Combining Artificial Intelligence and Virtual Reality to design new peptides inhibiting the ET domain of BRD4

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Introduction

- Bromodomain containing 4 (BRD4) is a viral protein [1] that can protect tumor cells and express both cancerous and non-cancerous diseases.
- When bound to the latency-associated nuclear antigen (LANA-1), LANA can inhibit BRD4's harmful functions [2].
- This study applies various mutations to LANA's interacting residues [3].

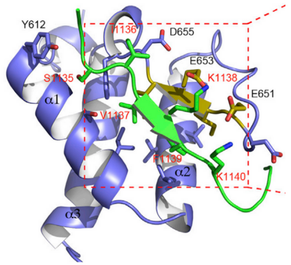

Figure 1 BRD4 with LANA Peptide [3].

- It uses artificial intelligence 3D protein predictor AlphaFold2 (AF2) [4] and virtual reality (VR) hardware Nanome [5] to build a novel peptide with stronger BRD4 interactions and a longer inhibition.

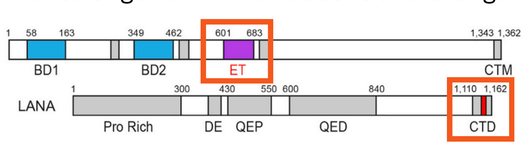

Figure 2 BRD4 Domain Organization with LANA Domain Organization [3]

Methodology

- AlphaFold2 (Google ColabFold) predicted 3D structures using BRD4-LANA experimental structure (PDB ID 2ND0) as a template.
- Single-point mutations were done on this output in Nanome using the Oculus Meta Quest 2.
- Phase 1 data collection focused on hydrogen bonding, steric clashing, and favored rotations.
- AF2 predicted the structures of the mutated peptides.
- In Phase 2, changes in hydrogen bonds and clashes were verified using Nanome.

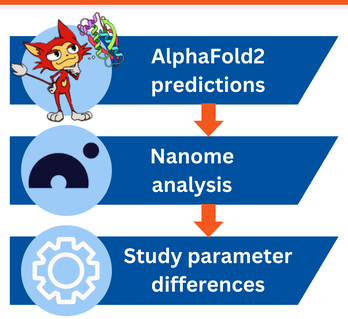

Figure 3 Simplified Methodology Flow Chart.

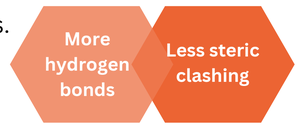

Figure 4 Parameters being measured, and the **desired** outcomes.

Results

Table 1 List of Successful Mutations Performed on LANA Peptide
Alanine (A), Valine (V), Leucine (L), Glycine (G), Isoleucine (I), Methionine (M), Tryptophan (W), Cysteine (C), Proline (P), Phenylalanine (F), Aspartic Acid (D), Glutamic Acid (E), Tyrosine (T), Asparagine (N), Glutamine (Q), Serine (S), Threonine (T), Arginine (R), Lysine (K), Histidine (H)..

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
	K11Y	+1	less	antiparallel
	K11R	+2	less	antiparallel
Leucine 13 (L13)	L13N	+2	same	antiparallel
Proline 14 (P14)	P14T	+3	same	antiparallel

- Hydrogen bonding increased by six additional bonds with fewer clashes (F9S).
- Residue mutations that weren't displayed in Table 1 had either more clashes or an pLDDT score of less than 75.

Green: Nonpolar	Yellow: Polar (0)
Orange: Polar (-ve)	Pink: Polar (+ve)

pLDDT Scores

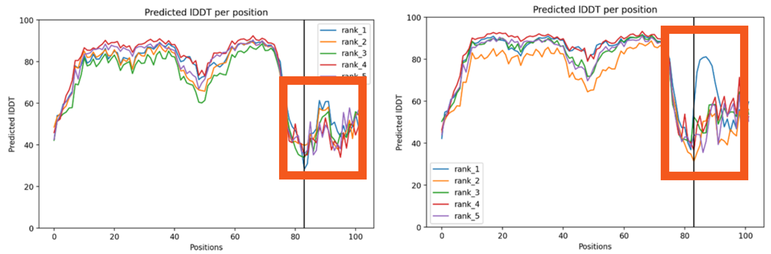

Figure 5 pLDDTScores for the Native BRD4-LANA (PDB ID 2ND0) and mutated F9S complex, respectively.

Nanome Visualization

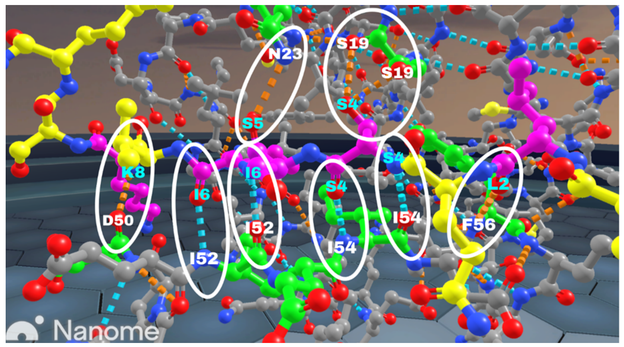

Figure 6 Phenylalanine 9 (F9) Mutated with Serine (F9S). Hydrogen bonds between the peptide (blue text) and protein (white text) residues are represented by the blue and red dotted lines. The yellow structure is the mutated peptide, and the grey structure is the protein BRD4. The interacting residues of the peptide are highlighted in pink, while the interacting residues of the protein are in green.

Conclusion and Dicussion

A maximum of six additional H-bonds with fewer clashes (F9S).

- Residue mutations that weren't displayed in Table 1 either had more clashes or an pLDDT score of less than 75.
- Residues are more likely to interact if:
- Surrounded by other residues of the same polarity, such as R and K (polar) for F9 (nonpolar).
- Close to other positive, negative, or neutral residues that have an opposite charge of the mutation, such as R (polar positive) for I6 (polar neutral).
- More hydrogen bonds and less clashing leads this novel peptide to potentially have a stronger interaction with BRD4, inhibiting it for longer and decreasing the likelihood of disease—myeloid leukemia and HIV—development.

References

[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.
[2] G. Stuber et al., "HHV-8 encoded LANA-1 alters the higher organization of the cell nucleus," vol. 6, no. 1, Apr. 2007.
[3] 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.
[4] J. Jumper et al., "Highly accurate protein structure prediction with AlphaFold," Nature, vol. 596, no. 7873, pp. 583–589, Jul. 2021.
[5] K. Funakawa, "New Harvard study shows the efficacy of Nanome & VR for Chemistry Education," Medium, Jan. 13, 2021.