FluxMateria Alzheimer's Amyloid Pathway White Paper

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WHITE PAPER
Alzheimer's Amyloid-Pathway
Candidate Discovery
with FluxMateria
48 strict BACE1-selective hits from 707 candidates. Two independent chemotypes. Root-cause discovery through amyloid-pathway biology.
April 2026 fluxmateria.com

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EXECUTIVE SUMMARY
FluxMateria ran a root-cause Alzheimer's discovery workflow centered on BACE1, an upstream amyloid-pathway
target, rather than symptomatic cholinergic mechanisms. The final strict search enumerated 707 candidates and returned 48 passing molecules under a hard CNS screen.
707
Candidates
enumerated
48
Strict passes
(broad space)
34
Native-space
passes
2
Independent
chemotypes
Top candidate: FM-AD-01, a lanabecestat-derived dual-hydroxymethyl analog with BACE1 pKi 11.09, AChE pKi 6.22, hERG pIC50 4.85, permeability -5.17, and PPB 0.872. The case study contains two independent BACE1-native chemotypes: lanabecestat-like and verubecestat-like.

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THE CHALLENGE

Alzheimer's discovery programs often blur two very different goals: symptomatic control and disease-modifying intervention.

The Problem

A search framed loosely around "Alzheimer's" collapses back into cholinergic chemistry. AChE-based symptomatic activity is easier to rediscover than a disease-modifying hypothesis. Most computational screens celebrate AChE hits rather than controlling for them.

FluxMateria's Approach

Frame the search explicitly as amyloid-pathway candidate discovery through BACE1 modulation. Encode AChE as an anti-target to prevent cholinergic drift. Apply hard CNS ADMET gates from the start - not as a post-hoc filter.

Can FluxMateria generate novel BACE1-directed Alzheimer's candidates that preserve CNS feasibility and avoid symptomatic rediscovery?

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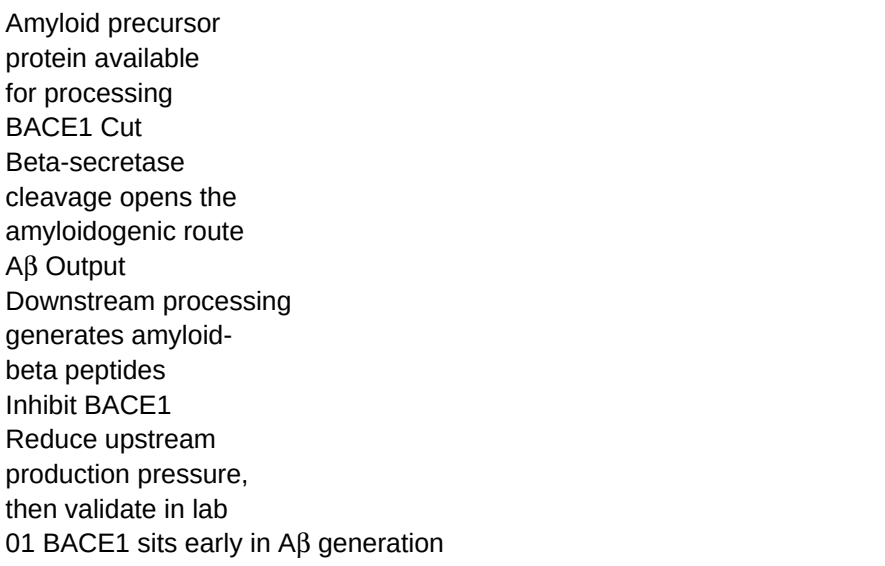
PROPOSED MECHANISM OF ACTION

Upstream amyloid-pathway suppression through BACE1 inhibition - not symptomatic cholinergic boosting.



01 BACE1 sits early in Aβ generation

APP can be processed down an amyloidogenic route in which BACE1 performs the beta-secretase cut - the upstream entry point for amyloid-beta production.

02 After BACE1 cleavage, Aβ peptides follow

Once APP is cut by BACE1, the resulting fragment becomes the substrate for subsequent processing that generates amyloid-beta peptides.

03 These candidates reduce upstream flux

FluxMateria predicts strong BACE1 inhibition while keeping candidates inside a CNS-feasible and early-safety-filtered envelope.

04 Different from symptomatic AChE drugs

AChE inhibitors can temporarily help cognition symptoms, but do not target the same upstream amyloid step. That is why AChE was an anti-target here.

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STUDY DESIGN

The Exact FluxMateria Brief

Desired Target

BACE1

Mechanism: inhibitor

Hard gate: pKi >= 6.8

Anti-Targets

AChE pKi <= 7.0 (anti-cholinergic drift)

KCNH2 pKi <= 5.0 (anti-cardiotoxic drift)

Both enforced as hard constraints

CNS ADMET Gates

BBB penetrant = true

PPB <= 0.95 | Permeability >= -6.0

hERG pIC50 <= 5.0 | Hepatotox <= medium

Discovery Scope

Broad: amyloid-oriented BACE1 space

Native-only: BACE1-native scaffold confirm

Max enumeration: 1,500 | Top results: 25

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EXECUTION WORKFLOW

1 Broad Selective Search

discovery workflow enumerated a broad amyloid-oriented BACE1 discovery space under the strict multi-target brief.

2 Verubecestat-Series Refinement

Focused scaffold sweep validated hydroxymethyl rescue motifs and established a clean verubecestat subseries.

3 Lanabecestat-Series Refinement

Second focused sweep exposed a dual-hydroxymethyl motif that became the top global hit.

4 Production Rerun & Confirmation

Validated motifs fed back into scaffold priorities. Both broad and native-only spaces rerun for confirmation.

Key Insight

The workflow did not just rank molecules. It identified where the discovery bottleneck moved.

By the end of the campaign, the main failure modes were narrow ADMET misses - not lack of BACE1 signal.

That is exactly where a serious triage engine should end up before wet-lab work begins.

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RESULTS OVERVIEW
One amyloid hypothesis. Two scaffold families. Both alive after full gate pressure.
48 / 707
Broad strict passes
Full BACE1 + AChE + KCNH2 + CNS gate
34 / 675
Native-only strict passes
Same top hit survived tighter space
7 / 100
Verubecestat sweep
Hydroxymethyl motifs validated
4 / 87
Lanabecestat sweep
Dual-hydroxymethyl opened top series

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TOP SHORTLIST
Candidate Series BACE1
pKi
AChE
pKi
hERG
pIC50 Perm. PPB Rationale
FM-AD-01 Lanabecestat
Dual-CH2OH 11.09 6.22 4.85 -5.17 0.872 Best overall balance
FM-AD-02 Verubecestat
Single-CH2OH
11.08 6.26 4.92 -5.33 0.753 Cleaner PPB profile
FM-AD-03 Lanabecestat
OH + CH2OH
11.05 6.19 4.80 -5.67 0.901 Confirms scaffold family
FM-AD-04 Lanabecestat
Dihydroxy-F
11.01 6.16 4.64 -5.49 0.923 Best hERG margin
FM-AD-05 Verubecestat
F + CH2OH
11.01 6.22 4.95 -5.35 0.783 Series remains competitive

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LEAD CANDIDATES
Top SMILES with disclosed structures
FM-AD-01 LANABECESTAT- LIKE
CC(C)Oc1ccc(-c2nc3c(s2)n(-c2cc(F)c(CO)c(CO)c2)c(=O)n3C)cc1
Dual-hydroxymethyl lead. Ranked #1 in both broad and native-only reruns.
FM-AD-02 VERUBECESTAT- LIKE
CC(NC(=O)c1ccc2c(c1)CN(C)C(=O)C2)c1nc2cccc(CO)c2s1
Single-hydroxymethyl. Nearly tied for first with cleaner PPB.
FM-AD-03 LANABECESTAT- LIKE
CC(C)Oc1ccc(-c2nc3c(s2)n(-c2cc(F)c(O)c(CO)c2)c(=O)n3C)cc1
OH + CH2OH. Confirms the scaffold family is not a one-hit artifact.

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WHAT WAS REJECTED AND WHY

The value of the workflow is not only what it ranked - it is also what it removed. The highest-ranked failures are narrow ADMET misses.

Permeability Near Miss PERMEABILITY
Verubecestat regioisomer: BACE1 11.08, AChE 6.26
Permeability -6.09 vs cutoff -6.0

Second Permeability Miss PERMEABILITY
Fluoro regioisomer: strong binding profile
Permeability -6.13 vs cutoff -6.0

hERG-Driven Rejection hERG
Dimethoxy BACE1 analog: strong potency
hERG 5.17 vs cutoff 5.0

Lanabecestat hERG Miss hERG
Amino + CH2OH analog: right amyloid signal
hERG 5.09 vs cutoff 5.0

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RUNTIME PERFORMANCE

Fast enough to function as an active discovery workflow, not a batch report.

11m 57s
Broad Confirmation Rerun
707 candidates under full multi-target gate

11m 31s
Native-Only Confirmation
675 BACE1-native candidates, same constraints

23m 28s
Combined Total
Two full production reruns, no GPU refinement

Typical Fragmented Workflow

- Potency, counter-screen, and CNS triage split across tools
- Strong binders survive too long before safety flags
- Human review accumulates across hours to days

FluxMateria Integrated Path

- Same campaign enforces target + anti-target + ADMET
- Near-miss reasons visible immediately
- Full confirmation in under 24 minutes

INTERPRETATION

The campaign behaved like a real discovery workflow: it opened a second chemotype, explained the surviving tradeoffs, and exposed exactly why the best near-misses failed.

Root-cause framing held

The workflow did not collapse back into symptomatic cholinergic chemistry. The AChE anti-target did its job.

Two real chemotypes emerged

Lanabecestat-like and verubecestat-like series both survived the strict screen - not a one-scaffold story.

Bottleneck moved to real med-chem

Top failures are narrow permeability and hERG misses, not absence of BACE1 strength.

Lead is robust across spaces

The same dual-hydroxymethyl lanabecestat analog ranked first in both broad and native-only reruns.

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LITERATURE CONTEXT

FluxMateria landed in the same two scaffold families that anchored major BACE1 programs - lanabecestat-like and verubecestat-like chemistry - in 23 minutes of confirmed local reruns.

The family match is meaningful

The top shortlist clusters around two medicinal-chemistry families that large pharmaceutical programs already treated as serious BACE1 starting points.

Real preclinical precedent exists

Published work on lanabecestat showed this chemical neighborhood can produce potent, orally active, brain-penetrant BACE1 inhibitors with strong amyloid-beta biomarker effects.

Clinical caution still applies

Verubecestat and lanabecestat programs showed the class can engage the target and move amyloid biomarkers, but did not deliver clear clinical success in Alzheimer's trials.

Why FluxMateria still matters

The value is speed and discrimination - reaching this historically credible scaffold neighborhood quickly, then filtering under explicit AChE, KCNH2, and CNS ADMET pressure.

What was not pre-fed: FluxMateria was not given lanabecestat, verubecestat, or an instruction to reproduce known pharma series. Those families emerged from the broad search. The workflow then deliberately ran chemotype-specific refinement sweeps.

Selected sources: Lanabecestat preclinical med-chem | Verubecestat mild-to-moderate AD trial | Lanabecestat neuroimaging follow-up | 2024 BACE1 inhibitor review

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NEXT STEPS: FROM IN SILICO TO WET LAB

FluxMateria has already done the discovery compression. The remaining step is experimental validation - that is the
point: make wet-lab work sharper, cheaper, and more defensible.

Done In Silico

- BACE1 activity predicted and prioritized across top shortlist and near-miss rescues
- AChE selectivity and hERG safety margins counter-screened computationally
- Permeability and PPB profiled for CNS feasibility
- Two independent chemotype families validated

Experimental Next

- Biochemical BACE1 potency assays on top shortlist and tight near-misses
- Counter-screen AChE and hERG experimentally
- Cell-based amyloid-beta production assays
- Confirm permeability and microsomal stability in vitro

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VALIDATION & LIMITATIONS

Final numbers come from the same strict local discovery workflow used in earlier benchmark work.
The native-only rerun retained the same top candidate as the broad search.
The lanabecestat focused sweep independently recovered the same top motif later seen at rank 1 in the full broad rerun.
All values in this study are computational predictions, not experimental assays.
The study supports amyloid-pathway targeting through BACE1 modulation - it does not prove plaque clearance, disease reversal, or clinical efficacy.

Research Use Notice

This document describes in-silico predictions and preclinical discovery workflows only. FluxMateria outputs are not intended to diagnose, treat, cure, mitigate, or prevent disease, and must not be used for patient-specific clinical decision-making. Any therapeutic use would require experimental validation, additional preclinical work, regulatory review, and where applicable controlled clinical trials.

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The remaining step is experimental validation in a lab.

FluxMateria already did the discovery, ranking, counter-screening, and prioritization.
The obvious next step is not more searching - it is focused experimental validation on the molecules with the highest predicted chance of success.

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