



# THE PROTEIN FOLDING PROBLEM

FROM A SEQUENCE TO A 3D STRUCTURE



## VIRAL PROTEINS

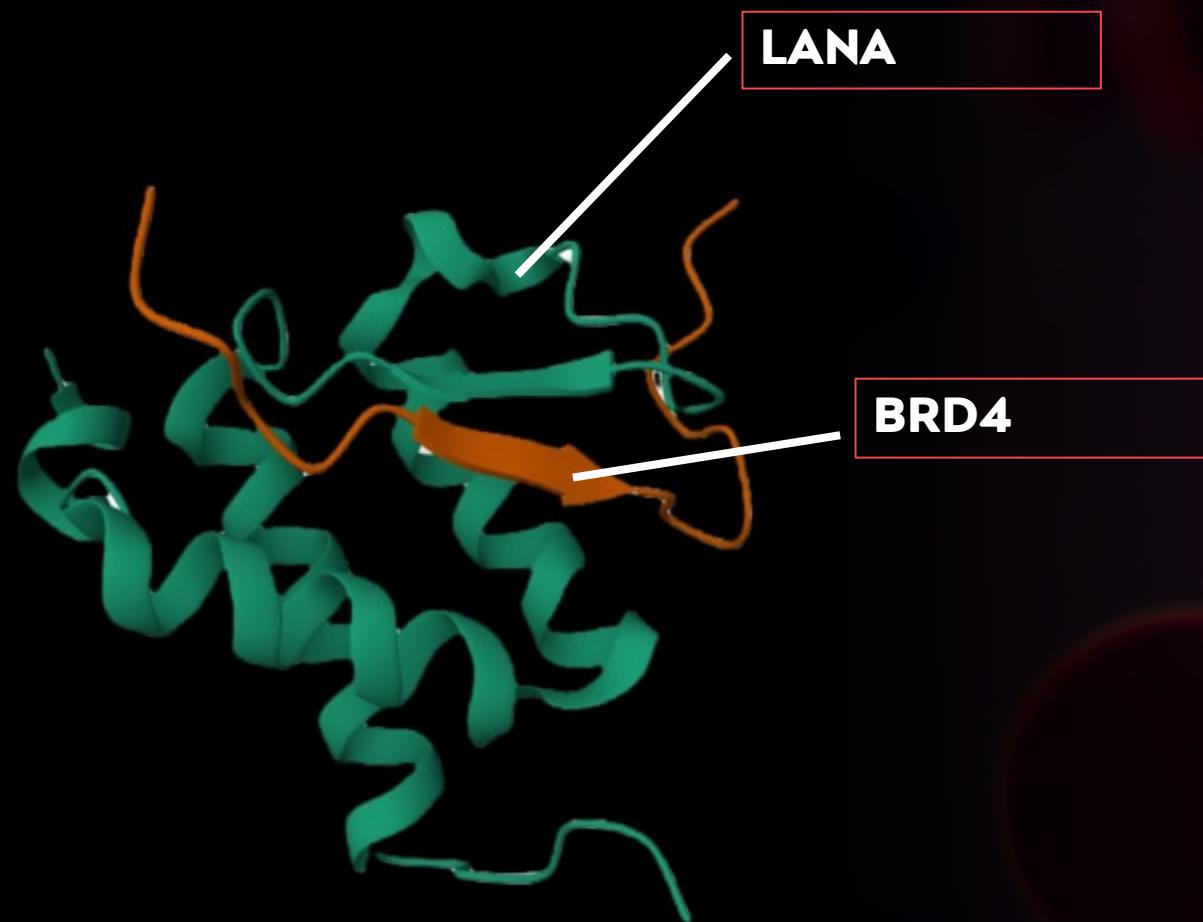
Viruses enter the body and hijack the protein to duplicate its DNA.

## PEPTIDE THERAPEUTICS

Other smaller proteins, or peptides, can be used to treat viral protein functions.



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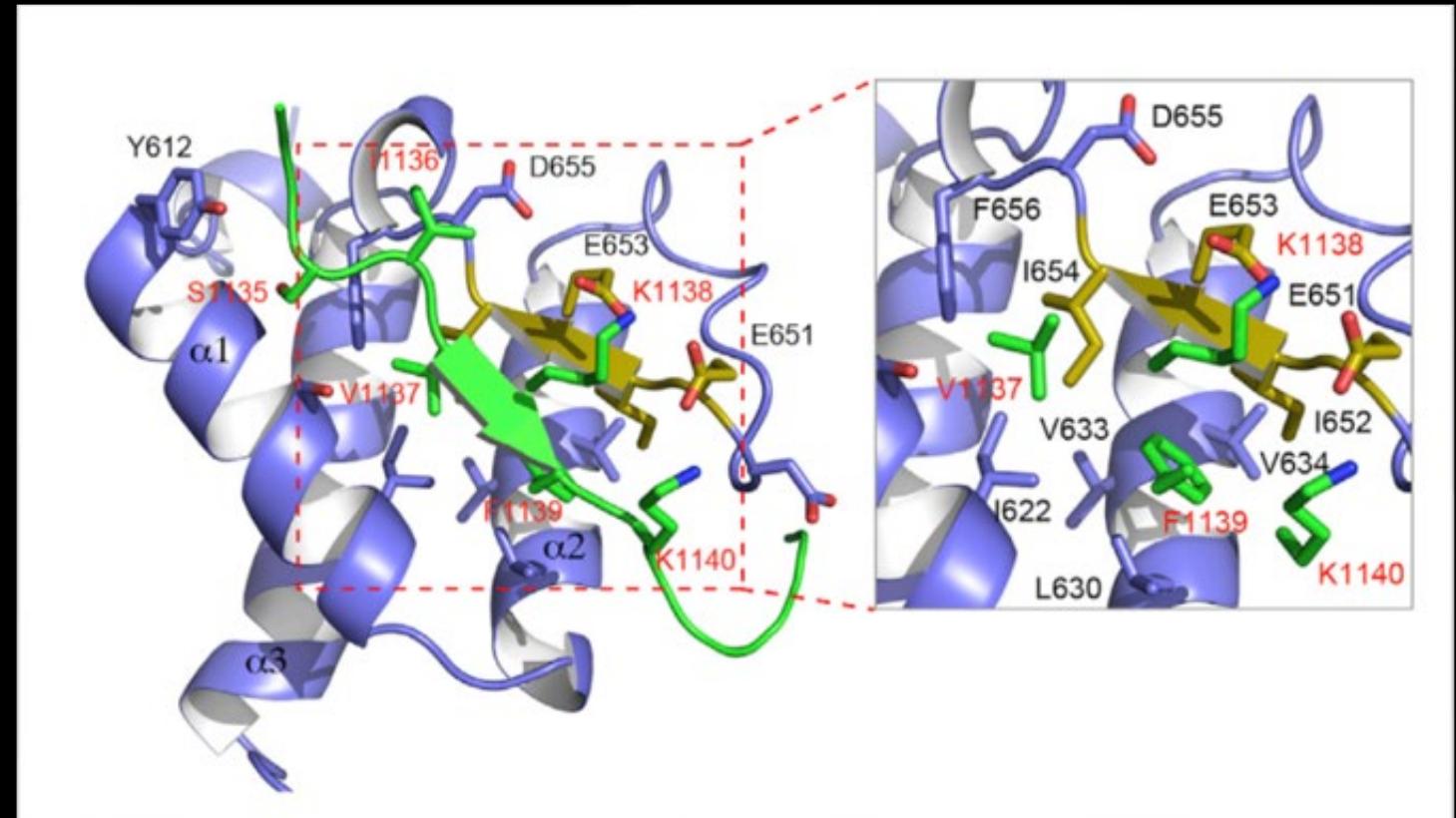


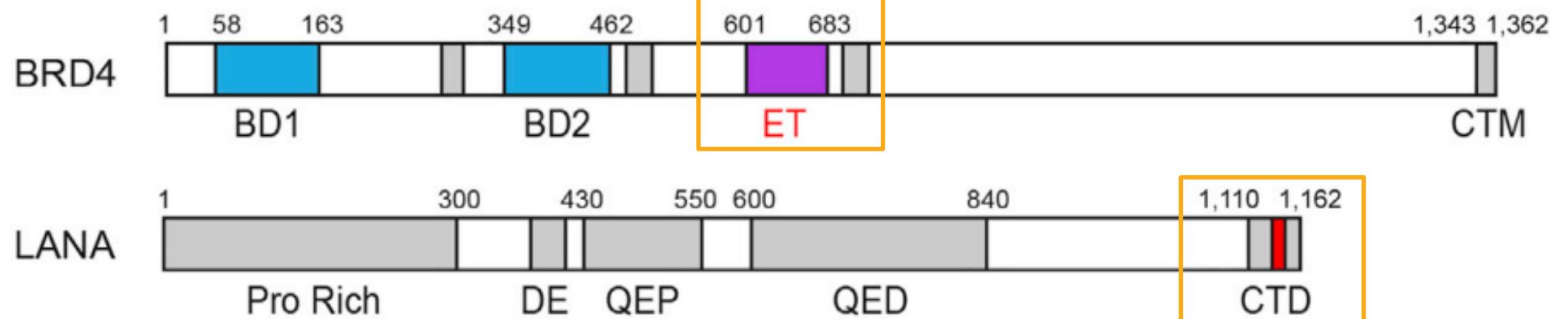
## BRD4 AND ITS ET DOMAIN

NLQS**SIVKF**KPLPLTQPG

- What can we improve, and how can we improve it?

- Hydrophobic pockets
- Opposite charges
- Polarity
- Unique side chains





# THE CODING BEHIND VARIANT PROTEINS

- Protein-peptide interactions can be predicted using artificial intelligence software AlphaFold2 and visualized in Nanome Virtual Reality (VR).

# METHODOLOGY

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1. Google CoLab prediction
2. Practice mutations
3. AlphaFold2 predictions
4. Actual mutations analysis
5. Data comparison
6. Final, favored mutations

**Utilize Nanome VR's mutation menu to predict the effects of the adjustments.**



**Produce mutated structures using AlphaFold2 via MobaXTerm.**



**Analyze in Nanome again to determine successful mutations.**



# THE IMPACT

- An overall decrease in developing related diseases—myeloid leukemia, aggressive carcinoma, and HIV.

# THE OUTCOME

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**Polar with Nonpolar**

Green: Nonpolar

Purple: Polar (-ve)

Yellow: Polar (0)

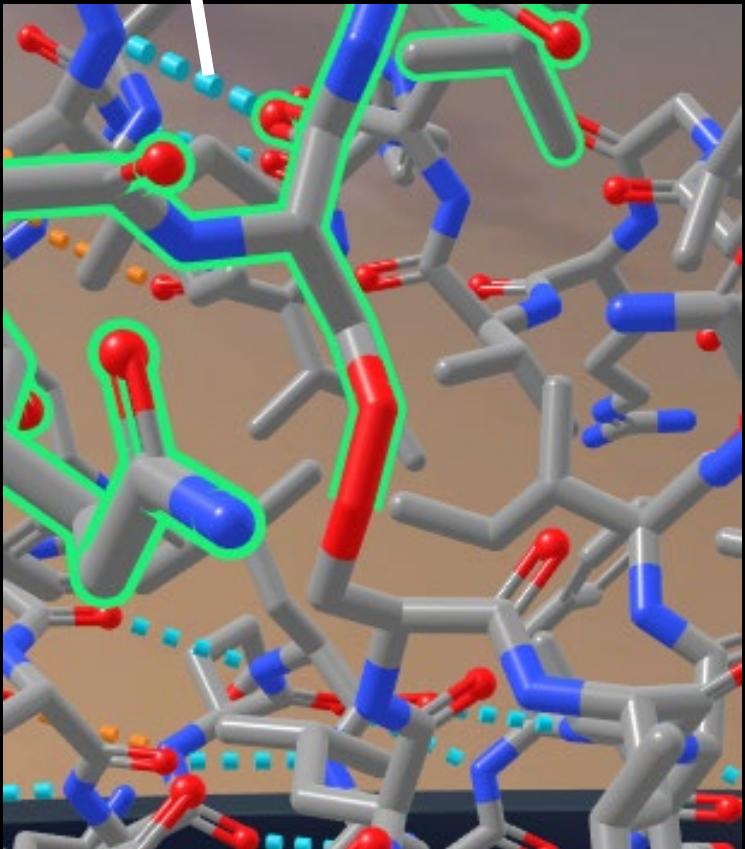
Pink: Polar (+ve)

Residue	Mutation	H-bond	Clashing	Changes in Secondary Structure
Serine 5 (S5)	S5D	+2	same	antiparallel
	S5N	+2	less	antiparallel
Isoleucine 6 (I6)	I6C	+5	same	antiparallel
	I6Q	+3	same	antiparallel
	I6S	+4	same	antiparallel
	I6R	+3	same	antiparallel
	I6H	+4	less	antiparallel
Phenylalanine 9 (F9)	F9S	+6	less	antiparallel
	F9R	+5	less	antiparallel
	F9K	+5	less	antiparallel
Lysine 11 (K11)	K11L	+2	less	antiparallel
	K11I	+3	less	antiparallel
	K11M	+1	same	parallel
	K11W	+4	less	antiparallel
	K11F	+2	less	antiparallel
Leucine 13 (L13)	K11Y	+1	less	Antiparallel
	K11R	+2	less	antiparallel
Proline 14 (P14)	L13N	+2	same	antiparallel
	P14T	+3	same	antiparallel

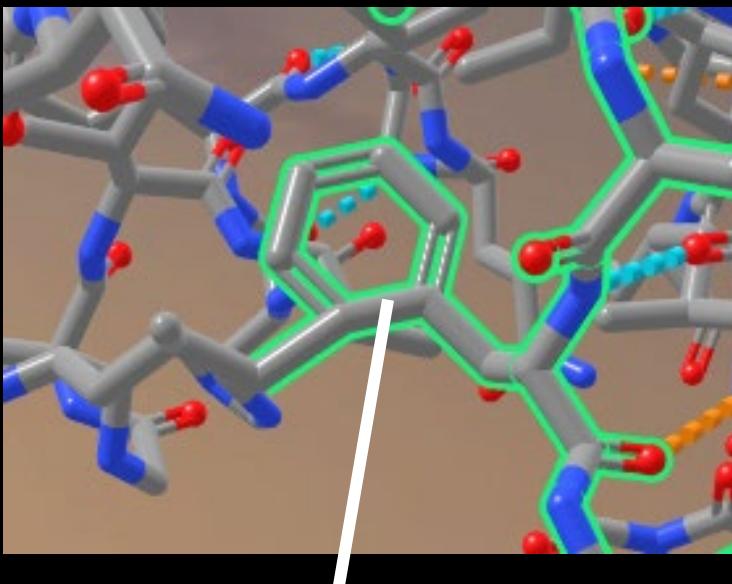
**Nonpolar with Polar**

## Hydrogen bonds

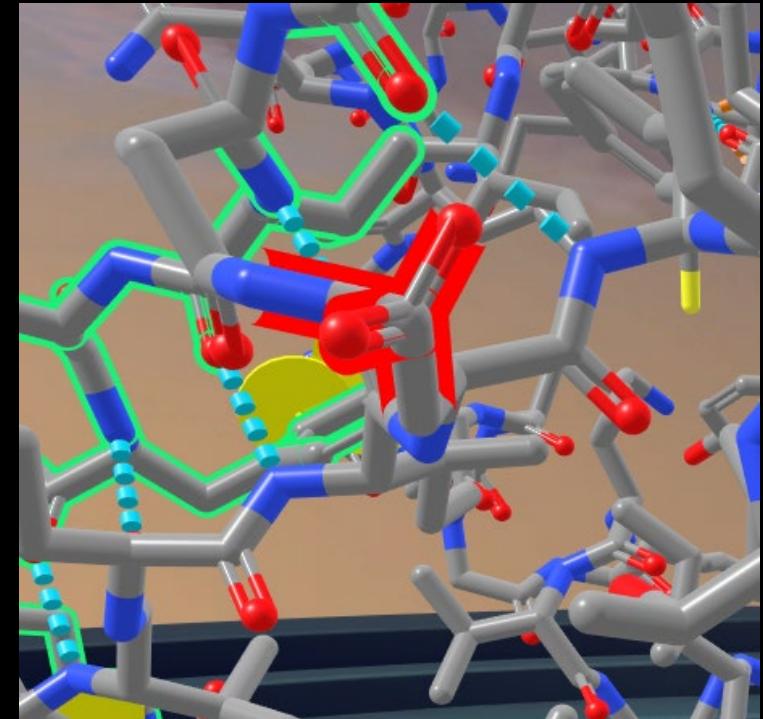
- Blue: Precise ("normal")
- Red: Relaxed (loose requirements)
- 3.50 Angstrom standard

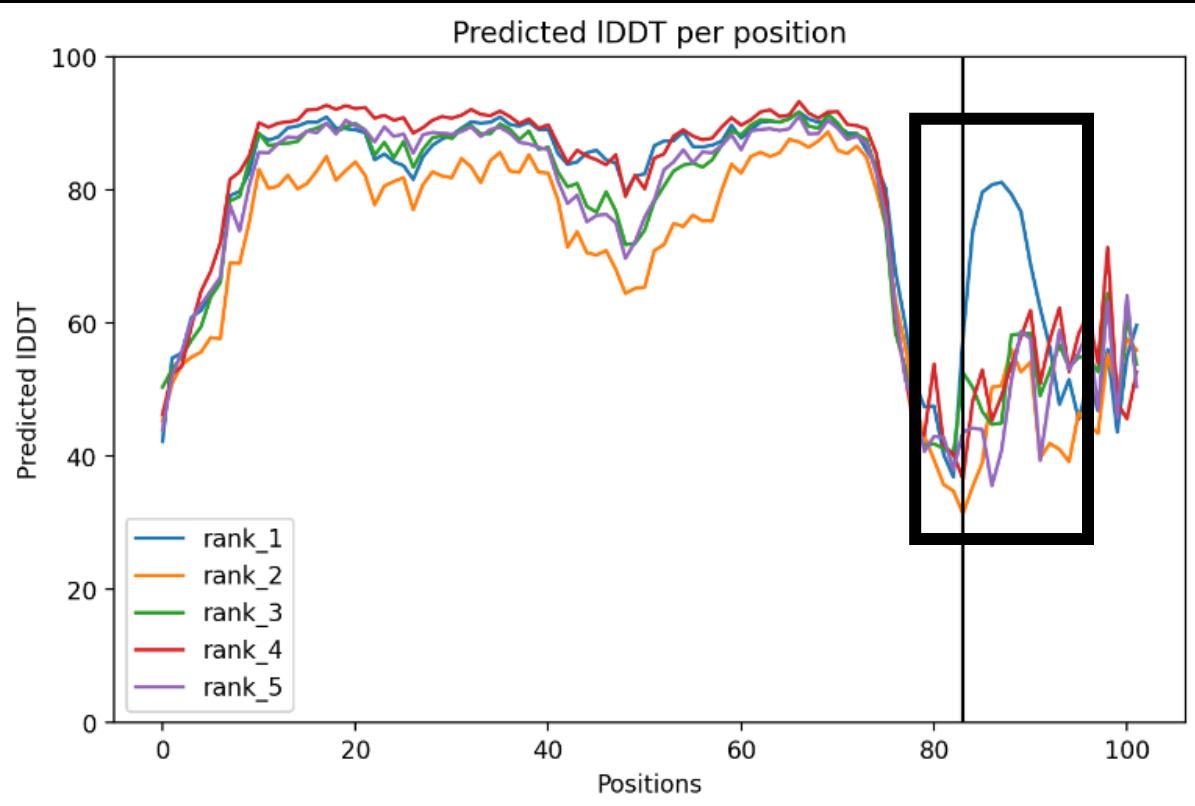


More hydrogen bonds, less clashes!



Helix bundle, cyclohexane

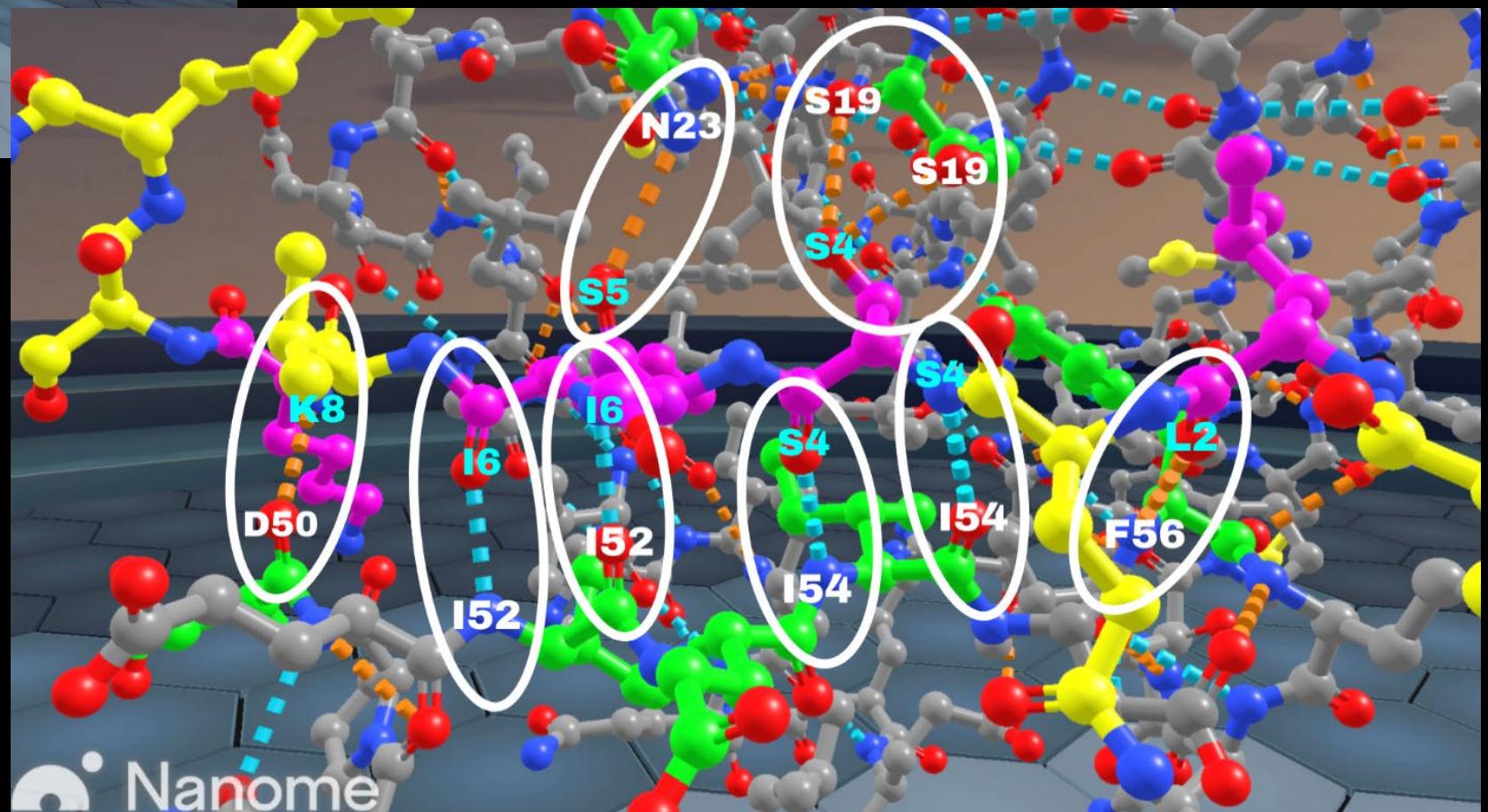
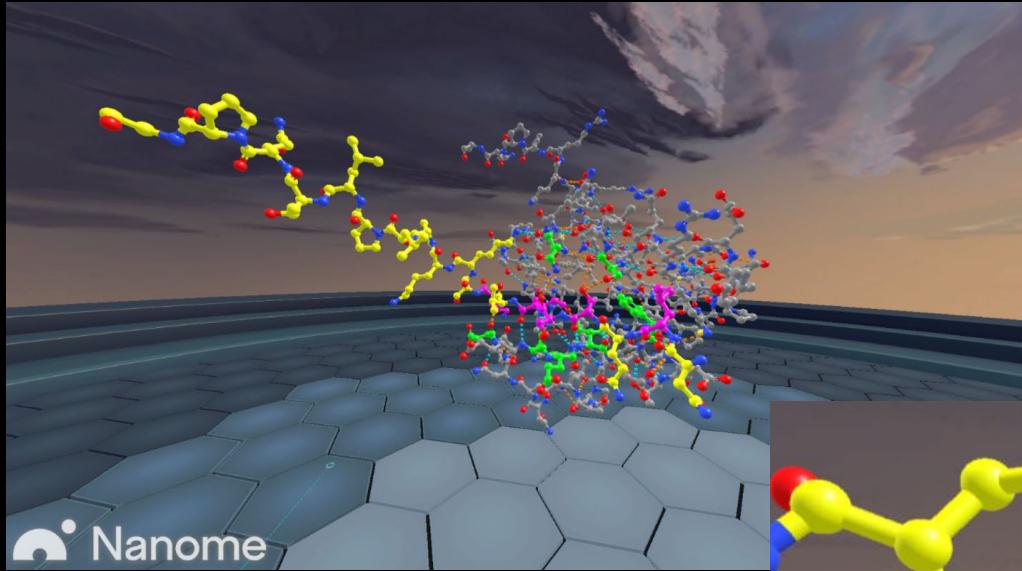




# CONCLUSION

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- As many as six additional hydrogen bonds with fewer clashes.



# ACKNOWLEDGEMENTS



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- Assistant Professor



- Singh Bhumika
- Graduate Student



- Reza Esmaeeli
- Graduate Student

# THE SOURCES

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- [1] Z. Liu et al., "Drug Discovery Targeting Bromodomain-Containing Protein 4," *Journal of Medicinal Chemistry*, vol. 60, no. 11, pp. 4533–4558, Mar. 2017, doi: <https://doi.org/10.1021/acs.jmedchem.6b01761>.
- [2] A. D. Cunningham, N. Qvit, and D. Mochly-Rosen, "Peptides and peptidomimetics as regulators of protein–protein interactions," *Current Opinion in Structural Biology*, vol. 44, pp. 59–66, Jun. 2017, doi: <https://doi.org/10.1016/j.sbi.2016.12.009>.
- [3] B. O. Villoutreix, C. M. Labbé, D. Lagorce, Guillaume Laconde, and O. Sperandio, "A Leap into the Chemical Space of Protein-Protein Interaction Inhibitors," *Current Pharmaceutical Design*, vol. 18, no. 30, pp. 4648–4667, Sep. 2012, doi: <https://doi.org/10.2174/138161212802651571>.
- [4] L. Wang et al., "Therapeutic peptides: current applications and future directions," *Signal Transduction and Targeted Therapy*, vol. 7, no. 1, p. 48, Feb. 2022, doi: <https://doi.org/10.1038/s41392-022-00904-4>.
- [5] T. Kanno et al., "BRD4 assists elongation of both coding and enhancer RNAs by interacting with acetylated histones," vol. 21, no. 12, pp. 1047–1057, Dec. 2014, doi: <https://doi.org/10.1038/nsmb.2912>.
- [6] G. Stuber et al., "HHV-8 encoded LANA-1 alters the higher organization of the cell nucleus," vol. 6, no. 1, Apr. 2007, doi: <https://doi.org/10.1186/1476-4598-6-28>.
- [7] B. N. Devaiah et al., "BRD4 is a histone acetyltransferase that evicts nucleosomes from chromatin," *Nature Structural & Molecular Biology*, vol. 23, no. 6, pp. 540–548, May 2016, doi: <https://doi.org/10.1038/nsmb.3228>.
- [8] D. L. Nelson, A. L. Lehninger, and M. M. Cox, *Lehninger Principles of Biochemistry*, 8th ed. Macmillan Higher Education: Basingstoke, 2021.
- [9] J. Jumper et al., "Highly accurate protein structure prediction with AlphaFold," *Nature*, vol. 596, no. 7873, pp. 583–589, Jul. 2021.
- [10] A. Krushtafoych, T. Schwede, M. Topf, K. Fidelis, and J. Moult, "Critical assessment of methods of protein structure prediction (CASP)–Round XIII," *Proteins: Structure, Function, and Bioinformatics*, vol. 87, no. 12, pp. 1011–1020, Oct. 2019, doi: <https://doi.org/10.1002/prot.25823>.
- [11] R. P. D. Bank, "RCSB PDB - 2ND0: Solution NMR structures of BRD4 ET domain with LANA peptide," [www.rcsb.org](http://www.rcsb.org). <https://www.rcsb.org/structure/2ND0> (accessed Jul. 12, 2023).
- [12] "Research | Oculus," [www.oculus.com](http://www.oculus.com). <https://www.oculus.com/research/>
- [13] K. Funakawa, "New Harvard study shows the efficacy of Nanome & VR for Chemistry Education," *Medium*, Jan. 13, 2021. <https://blog.matryx.ai/new-harvard-study-shows-the-efficacy-of-nanome-vr-for-chemistry-education-cb45da304ea2> (accessed Jul. 12, 2023).
- [14] Q. Zhang et al., "Structural Mechanism of Transcriptional Regulator NSD3 Recognition by the ET Domain of BRD4," vol. 24, no. 7, pp. 1201–1208, Jul. 2016, doi: <https://doi.org/10.1016/j.str.2016.04.019>.

# THANK YOU

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