Targetome

COMMENTARY

Open Access

https://doi.org/10.48130/targetome-0025-0007

Targetome **2025**, 1(2): e007

Saving the "brain rainforest" in Alzheimer's disease: from single-node protection to ecosystem restoration

Ke Xia[1], Joao Relvas[2,3*], Xiao Zheng[1*] and Haiping Hao[1*]

[1] *State Key Laboratory of Natural Medicines, School of Pharmacy, China Pharmaceutical University, Nanjing 210009, China*
[2] *Institute of Research and Innovation in Health (i3S) and Institute for Molecular and Cell Biology (IBMC), University of Porto, Porto, Portugal*
[3] *Department of Biomedicine, Faculty of Medicine of the University of Porto (FMUP), Porto, Portugal*
* Correspondence: jrelvas@ibmc.up.pt (Relvas J); xzheng@cpu.edu.cn (Zheng X); haipinghao@cpu.edu.cn (Hao H)

Abstract

The high failure rate of Alzheimer's disease (AD) drugs highlights the limitation of traditional single-target therapies for a disease with a heterogenous pathology. A recent study published in *Cell* by Li et al. pioneers a paradigm shift towards cell-type-directed combination therapy. By integrating snRNA-seq and real-world data, they repurposed letrozole and irinotecan and demonstrated that this combination effectively reverses multifaceted AD pathologies in mice.

Citation: Xia K, Relvas J, Zheng X, Hao H. 2025. Saving the "brain rainforest" in Alzheimer's disease: from single-node protection to ecosystem restoration. *Targetome* 1(2): e007 https://doi.org/10.48130/targetome-0025-0007

Traditionally, research on Alzheimer's disease (AD) has largely focused on neurons and proteins like Aβ and Tau[1,2], akin to preserving only the tallest trees while neglecting the underlying forest structure. Regrettably, the failure rate for AD drugs over recent decades has been as high as 98%, presenting a significant challenge[3]. Recent studies have revealed that glial cells, such as microglia, astrocytes, and oligodendrocytes, play crucial roles in the pathogenesis of AD, involving processes like neuroinflammation, metabolic impairment, and demyelination[4,5]. This underscores the need to view the brain not as a collection of isolated components, but as a "rainforest": an intricate ecosystem where each cell type contributes to its overall health and function, and therapeutic success depends on holistic restoration rather than isolated interventions. Given the pathological and genetic heterogeneity of AD, the traditional "single gene–single target–single drug" therapeutic paradigm, which focuses on a single disease feature or tissue-level pathology, is no longer adequate. This is especially true in the context of the global drug discovery landscape, which is facing the challenges of Eroom's Law and target depletion[6,7]. Against this backdrop, the study by Li et al., published in *Cell*, holds significance far beyond the proposal of a specific combination therapy (letrozole and irinotecan)[8]. It stands as a robust practice of shifting the research paradigm from monotherapy to combinatorial drugs, and from a single target to a targetome.

This study established a closed-loop research pathway integrating computation and clinical experiments, enabling cell-type-directed combination therapy. The authors integrated publicly available data from three independent studies into a single-nucleus RNA sequencing (snRNA-seq) dataset, which allowed them to identify differentially expressed genes (DEGs) in six major brain cell types, namely excitatory neurons, inhibitory neurons, microglia, astrocytes, oligodendrocytes, and oligodendrocyte precursor cells (OPCs), comparing AD patients with controls. Using the CMap database for drug repositioning screening, they matched AD signature genes with drug-induced gene expression profiles, predicting 25 candidate drugs capable of reversing these cell-type-specific AD signatures. Subsequently, the authors innovatively leveraged large-scale real-world electronic medical record (EMR) databases, finding that the use of letrozole and irinotecan among the candidates was associated with a significantly reduced risk of an AD diagnosis in older adults, providing clinical correlative support for their potential protective effects.

On the basis of computational and clinical evidence, the authors proposed a combination therapy strategy using letrozole and irinotecan. Their analysis suggested this drug pair could target five cell types in AD, as shown in Table 1. After defining the therapeutic strategy, they applied it to an AD mouse model. The combination significantly improved the mice's short-term and long-term spatial memory and ameliorated multiple pathologies, including Aβ deposits, hyperphosphorylated tau (p-tau) accumulation, gliosis, and neuronal loss. The therapeutic effect was consistently superior to that of either drug alone. The snRNA-seq analysis of the hippocampi of the mice confirmed that the combination treatment promoted neuroprotective functional pathways in a cell-type-specific manner, and effectively reversed multiple cell-type-specific transcriptional signatures of AD.

The study by Li et al. heralds a paradigm shift in drug discovery[8]. It successfully integrated big data analysis, real-world evidence, and animal experimental models, strongly demonstrating the significant potential of cell-type-directed combination therapy for treating complex diseases like AD. Although highly promising, the study still leaves several questions to be addressed. For instance, the authors noted that the CMap database is built on cancer cell data, which might not accurately reflect brain tissues' characteristics. Furthermore, the animal experiments revealed sex-specific differences in the outcomes, whereas the analysis of the UC-wide EMR did not, highlighting the complexity of extrapolating animal findings to real-world patients. The remarkable efficacy of the letrozole–irinotecan combination in animal models also raises the question of whether the underlying mechanism is true drug synergism or merely an addition effect. The precise molecular mechanisms involved require further elucidation.

Looking ahead, the artificial intelligence (AI) era provides powerful tools for drug development. Establishing cell-type-specific databases (e.g., for brain cells), integrating multi-omics data with real-world evidence, and ultimately building more sophisticated AI predictive models can transform the success of this study from an isolated case into a replicable research paradigm. This offers a

Table 1. Rationale for the combination of letrozole and irinotecan.

Drug	Original use	Mechanism	Target cells in AD*
Letrozole	Breast cancer	Aromatase inhibitor	Neurons (excitatory/inhibitory)
Irinotecan	Colorectal cancer, pancreatic cancer	Topoisomerase inhibitor	Glial cells (astrocytes, microglia, OPCs)

* This assignment is based on computational predictions from the CMap database in the study by Li et al., where each drug's transcriptomic profile significantly reversed the disease-associated signatures in the respective cell types[8].

reference research idea for many other complex diseases lacking effective treatments. It is hoped that with technological advancements, such models will not only be limited to repurposing existing drugs but could also autonomously design novel drug molecules. Coupledwithpopulation-effectivestrategies,thiscouldfurthertranslate into precise combination therapies tailored to individual patient specifics, truly paving humanity's way into the era of precision medicine[9] and, in doing so, restoring the vibrant diversity of the brain's own rainforest.

Ethical statements

Not applicable.

Author contributions

The authors confirm their contributions to the paper as follows: conceptualization: Zheng X, Hao H; writing of this manuscript: Zheng X, Hao H, Xia K, Relvas J; manuscript revision: Xia K, Relvas J. All authors reviewed the results and approved the final version of the manuscript.

Data availability

Not applicable.

Acknowledgement

This work was supported by the National Key Research and Development Program of China (grant 2021YFA1301300 to Haiping Hao) and the Natural Science Foundation of Jiangsu Province (grant BK20240095 to Xiao Zheng).

Conflict of interest

The authors declare that they have no conflict of interests.

Dates

Received 22 October 2025; Revised 9 November 2025; Accepted 14 November 2025; Published online 10 December 2025

References

[1] Bloom GS. 2014. Amyloid-β and tau: the trigger and bullet in Alzheimer disease pathogenesis. *JAMA Neurology* 71:505–508

[2] Gulisano W, Maugeri D, Baltrons MA, Fà M, Amato A, et al. 2018. Role of Amyloid-β and Tau proteins in Alzheimer's disease: confuting the amyloid cascade. *Journal of Alzheimer's Disease* 64:S611–S631

[3] Kim CK, Lee YR, Ong L, Gold M, Kalali A, et al. 2022. Alzheimer's disease: key insights from two decades of clinical trial failures. *Journal of Alzheimer's Disease* 87:83–100

[4] De Strooper B, Karran E. 2016. The cellular phase of Alzheimer's disease. *Cell* 164:603–615

[5] Nirzhor SSR, Khan RI, Neelotpol S. 2018. The biology of glial cells and their complex roles in Alzheimer's disease: new opportunities in therapy. *Biomolecules* 8:93

[6] Ringel MS, Scannell JW, Baedeker M, Schulze U. 2020. Breaking Eroom's Law. *Nature Reviews Drug Discovery* 19:833–834

[7] Alteri E, Guizzaro L. 2018. Be open about drug failures to speed up research. *Nature* 563:317–319

[8] Li Y, Pereda Serras C, Blumenfeld J, Xie M, Hao Y, et al. 2025. Cell-type-directed network-correcting combination therapy for Alzheimer's disease. *Cell* 188:5516–5534.e18

[9] Coleman K, Tatonetti NP. 2025. Decoding Alzheimer's disease at the cellular level reveals promising combination therapy. *Cell* 188:5433–5435