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Predicting Mimotopes of Amyloid beta ($A\beta_{42}$) from Non-Coding DNA as candidates for Synthetic Peptide Vaccine Design against Alzheimer's Disease

Navya Raj[1*], Shidhi P R[2], Deepthi Varughese[3], Achuthsankar Nair[2], Pawan Dhar[4]

[1]Department of Health Informatics, College of Health Sciences, Saudi Electronic University, Dammam, Kingdom of Saudi Arabia.
[2]University of Kerala, India; [3]Mahatma Gandhi University Campus, India; [4]Jawaharlal Nehru University, New Delhi, India.

*Presenting Author

INTRODUCTION & AIM

Until recently, the non-coding junk regions of the genome were poorly studied when compared to the functional coding regions. Six proteins (named *Eka*, meaning 'first' in Sanskrit) originating from the not-coding regions of the bacterial genome were artificially expressed, and their phenotypic implications were studied experimentally[1].

In this study, we hypothesized that the intergenic space of a genome could be a key resource for the design of novel synthetic biomolecules with therapeutic implications, which we refer to as our *Project Synthetic Proteome (PSP)* dataset.

With a handful of novel peptides which we refer to as *Synpeps*, predicted from not-coding regions, our interest was to computationally analyze the antigenic role of the peptides and identify the best possible candidates with applications in epitope-based vaccine design.

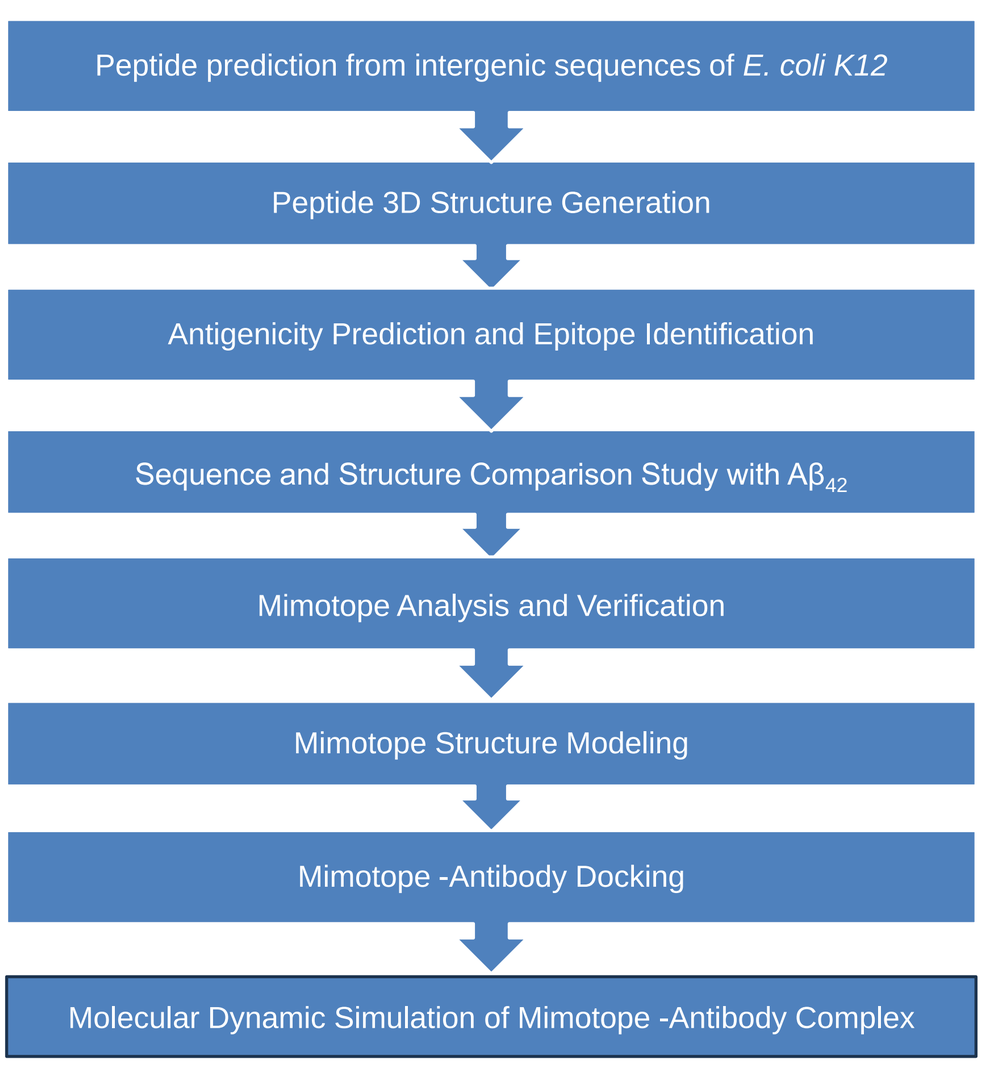
We used Alzheimer's Disease (AD) as an example use case to analyze the scope of identifying mimotopes (a peptide that mimics the structure of an epitope) with application in Amyloid beta$_{42}$ ($A\beta_{42}$) immunotherapy[2].

AIM: This research aims to identify the potential mimotopes of the $A\beta_{42}$ peptide, from the not-coding DNA-derived peptides as candidates for Alzheimer's immunotherapy.

METHOD

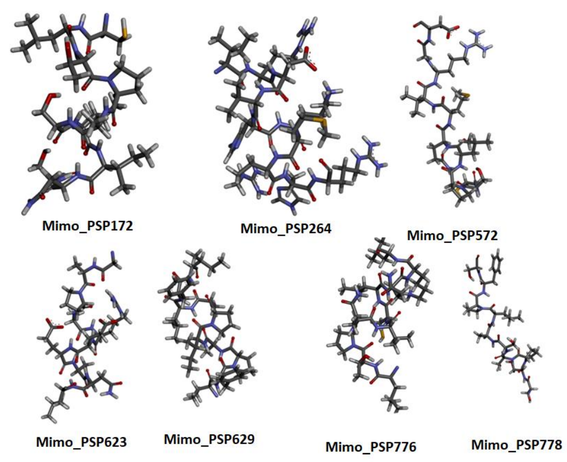
Translation of not-coding DNA to generate novel peptides. → *Project Synthetic Proteome (PSP)* multi-parametric library construction → Identification of antigenic peptides with epitopes structurally similar to $A\beta_{42}$ epitope → Potential mimotopes of $A\beta_{42}$ for Alzheimer's Disease Immunotherapy

Overview of the methodology identifying mimotopes applicable in Amyloid-beta immunotherapy for Alzheimer's disease.



RESULTS & DISCUSSION

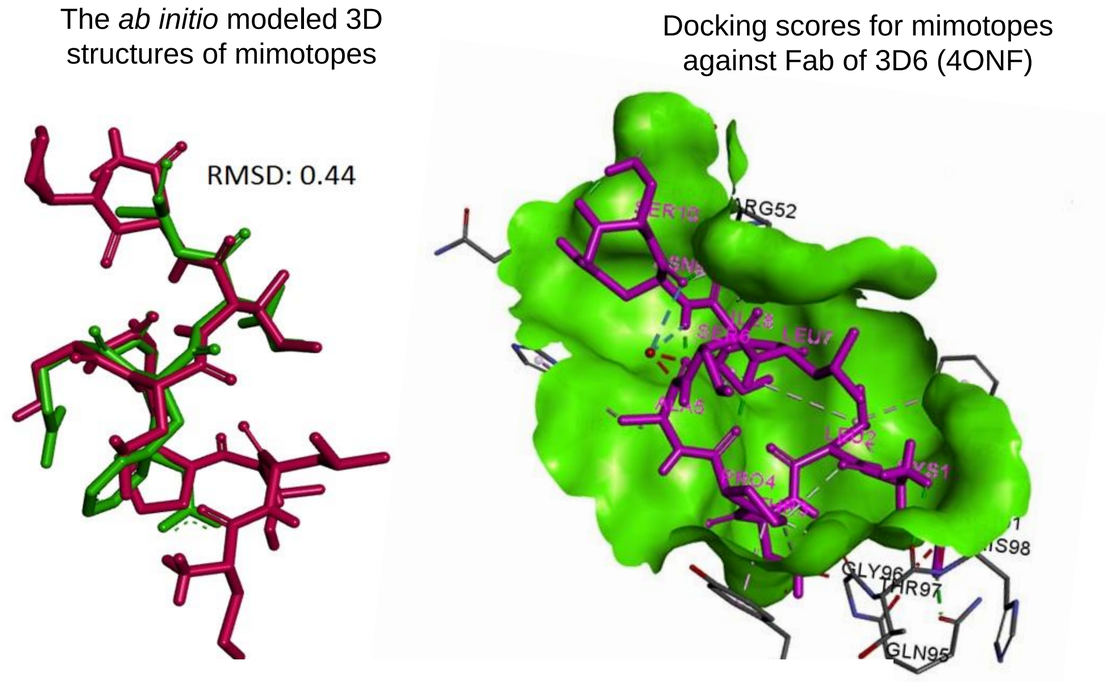
This study is the first of its kind to propose the non-coding regions of a genome as the potential source of therapeutic biomolecules.

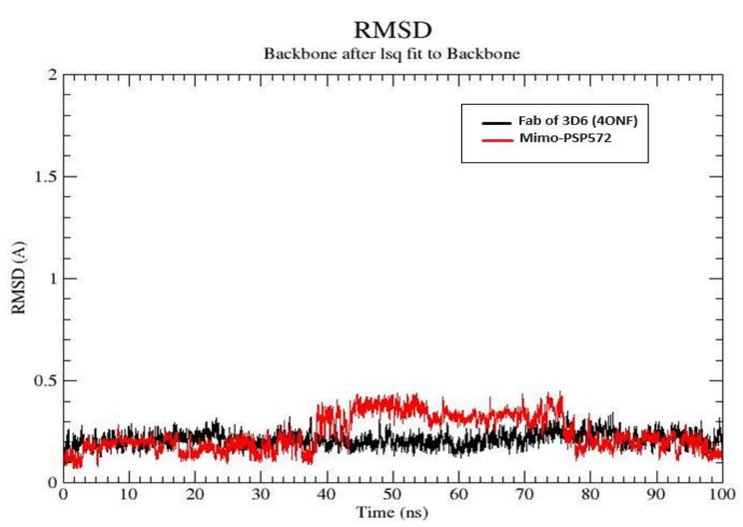


The *ab initio* modeled 3D structures of mimotopes

Ligands	ZDOCK score	ZRANK score	Global energy (FireDock)	No. of favorable interactions
Aβ epitope	11.52	-86.231	-53.72	18 (Salt Bridge: Arg5: L:Asp31)
Mimo_PSP172	9.16	-78.299	-58.7	19
Mimo_PSP264	8.44	-49.119	-35.12	30 (Salt Bridge: Arg8:L: Asp31)
Mimo_PSP572	7.42	-92.014	-43.11	26 (Salt Bridge: Cys1:L: Asp31)
Mimo_PSP623	9.8	-71.723	-57.58	20 (Salt Bridge: Arg5 :L: Asp31)
Mimo_PSP629	9.84	-86.392	-56.10	14
Mimo_PSP776	10.14	-64.491	-51.60	16
Mimo_PSP778	8.36	-79.553	-58.81	12

Docking scores for mimotopes against Fab of 3D6 (4ONF)





RMSD plot of mimo_PSP572 -Fab complex (red) in comparison with Fab (4ONF)(black) during MD simulation.

CONCLUSION

We present an immunoinformatics approach to fine-tune an apparently useless portion of DNA into a valuable therapeutic molecule. Tapping the hidden potential of the less explored landscapes of the genome towards therapeutic endpoints offers interesting, therapeutically viable biomolecules.

FUTURE WORK / REFERENCES

Further experimentation is necessary to validate the mimotope-antibody affinity *in vitro* and *in vivo*.

1. Dhar PK, Thwin CS, Tun K, Tsumoto Y, Maurer-Stroh S, Eisenhaber F, Surana U. Synthesizing non-natural parts from natural genomic template. J Biol Eng. 2009 Feb 3;3:2. doi: 10.1186/1754-1611-3-2. PMID: 19187561; PMCID: PMC2642765.

2. Ghochikyan A. Rationale for Peptide and DNA based Epitope Vaccines for Alzheimer's Disease Immunotherapy.CNS Neurol. Disord. Drug Targets. 2009;8(2):128.