



AI-DRIVEN DESIGN OF β -SECRETASE 1 INHIBITORS

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INTRODUCTION



EVERY 12 SECONDS, SOMEONE IN THE WORLD IS DIAGNOSED WITH DEMENTIA

Alzheimer's disease and other dementias have become the **7th leading cause of death worldwide**. With a 181% rise in the global mortality rate between 2000 and 2019, and with population aging occurring at an unprecedentedly fast pace, **dementia is expected to become the predominant factor of disability and dependency** [1].

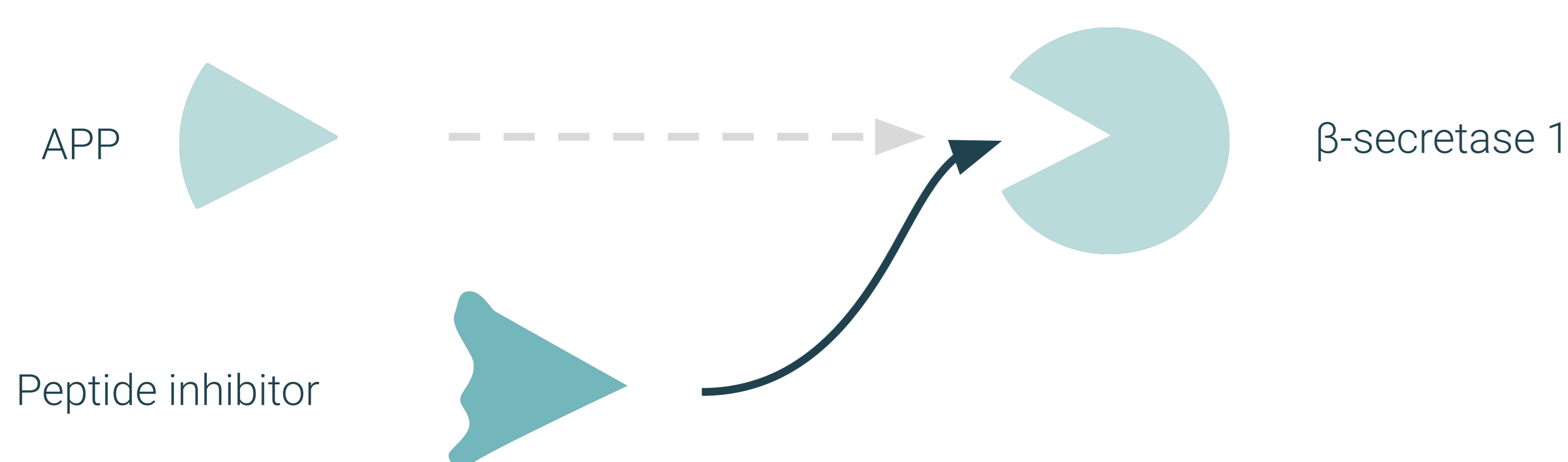
ESTIMATED NUMBER OF PEOPLE WITH DEMENTIA

55 M | **139 M**
2019 | 2050

Disrupting the Amyloid-beta precursor protein (APP) processing pathway has been proven to be a viable way of tackling Alzheimer's [2]. However, **designing drugs** that can cross the blood-brain barrier (BBB) and act upon a specific mechanism in the brain **is a challenging endeavor**, encompassing lead identification, optimization, and experimental validation, **requiring a substantial amount of effort with success rates as low as 1%** [3].

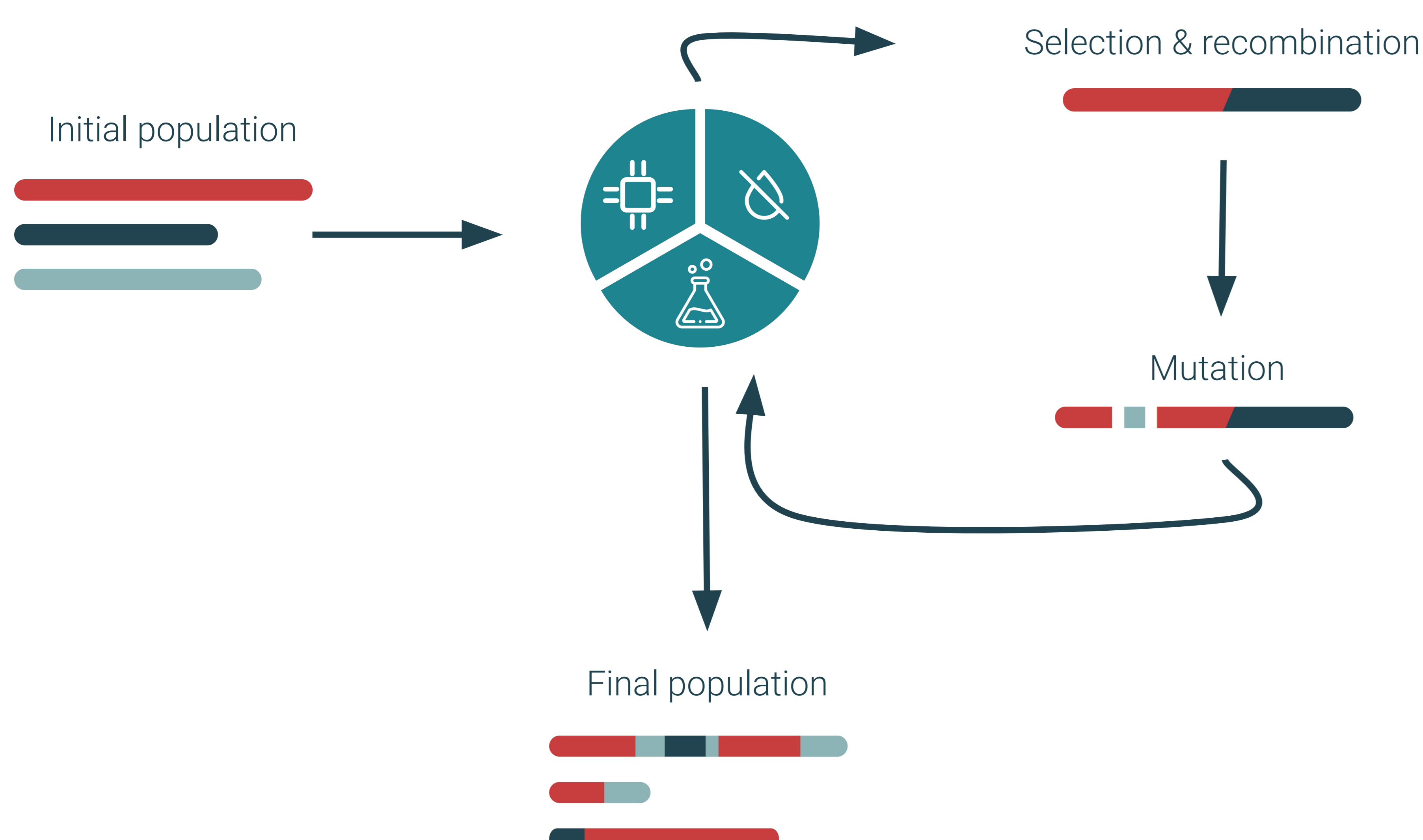
METHODOLOGY

Due to the established capability of **artificial intelligence (AI)** to efficiently search through extensive chemical spaces [4], we used it in this study **to rapidly identify lead compounds with a high probability of inhibiting β -secretase 1 enzyme**.



We utilized **NSGA-II genetic algorithm** as a backbone of our AI system [5], **guided by the following criteria:**

- Binding affinity of a peptide towards β -secretase 1**
- ML-estimated probability of a peptide crossing the BBB** [6]
- Wildman-Crippen logP value indicating peptide's lipophilicity**



RESULTS



AI-DESIGNED INHIBITORS

Peptide	Binding affinity towards β -secretase 1 [kcal/mol]	Probability of BBB penetration	LogP
WLWWWPF	-9.4	75.4%	6.00
WWWPF	-10.2	72.9%	4.26
GIHAYWT	-7.8	91.7%	-0.98
MHLAFKW	-7.9	89.7%	1.19

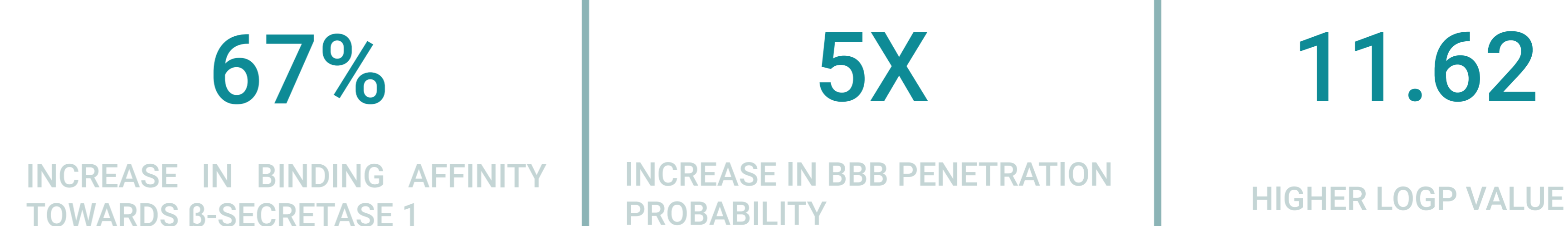


PATENTED INHIBITORS FROM THE LITERATURE

Peptide (source: [7])	Binding affinity towards β -secretase 1 [kcal/mol]	Probability of BBB penetration	LogP
NEESMYCRLLGIGCG	-6.1	14.8%	-7.36
PEESLYCRLLAGCG	-6.3	10.6%	-5.13



COMPARISON OF DESIGNED AND PATENTED INHIBITORS



DISTRIBUTION OF AMINO ACIDS IN THE POPULATION



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