

Exploiting The Cryptic Hydrophobic Pocket In ApoE4 To Suppress Neurotoxic Aggregation

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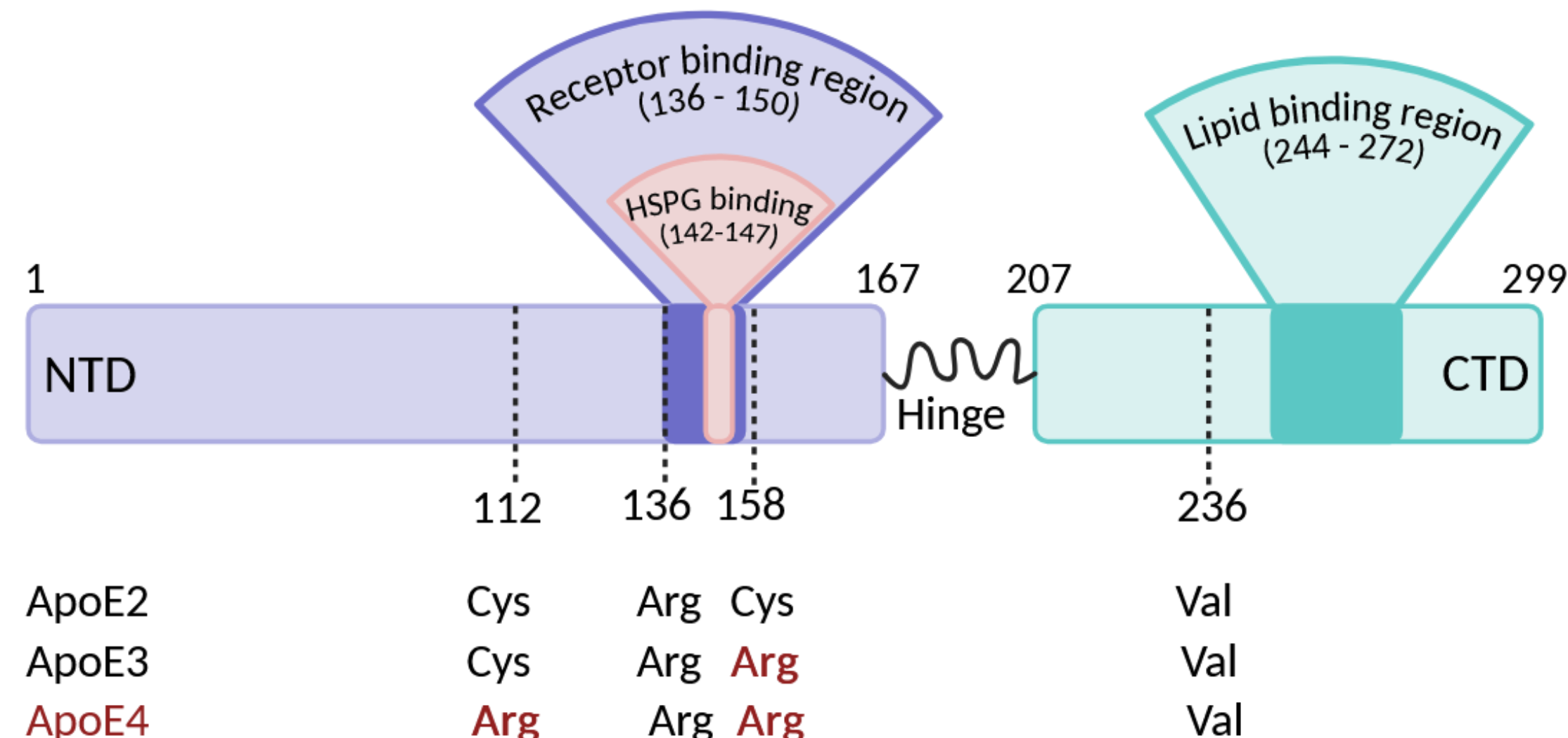
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INTRODUCTION

ApoE is a glycoprotein responsible for lipid and cholesterol transport in the brain



ApoE4 is the strongest and most prevalent genetic risk factor for Sporadic Alzheimer's disease

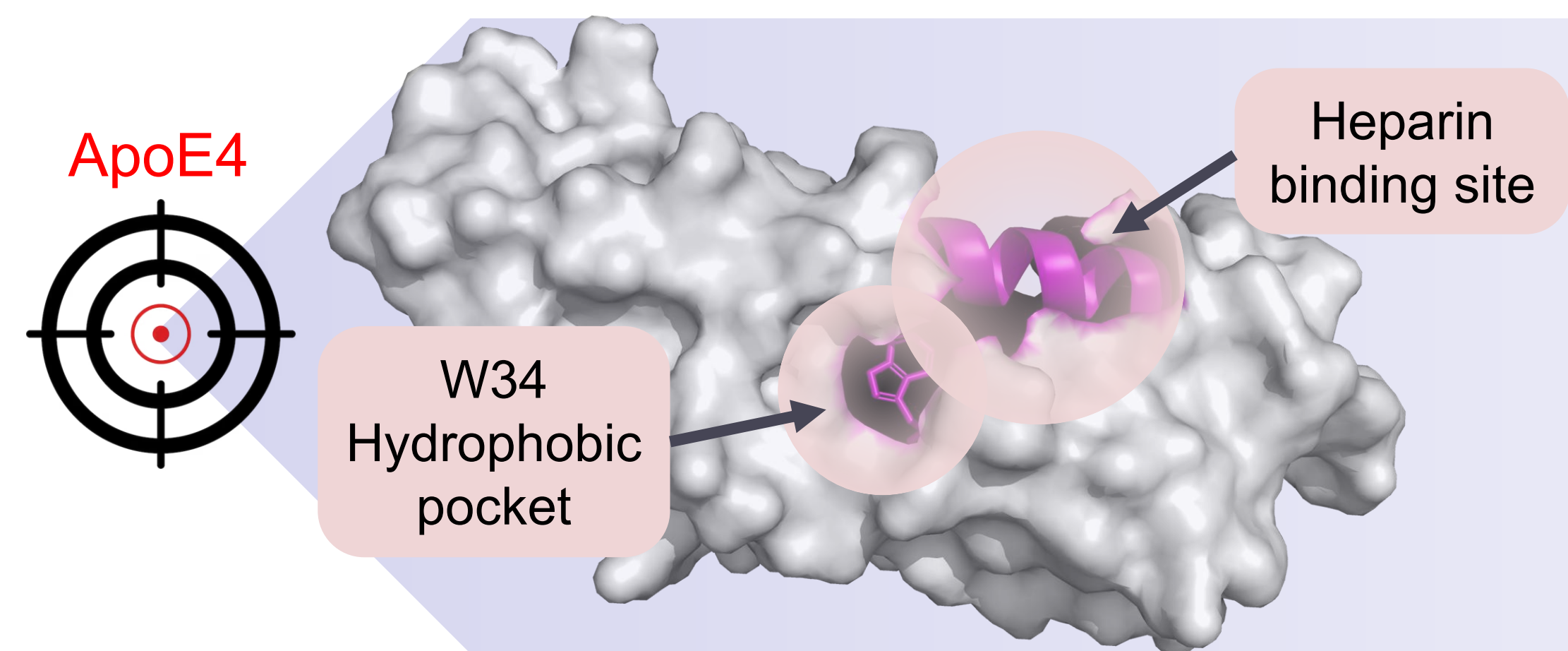
MOTIVATION & OBJECTIVES

- ApoE4 exhibits pathological aggregation and promotes amyloid- β plaque formation¹
- The complexity of ApoE biology makes the development of targeted therapies challenging

Establish a screening pipeline for the identification and biophysical validation of FDA-approved small molecules that inhibit ApoE4 aggregation

METHODOLOGY

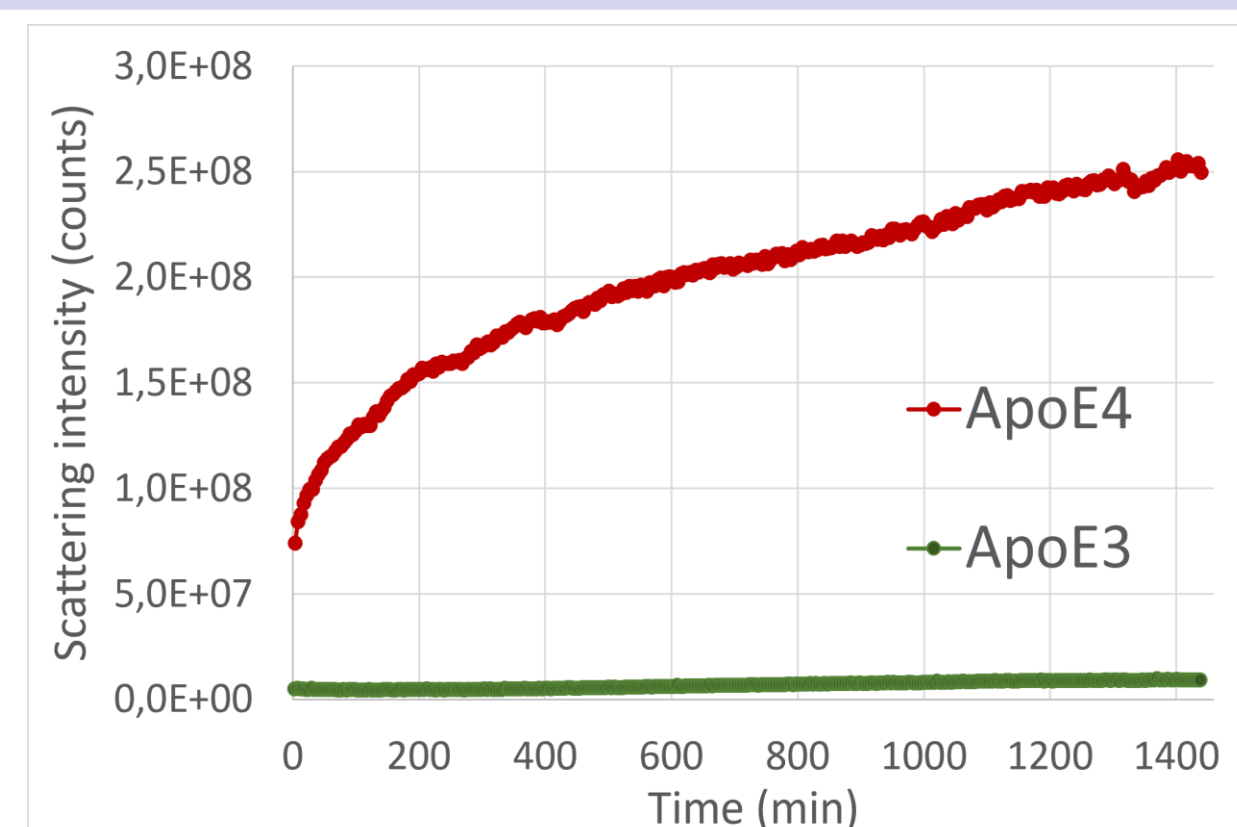
I. Screening of FDA-approved drugs from the ZINC database and blind docking against ApoE4 (PDB: 6NCO)²



II. Tryptophan fluorescence – binding affinity determination

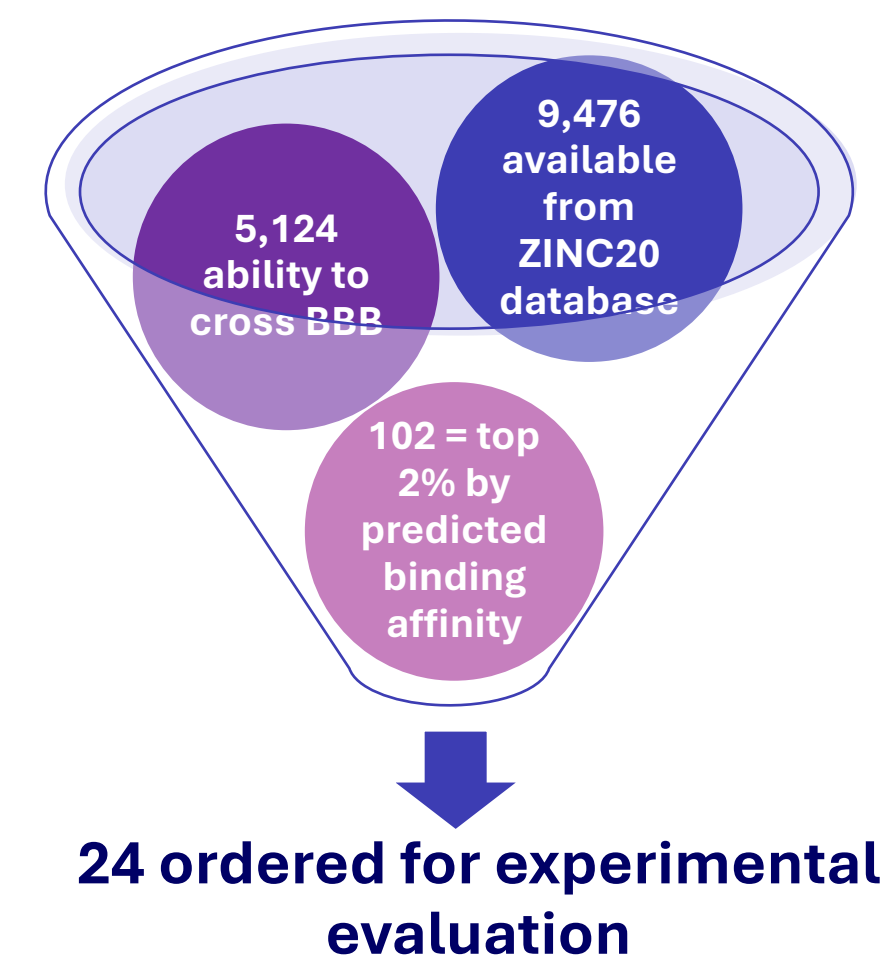
III. Static light scattering – aggregation process monitoring

Differences in ApoE3 and ApoE4 aggregation levels at 37 °C

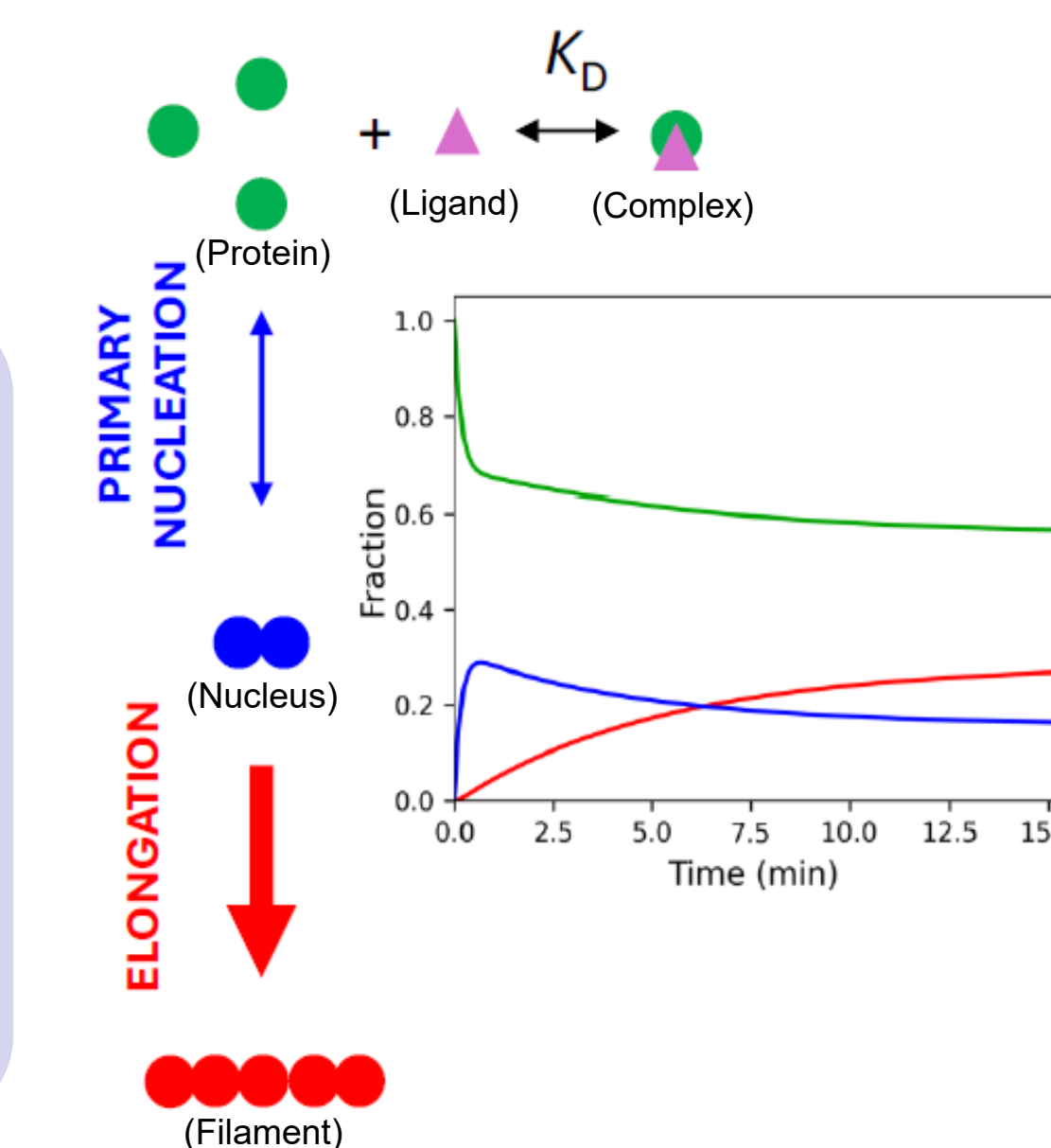


RESULTS

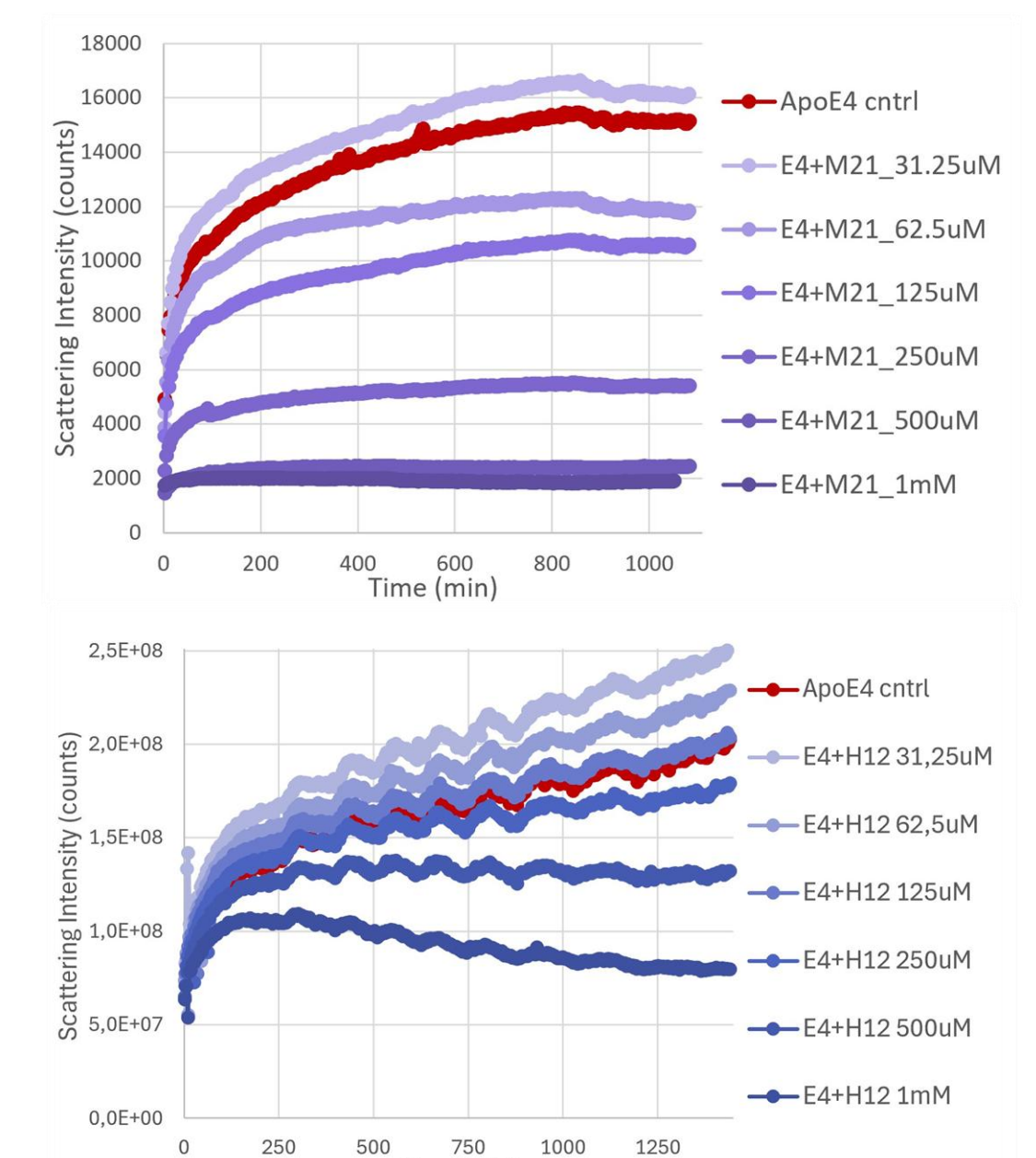
I. Most of the promising candidates were FDA-approved antibiotics, some were drugs used to treat breast cancer and multiple sclerosis



II. The mechanism of ApoE aggregation comprises fragile nucleus formation and nucleation elongation



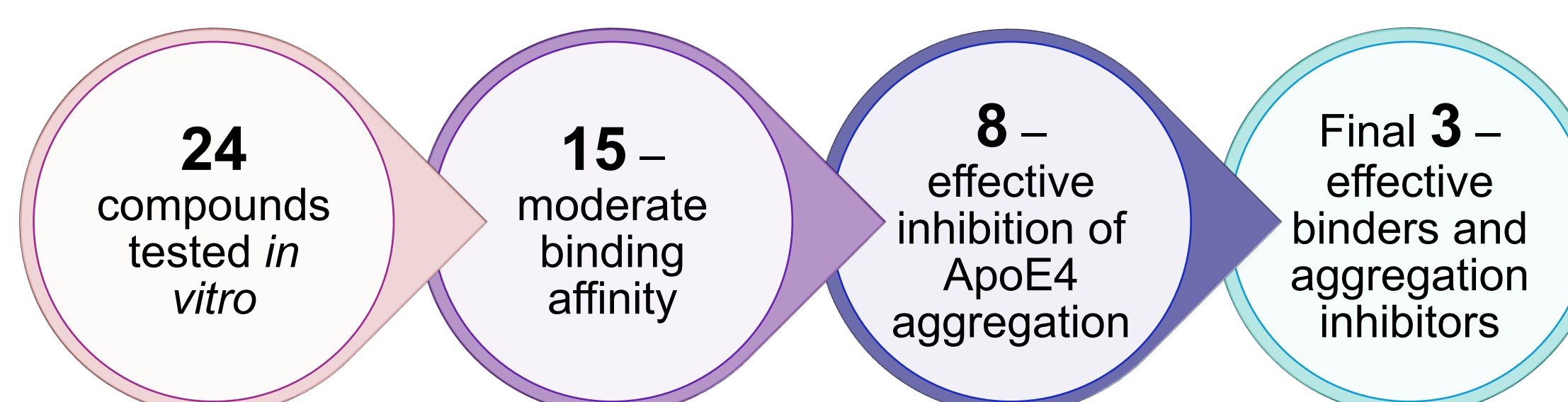
III. Total of 8 compounds showed anti-aggregation properties



We have established a pipeline for screening FDA-approved drug compounds targeting neurotoxic aggregation of ApoE4 protein, which is the strongest known genetic risk factor for late-onset Alzheimer's disease

CONCLUSIONS

- In this study, we have established a pipeline to identify small molecules targeting the hydrophobic pocket of ApoE4, combining a blind docking approach with experimental evaluation of the binding affinity and anti-aggregation properties
- Repurposing FDA-approved drugs represents a promising approach to finding new candidates for Alzheimer's treatments



ACKNOWLEDGMENTS & REFERENCES

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- Nemergut, M. et al., **Mol. Neurodegener.** 2023, **18**, 38.

