

Computational Design of Peptide Recognition Elements for Rapid Detection of Neurotoxin Exposure

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Summary:

This project aims to identify neurotoxic exposure to organophosphate compounds by developing peptides that bind to acetylcholinesterase (AChE). Peptides were generated using the In-Silico Protein Synthesizer (InSiPS) platform to bind human acetylcholinesterase. Peptide interaction with native and inhibited enzyme structures was modeled using molecular docking to predict interaction affinities and binding confirmations. The best peptides demonstrated confirmation-dependent interaction patterns, which will be used for laboratory validation and future field-deployable chemical detection applications.

Keywords: peptide, acetylcholinesterase, molecular recognition elements, chemical hazards, field-deployable

Background, Motivation and Objective

Rapid identification of exposure to chemical hazards, including organophosphate compounds, remains an important challenge in chemical threat defense and emergency response. Acetylcholinesterase (AChE) is a relevant target in this context because inhibition of the enzyme is closely associated with toxic exposure [1]. Synthetic peptides offer a flexible and scalable route for developing recognition elements that may be adapted for a future chemical exposure detection platform. Additionally, peptides are more suitable for cold-chain independent deployment when compared to standard molecular affirmers available. In this study, peptides were generated using the In-Silico Protein Synthesizer (InSiPS) platform [2] to bind AChE and were further evaluated using comparative docking analysis.

Description of the New Method or System

A panel of AChE-binding peptides was generated through the InSiPS workflow for downstream structural and experimental evaluation. InSiPS was used to identify peptide candidates targeting human AChE based on sequence-level recognition features, while accounting for off-target binding. This generated peptide panel formed the basis for subsequent structural assessment and future laboratory testing. To further evaluate peptide-AChE interactions, the candidates were subjected to preliminary

HADDOCK docking [3] against selected native and inhibited human AChE structures. Docking was used to visualize likely peptide binding conformations in a three-dimensional space and compare predicted interaction behavior between enzyme states. This workflow combines sequence-based peptide generation with structure-based evaluation of peptide interactions with native and inhibited AChE, providing additional context for upcoming experimental validation (Fig. 1).

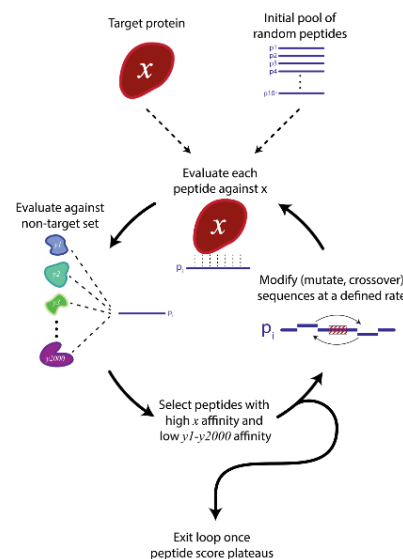


Fig. 1. Schematic overview of the InSiPS workflow used to generate candidate acetylcholinesterase-

binding peptides for downstream docking analysis and experimental validation [4]

Results

Representative docking analysis of peptide P8 against native and inhibited human AChE provided a three-dimensional view of likely peptide binding regions on the enzyme surface. Comparative visualization suggested that peptide positioning and surface contacts differed between the two AChE conformations. P8 also showed a more favorable mean HADDOCK docking score for the inhibited structure than the native structure, supporting its use as a representative example of conformation-dependent docking behavior.

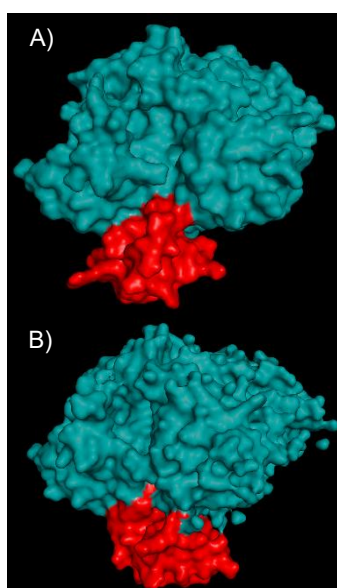


Fig. 2. Representative docking of peptide P8 against human acetylcholinesterase. (A) Docking pose of P8 with native AChE. (B) Docking pose of P8 with inhibited AChE. The models illustrate likely peptide binding regions in three-dimensional space.

Comparative mean docking scores showed mixed interaction behavior across the peptide panel. Five peptides (P8, P1, P10, P2, and P7) had more favorable mean docking scores for inhibited AChE than for native AChE, while five (P5, P6, P3, P9, and P4) showed the opposite trend. The strongest shift toward inhibited AChE was observed for P8 ($\Delta = -2.336$), followed by P1 ($\Delta = -2.141$) and P10 ($\Delta = -1.801$). In contrast, P4 showed the largest shift toward native AChE ($\Delta = +7.802$), followed by P9 ($\Delta = +4.053$). These preliminary docking results indicate that peptide-AChE interactions vary across enzyme conformations and provide initial observation of peptide affinity ahead of laboratory validation of the full peptide set.

Tab. 1: Comparative mean HADDOCK docking scores of top 5, AChE-binding peptides against native and inhibited human AChE. Negative Δ values

indicate more favorable docking to inhibited AChE, whereas positive Δ values indicate more favorable docking to native AChE.

Peptide name	Native mean	Inhibited mean	Δ
P8	-16.447	-18.783	-2.336
P1	-15.376	-17.517	-2.141
P10	-11.473	-13.274	-1.801
P2	-23.461	-24.640	-1.179
P7	-12.096	-12.361	-0.265
P5	-23.081	-22.789	+0.292
P6	-16.340	-14.824	+1.516
P3	-19.927	-17.650	+2.277
P9	-25.972	-21.919	+4.053
P4	-32.514	-24.712	+7.802

Conclusions

These preliminary docking results provide structural context for AChE-binding peptides and support ongoing laboratory validation toward future field-deployable detection of chemical hazard exposure.

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