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Acitretin-inspired medicinal chemistry for Alzheimer's disease: A biomarker-gated central nervous system (CNS) discovery framework

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SUMMARY: Alzheimer's disease (AD) still lacks scalable oral strategies for early intervention. This article examines acitretin, a systemic retinoid used for severe psoriasis, as a clinically characterized scaffold for central nervous system (CNS) medicinal chemistry—not as a parent drug for direct repurposing or as a predefined candidate. Retinoic acid receptor/retinoid X receptor signaling can induce a disintegrin and metalloprotease 10 (ADAM10), the principal neuronal α-secretase of amyloid precursor protein, thereby encouraging non-amyloidogenic cleavage and soluble amyloid precursor protein-α (sAPPα) production. Supporting evidence includes mechanistic studies, murine blood-brain barrier penetration, functional observations in an amyloid mouse model, and a small randomized human study showing a short-term increase in cerebrospinal fluid sAPPα. These findings provide a human biomarker anchor but do not establish adequate unbound brain exposure, durable target engagement, clinical efficacy, or a safe chronic therapeutic window. The resulting concept is an evidence-gated scaffold-redesign strategy: future work may test whether retinoid-ADAM10-APP signaling can be retained while systemic retinoid burden and metabolite persistence are reduced. Further progression would require convergence of unbound CNS exposure, bounded sAPPα modulation, and acceptable safety within the same concentration range.

Keywords: Alzheimer's disease, acitretin, ADAM10, α-secretase, soluble APP-α, retinoid signaling

1. Introduction

Alzheimer's disease (AD) remains a major unmet need in drug discovery. Clinically familiar interventions outside neurology can generate useful neuroprotective hypotheses, as illustrated by the recent discussion of herpes zoster vaccination and dementia, but such observations require rigorous mechanistic and translational validation (*1*). The World Health Organization estimated that 57 million people were living with dementia in 2021, with almost 10 million new cases each year (*2*). Disease-modifying antibodies have advanced the treatment of early AD, and yet infusion requirements, amyloid-related imaging abnormalities, and eligibility restrictions preserve a need for lower-burden oral strategies that engage disease biology upstream of plaque removal (*3-5*).

This article examines one such strategy: using acitretin as a starting scaffold for central nervous system (CNS) medicinal chemistry. The proposal is not to administer psoriasis-dose acitretin to older adults with AD, to label an unsynthesized analog as a drug candidate, or to describe conventional drug repurposing. The central question is whether the scaffold's experimentally supported connection to retinoid signaling and ADAM10-dependent amyloid precursor protein (APP) processing can be retained while systemic retinoid liabilities are reduced.

The distinctive contribution is an evidence-gated scaffold discovery framework: acitretin-inspired analogs advance only when adequate unbound CNS exposure, bounded APP-processing target engagement, and acceptable safety converge within the same concentration range. By converting a compound-specific human CSF biomarker signal into explicit progression and stop criteria, the framework links published evidence to design questions and translational gaps (Figure 1; Table 1).

2. Why the acitretin scaffold?

Acitretin is licensed for severe psoriasis and is accompanied by a mature clinical safety vocabulary that includes pregnancy prevention, liver-enzyme

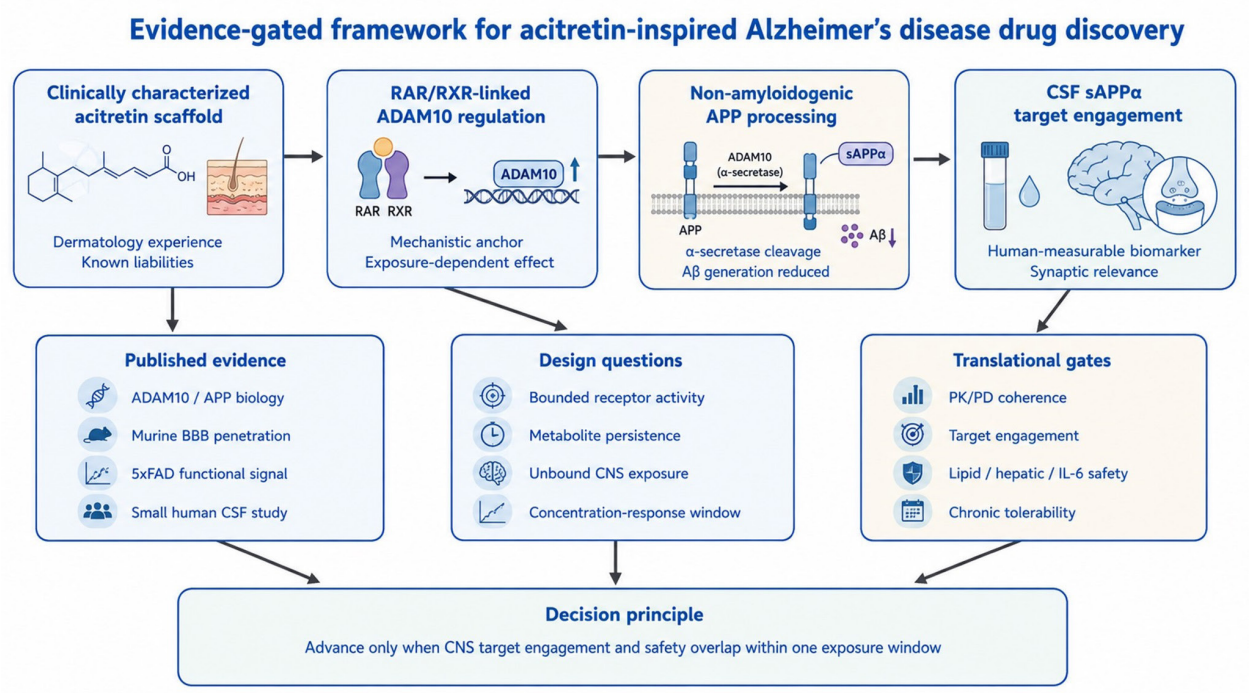

Figure 1. Evidence-gated framework for an acitretin-inspired Alzheimer's disease drug-discovery strategy. The upper pathway connects a clinically characterized dermatologic scaffold to RAR/RXR-linked ADAM10 regulation, non-amyloidogenic APP processing, and CSF sAPPα as a measurable target-engagement signal. The lower row separates published evidence from the questions that medicinal chemistry and translational pharmacology must resolve. Existing support includes ADAM10/APP biology, murine blood-brain barrier penetration, functional observations in a 5xFAD mouse model, and a small human CSF biomarker study. These findings do not define a drug candidate. Future analogs would need bounded receptor activity, a known metabolite profile, adequate unbound CNS exposure, and a concentration range in which sAPPα modulation occurs without unacceptable lipid, hepatic, mucocutaneous, inflammatory, skeletal, neuropsychiatric, or reproductive liabilities. Further progression would depend on the convergence of pharmacokinetic, biomarker, and safety evidence within the same exposure window. *Abbreviations*: ADAM10, a disintegrin and metalloprotease 10; APP, amyloid precursor protein; Aβ, amyloid-β; BBB, blood-brain barrier; CNS, central nervous system; CSF, cerebrospinal fluid; IL-6, interleukin-6; PK/PD, pharmacokinetics/pharmacodynamics; RAR/RXR, retinoic acid receptor/retinoid X receptor; sAPPα, soluble APP-α.

monitoring, fasting lipids, and mucocutaneous toxicity (*6*). This history does not make the parent drug suitable for chronic use in older adults with AD. It does, however, make the scaffold unusually informative: major liabilities are visible before neurological development begins, allowing them to function as design constraints rather than late clinical surprises.

The scaffold is not selected because acitretin is presumed to be the most potent or selective retinoid. Its value lies in the convergence of features reviewed below: a defined receptor-to-ADAM10 mechanism, evidence of murine brain access, a human CSF target-engagement signal, extensive dermatologic exposure, and clear opportunities for structural optimization. Few proposed CNS scaffolds enter discovery with both a measurable human pharmacodynamic observation and such a well-described liability profile.

Within the evidence reviewed here, acitretin is prioritized over other RAR/RXR-related retinoids because its compound-specific evidence aligns unusually well with the proposed gates: murine brain penetration, a human CSF sAPPα signal, extensive clinical exposure, and a well-defined liability profile (*6,15,16*). Bexarotene remains an informative class comparator, but its different receptor pharmacology, negative proof-of-concept clinical result, and triglyceride liability do not provide the same ADAM10-centered biomarker bridge (*14*). Other retinoids should therefore be treated as comparators or alternative scaffolds rather than assumed substitutes.

This combination changes the development question. The relevant comparison is not whether acitretin can outperform current AD therapies, but whether medicinal chemistry can separate the desired CNS pharmacology from the parent drug's systemic retinoid burden. A negative answer would be scientifically useful because it would finally refute a clearly defined scaffold hypothesis rather than prolong an open-ended repurposing narrative.

3. Biological rationale: The RAR/RXR-ADAM10-APP axis

3.1. ADAM10 and non-amyloidogenic APP processing

ADAM10 is the principal constitutive neuronal α-secretase of APP; cleavage within the amyloid-β (Aβ) sequence shifts processing away from β- and γ-secretase-dependent Aβ generation (*7,8*). Neuronal ADAM10 overexpression increased sAPPα, reduced amyloid deposition, and rescued hippocampal abnormalities in APP-transgenic mice (*9*), supporting APP shunting as a

Table 1. Evidence, limitations, and decision gates for acitretin-inspired CNS medicinal chemistry

Dimension	Current evidence	Evidence level	Decision gate or limitation
Clinical scaffold	Acitretin is used for severe psoriasis, with established monitoring for pregnancy, liver enzymes, lipids, and mucocutaneous toxicity (*6*).	Established clinical use	Known liabilities inform design but do not eliminate the risk of prolonged treatment of the CNS in older adults.
Mechanistic axis	ADAM10 is the principal neuronal α-secretase of APP; RAR/RXR signaling and acitretin can increase ADAM10 and α-secretase activity (*7-11*).	Mechanistic and preclinical	The relevant question is whether target engagement can be bounded given ADAM10's multiple neuronal substrates.
CNS exposure	Acitretin crossed the murine blood-brain barrier and was not apparently eliminated by P-glycoprotein (*15*).	Murine preclinical	Human unbound brain exposure and the distribution of redesigned analogs remain unknown.
Human biomarker	Four weeks of acitretin increased CSF sAPPα in a small randomized study of 21 patients with AD (*16*).	Small human pilot	The finding supports target-engagement testing, not disease-modification or cognitive-efficacy claims.
Functional and safety signals	Acitretin increased IL-6 in AD-model mice and human CSF and improved early network and behavioral abnormalities in 5xFAD mice (*17,18*).	Translational and mouse-model evidence	Whether a concentration window can separate APP-processing effects from inflammatory and systemic retinoid liabilities remains to be determined.
Scaffold redesign	No CNS-oriented acitretin analog has been structurally defined or validated in the evidence summarized here.	Hypothesis requiring validation	A basis for progression would require convergence of unbound CNS exposure, sAPPα modulation, and safety within the same exposure range.

Abbreviations: AD, Alzheimer's disease; ADAM10, a disintegrin and metalloprotease 10; APP, amyloid precursor protein; CNS, central nervous system; CSF, cerebrospinal fluid; IL-6, interleukin-6; RAR/RXR, retinoic acid receptor/retinoid X receptor; sAPPα, soluble APP-α.

mechanistic rationale rather than evidence of therapeutic efficacy.

The target is nevertheless pleiotropic. ADAM10 processes multiple neuronal and developmental substrates, making indiscriminate maximization biologically implausible and potentially unsafe (*10*). The desired pharmacology is therefore bounded target engagement: sufficient change in APP cleavage to produce a reproducible sAPPα signal without evidence that broader ADAM10 activity is causing unacceptable effects.

3.2. Retinoid regulation and the role of sAPPα

Retinoic acid receptor/retinoid X receptor (RAR/RXR) signaling provides the regulatory bridge between the acitretin scaffold and ADAM10: retinoic acid receptors can increase ADAM10 expression, and acitretin increased ADAM10 promoter activity and α-secretase activity in experimental systems (*11*). For development, the key question is not whether the pathway can be activated, but whether it can be engaged reproducibly at exposures compatible with prolonged treatment of the CNS.

sAPPα provides a practical pharmacodynamic readout and is reported to have neurotrophic and synaptic actions (*12*). However, its increase should be interpreted as target engagement, not proof of neuroprotection or disease modification; the transfer of this mechanism to a redesigned analog must be demonstrated in human-relevant neuronal systems.

3.3. A class-level caution from bexarotene

The retinoid class also provides a cautionary comparator. Bexarotene produced striking amyloid and behavioral findings in mouse models (*13*), but a subsequent proof-of-concept study in moderate AD did not meet its primary clinical objective and raised clinically relevant triglyceride concerns (*14*). This experience argues against treating receptor activity or favorable animal data as sufficient evidence. Human exposure, target engagement, and safety would need to be evaluated together.

4. Translational evidence for the acitretin scaffold

4.1. Brain access: Suggestive but unresolved

Acitretin crossed the murine blood-brain barrier and was not apparently eliminated by P-glycoprotein (*15*). This result supports biological plausibility, but it does not establish adequate unbound human brain exposure, and it cannot predict the distribution of a redesigned analog. Total plasma or tissue concentration would also be insufficient if protein binding, active transport, or metabolite formation prevents pharmacologically relevant free-drug exposure in the CNS.

4.2. The human CSF biomarker signal

The strongest translational anchor is a four-week randomized pilot study of 21 patients with mild-to-moderate AD, in which acitretin at 30 mg/day increased CSF sAPPα relative to a placebo (*16*). Although too small and brief to assess durable target engagement, cognition, or disease modification, the study provides compound-specific human evidence that systemic acitretin can alter an AD-relevant APP-processing biomarker.

This finding supports exposure-response testing of redesigned analogs at lower systemic retinoid burden, not chronic acitretin treatment. Paired plasma/CSF pharmacokinetics and a related APP-cleavage biomarker panel would be required to determine whether target engagement occurs within a viable therapeutic window.

4.3. Functional signals and inflammatory caution

The broader record is mixed in a way that is informative for development. Acitretin increased interleukin-6 (IL-6) in AD-model mice and in human CSF, indicating that retinoid immunopharmacology may not be uniformly beneficial (*17*). In 5xFAD mice, acitretin rebalanced early cortical network abnormalities and improved behavioral deficits (*18*). The functional observation supports plausibility, but a familial amyloid model cannot establish efficacy in sporadic human AD.

Taken together, the evidence spans molecular studies, a mouse brain-distribution experiment, a functional mouse model, and a small human biomarker trial. The signal is therefore broader than a single *in vitro* mechanism, yet it remains insufficient for a clinical-efficacy claim. Its value is to motivate the next falsifiable experiments.

5. Central innovation: Evidence-gated scaffold redesign

Here, acitretin functions as a clinically characterized scaffold and human biomarker anchor, not as the therapy to be repurposed. Advancement is therefore compound-agnostic: any analog must earn progression through predefined exposure, pharmacodynamic, and safety evidence rather than through resemblance to a prespecified molecular candidate.

The framework contains three linked gates. The exposure gate asks whether a compound achieves predictable unbound CNS concentrations without excessive peripheral exposure or persistent metabolites. The pharmacodynamic gate asks whether those concentrations produce a bounded increase in non-amyloidogenic APP processing, ideally supported by coherent changes in sAPPα and related APP-cleavage markers. The safety gate asks whether the same exposure range avoids unacceptable lipid, hepatic, mucocutaneous, skeletal, neuropsychiatric, reproductive, and inflammatory effects.

The three evidence domains are informative only if they overlap. Brain exposure without target engagement, or sAPPα modulation only at systemically toxic concentrations, would argue against further development. This decision architecture addresses a recurring difficulty in ADAM10 modulation: its mechanistic plausibility is high, but its target pleiotropy and translational uncertainty are substantial (*19*).

6. Remaining challenges and testable next steps

6.1. Medicinal chemistry and pharmacokinetics

Near-term medicinal chemistry should first define the chemical and pharmacological design space rather than optimize against a fixed potency target. Core measurements include RAR/RXR activity and selectivity, transporter interactions, plasma and brain protein binding, microsomal and hepatocyte stability, metabolite identity, and unbound brain exposure. Optimization should prioritize concentration-response relationships and the widest overlap between CNS target engagement and tolerability, while explicitly testing whether etretinate-like metabolite persistence and systemic retinoid pharmacology can be reduced.

6.2. Human-relevant translational models

Candidate analogs should be compared across human-relevant neuronal, hepatic, and inflammatory systems at matched concentrations, integrating ADAM10 induction, APP-cleavage products, IL-6 signaling, lipid-related effects, and cytotoxicity. This design would test pathway-liability separation before animal efficacy is used to justify progression. The framework should be considered falsified if APP-processing activity is lost after liability-reducing structural changes, requires broad retinoid saturation, or occurs only at concentrations that also produce clinically unacceptable hepatic, lipid, inflammatory, or other signals.

6.3. Potential human biomarker bridge

Only after a credible preclinical exposure window is established would a human biomarker study be informative. Its purpose should be to test whether plasma and CSF exposure co-varies with sAPPα and related APP-processing markers within prespecified tolerability and stopping boundaries, not to seek preliminary cognitive efficacy. Population, dose, and design should therefore remain contingent on a structurally defined analog and reproducible preclinical target engagement; clinical-efficacy testing lies beyond the present evidence.

7. Conclusion

Available evidence does not justify recommending acitretin for AD or naming a specific acitretin-derived

drug candidate. It supports a narrower and more testable conclusion: the acitretin scaffold merits evaluation as a human-biomarker-anchored starting point for CNS medicinal chemistry centered on ADAM10 and non-amyloidogenic APP processing.

The framework's value lies in its falsifiability. Further progression would depend on the convergence of unbound CNS exposure, bounded sAPPα target engagement, and an acceptable safety profile within the same concentration window. Failure to achieve this overlap would weaken or close the scaffold hypothesis; evidence of overlap would justify more extensive translational evaluation. Thus, acitretin-inspired chemistry is best viewed as a testable drug-discovery framework rather than a claim for a specific candidate. More broadly, the same evidence-gated logic may be transferable to other clinically characterized drug scaffolds for which a human pharmacodynamic anchor and a well-defined liability profile can be converted into explicit medicinal-chemistry decision gates.

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