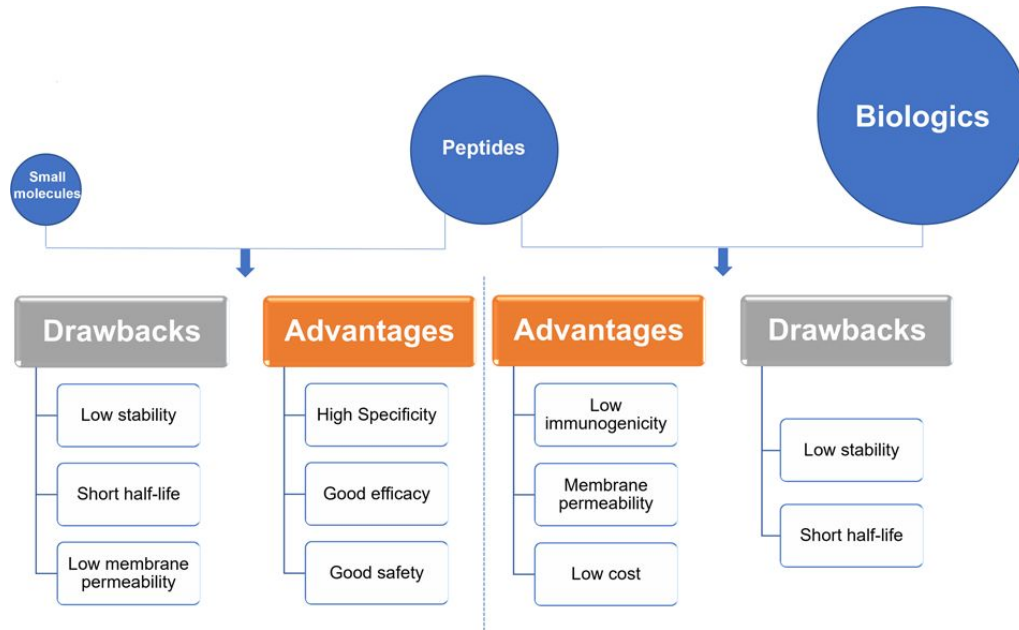
Exploration of peptide structures and generation of therapeutic peptide candidates using Protein Language Model

Mateusz Chojnacki, Paweł Park, Łukasz Milewski, Hubert Wąsiewicz



Under the Supervision of:
Wanda Niemyska PhD, prof. Joanna Sułkowska

Peptide therapeutics



SARS-CoV-2 nsp13 helicase

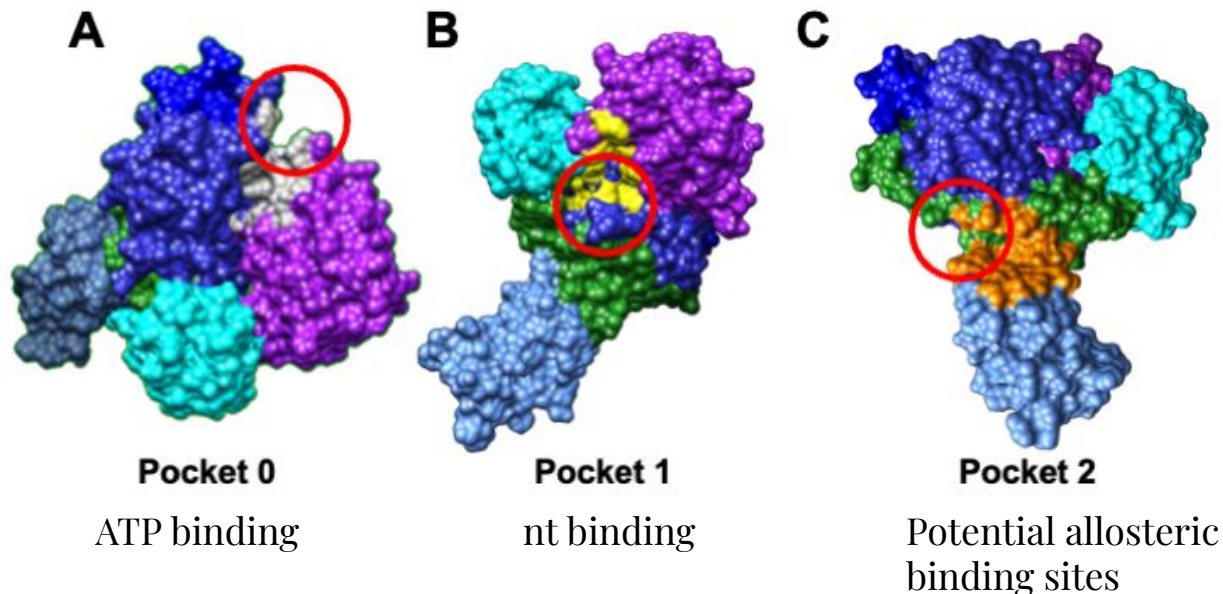
► Nat Commun. 2021 Aug 11;12(1):4848. doi: 10.1038/s41467-021-25166-6.

Structure, mechanism and crystallographic fragment screening of the SARS-CoV-2 NSP13 helicase

Joseph A Newman ¹, Alice Douangamath ², Setayesh Yazdani ³, Yuliana Yosaatmadja ⁴,
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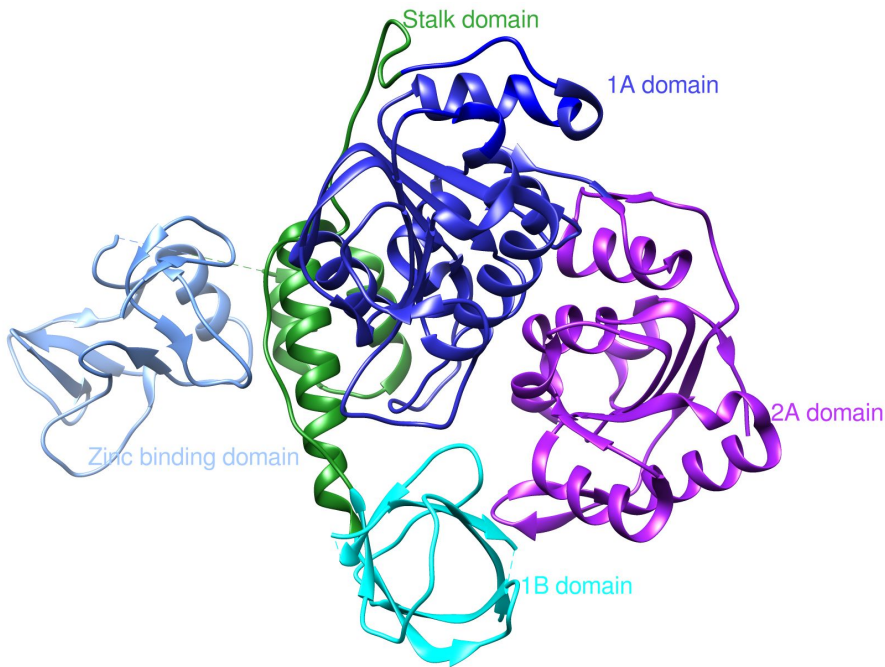
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PMID: 34381037 PMID: PMC8358061 DOI: 10.1038/s41467-021-25166-6



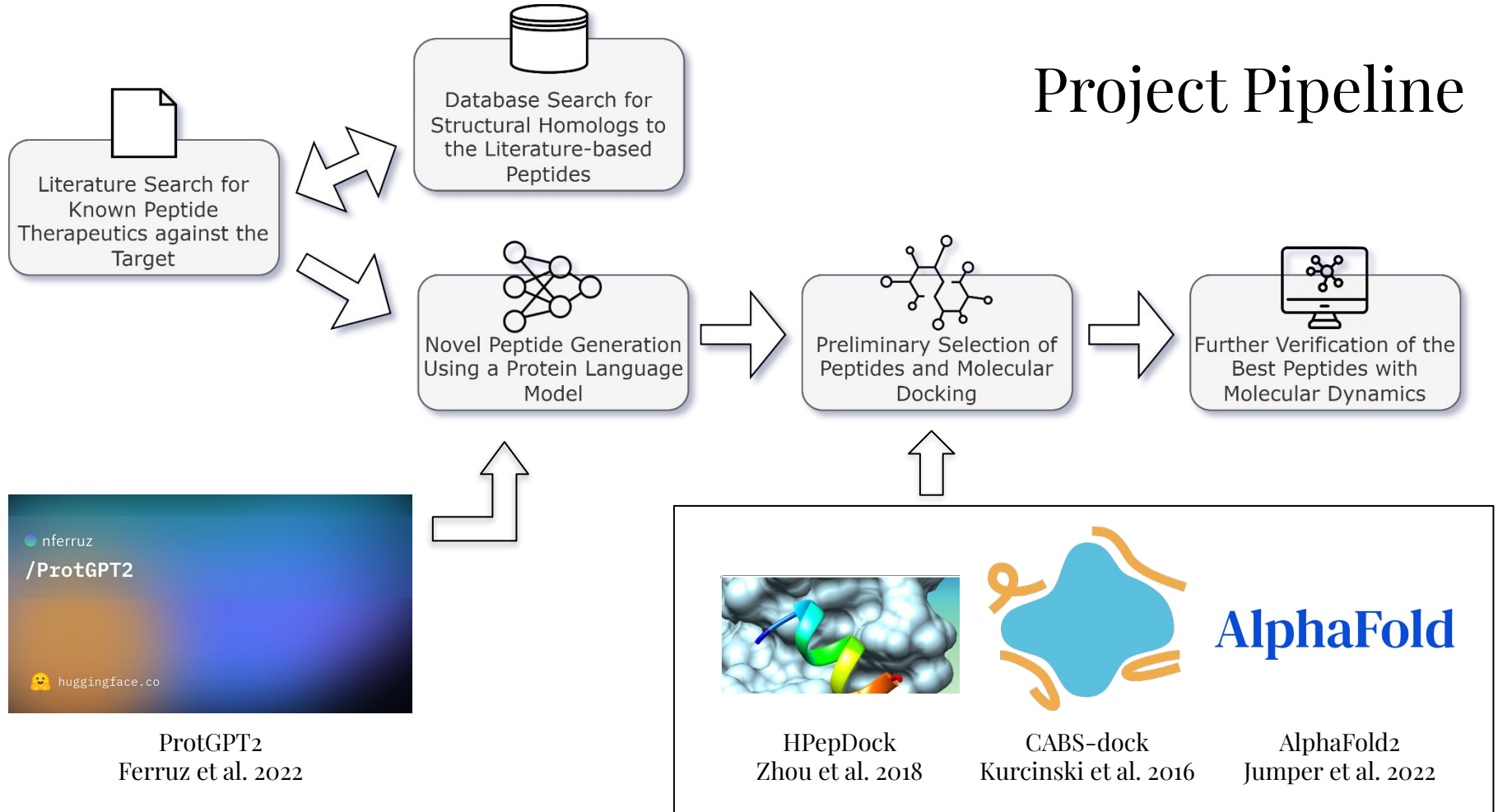
Our Goal

Explore the space of possible peptide structures using a protein language model and attempt to generate plausible therapeutic peptide candidates against the nsp13 helicase



SARS-CoV-2 Nsp13 helicase

Project Pipeline



1) Peptides from the Literature Review

Almost no research on antiviral peptides against SARS CoV-2's nsp13

The only publication includes 45 peptides potentially binding to nsp13 helicase.

[Protein J.](#) 2021; 40(3): 310–327.

Published online 2021 Apr 11. doi: [10.1007/s10930-021-09983-8](https://doi.org/10.1007/s10930-021-09983-8)

PMCID: PMC8036162

PMID: [33840006](https://pubmed.ncbi.nlm.nih.gov/33840006/)

Milk Peptides as Novel Multi-Targeted Therapeutic Candidates for SARS-CoV2

[H. Pradeep](#), [Umme Najma](#), and [H. S. Aparna](#) 

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Sequence	Dockscore	E-model
SVFSGYRK	-12.95	-191.21
CLANGMIMY	-12.50	-172.26
RQQPGKGPRY	-12.26	-139.90
ALEATCKSL	-11.73	-153.84
LDAQSAPLRV	-11.59	-165.69
FLRQNEVL	-11.28	-156.53
IDALNENK	-11.03	-159.33
DIEQLRSQL	-10.91	-161.25
IQKVAGTW	-10.74	-124.27

2) Construction of Peptide Database

The structure homology search yielded 27 more peptides.

Docking with Hpepdock and CABS-dock showed, that they bind to at least one of described binding sites with high scores.



3) Generating Peptides

ProtGPT2 speaks the ‘language of the proteins’

Problems with fine-tuning – not enough data to generate completely novel peptides without overfitting

The literature peptides are fed into the pre-trained model, treated as ‘context’ and new amino acids are appended to the known peptide



main ▾ ProtGPT2

<https://huggingface.co/nferruz/ProtGPT2>

Article | [Open access](#) | [Published: 27 July 2022](#)

ProtGPT2 is a deep unsupervised language model for protein design

[Noelia Ferruz](#) ✉, [Steffen Schmidt](#) & [Birte Höcker](#)

[Nature Communications](#) **13**, Article number: 4348 (2022) | [Cite this article](#)

52k Accesses | **76** Citations | **195** Altmetric | [Metrics](#)

Ferruz et al. 2022

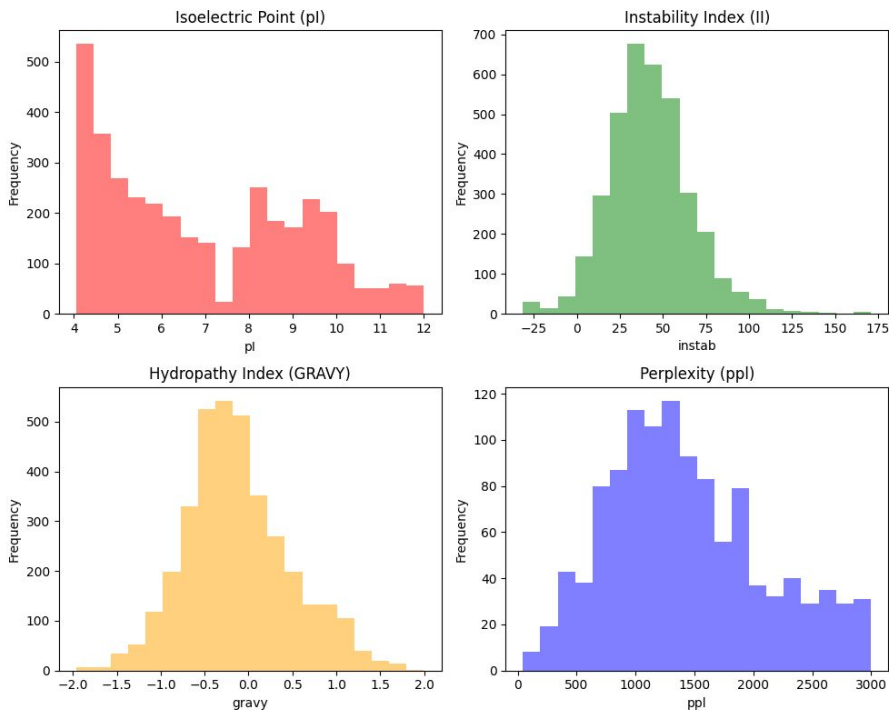
4) Preliminary Filtering

Isoelectric point - 6-8 to mimic physiological conditions

Instability index - anything below 40 can be considered stable (Guruprasad et al 1990)

GRAVY - balance between hydrophilic and lipophilic (-1, 1)

Perplexity - predictive performance of a language model (the lower the better)

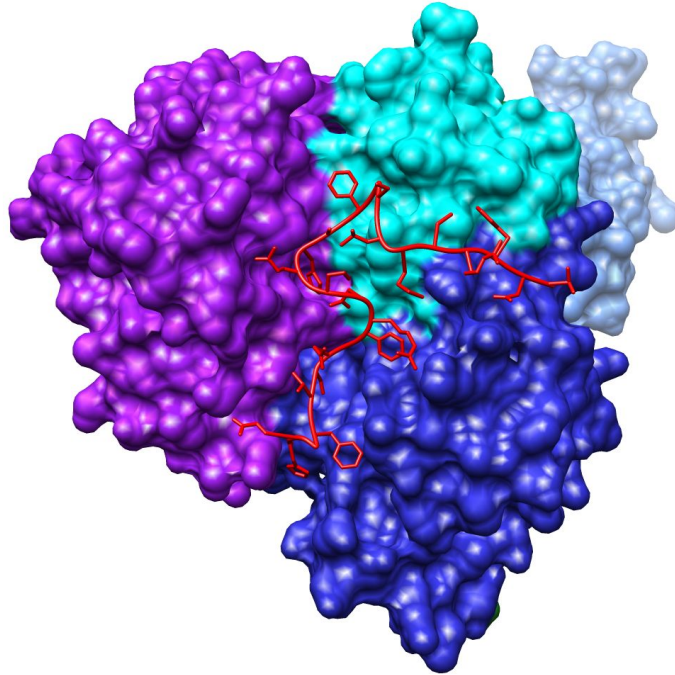


Histogram of the preliminary metrics used to filter out undesirable peptides

Table 2: Sequences generated with ProtGPT2 with selected preliminary metrics (pI - isoelectric point, II - instability index, gravity - grand average of hydropathicity index, ppl - perplexity), sorted by ppl

Alias	pI	II	gravity	ppl	Sequence
G1	6.46	21.70	-0.48	844.69	SLPYPFIWGNQMWMILTWP DHR
G2	6.74	32.63	-0.56	868.12	HMWPGDIKPAAVSRDLSQ
G3	6.92	27.30	0.21	904.70	IIVTQTMKSGDVSILHQIHYKAD
G4	6.06	19.66	-0.38	1007.95	WNPADYGGIKPLLTETNIVGKY
G5	7.84	25.80	-0.41	1020.43	GCCSDPLCAWRCHAGRCGRD
G6	7.94	35.50	0.74	1063.46	CKFFWATYTSCLSGGNLGIFVPS
G7	6.22	18.45	-0.37	1089.33	LSITENGFEKPLGFQFSQKSIEKV
G8	6.77	29.40	0.18	1100.54	LVGPTIWRAALLESAPRHAAE
G9	7.82	11.31	-0.03	1200.32	GCCSDPRCAWRRCYGCLS
G10	6.80	35.61	0.29	1287.75	ALKIPISKIYIDSHSVLSPE
G11	6.75	35.87	0.02	1371.14	LHTPLPLTRRDKALLDDALSLFG
G12	6.21	39.74	-0.47	1400.99	GWLEPLLARPWLIVGRDQRGVMTRPYDEG
G13	6.91	14.87	-0.71	1567.13	HEGFTSDFRNPQHAFGSLMCRFNT
G14	7.02	27.67	-0.31	1689.99	LTFQHNQFQTHRGHEVGSAQGFTAILW
G15	6.05	34.96	0.60	1731.80	YCKFEWATFAKSCAFPVDGLSFPPFFGI
G16	6.00	33.07	-0.33	1800.79	QIPTVNNLKVSEPFTP
G17	6.12	6.10	-0.03	1831.41	GLDIQKVKDMEQLLTQVRLSI
G18	6.74	27.94	-0.04	1927.21	VLEKYKDVIMNSSSLLEHIATGIKKFE
G19	6.40	3.73	-0.26	1964.08	TLPFHSVIYVDSATGQTWTGNR
G20	6.21	37.61	-0.89	2220.56	GYDPETGTWGRRMTLFTPD SRAEVAAR

5) Docking Results

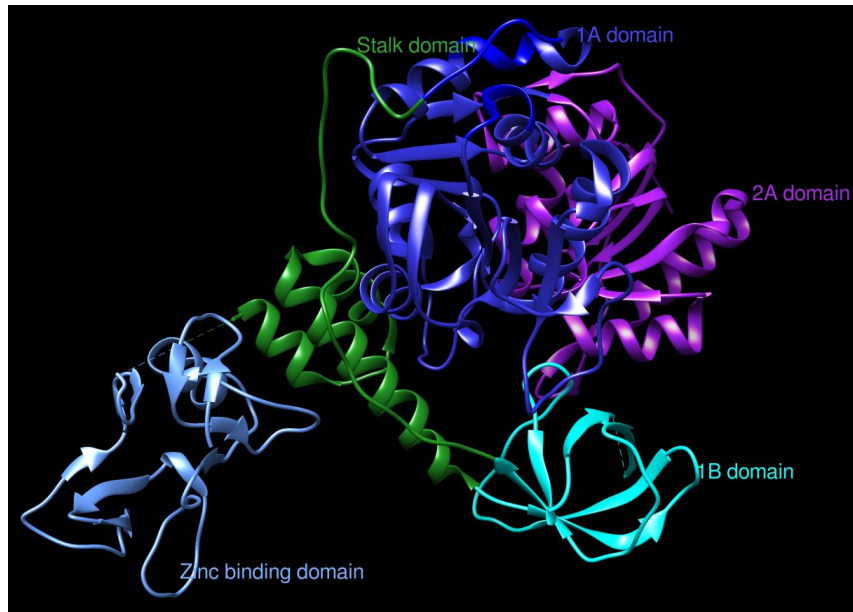


Alias	HpepDock			CABS-dock		
	0	1	2	0	1	2
G1		1	6	3	5	1
G2	1	3	3	4	2	1
G3	1	1	8	7	1	
G4	1	1	4	1	3	4
G5	2	3	4	1	6	1
G6	2	1	7	2	3	5
G7		2	6	5	3	
G8		1	7	4	4	
G9	2	1	7	6	1	
G10		3	3	4	4	1
G11		1	8	4	4	1
G12		3	5	6	4	
G13	1	3	6	8		
G14	2	3	3	3	2	1
G15		2	6	3	5	1
G16	2	1	7	4	2	
G17	1	1	7	3	2	2
G18	1		4	4	3	1
G19		1	8	5	5	
G20	1	2	7	8	2	

Number of G peptide models that docked to specific binding pockets (0 - ATP binding pocket, 1 - RNA binding pocket, 2 - unnamed potential pocket between Zinc/stalk domains) from docking runs performed using HPepDock and CABS-dock to helicase 6zsl with 10 results with the best binding score.

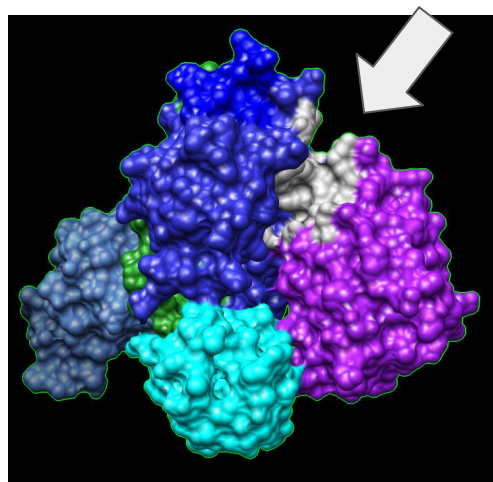
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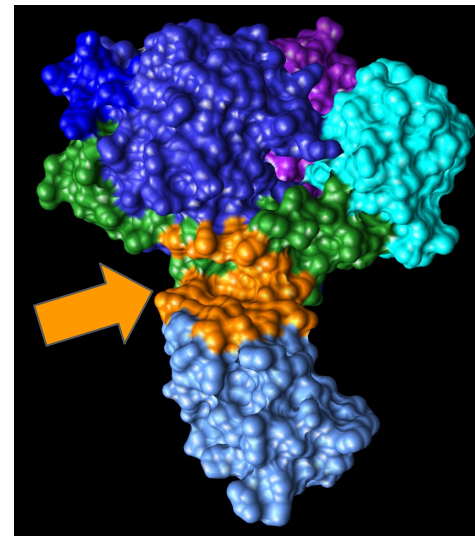
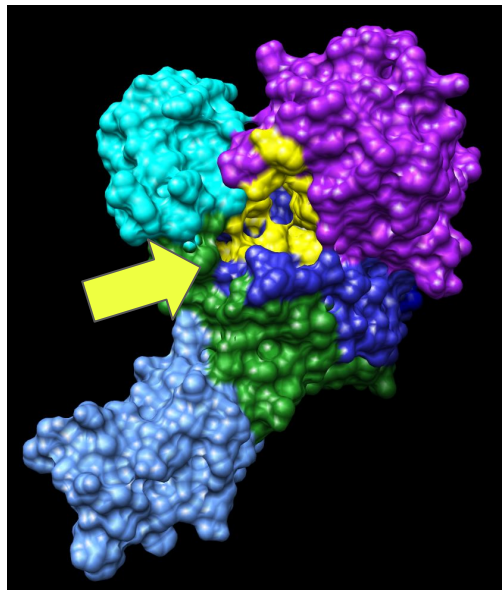
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Pocket 0
ATP binding

Pocket 1
nt binding



Pocket 2
Potential allosteric
binding sites

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