Received: 15 October 2025 | Revised: 29 December 2025 | Accepted: 6 January 2026

DOI: 10.1002/trc2.70231

Alzheimer's & Dementia
Translational Research & Clinical Interventions

PERSPECTIVE

Oncology drug repurposing as a blueprint for Alzheimer's therapy

Viswanath Das[1,2] | **Marián Hajdúch**[1,2]

[1]Institute of Molecular and Translational Medicine, Faculty of Medicine and Dentistry, Palacký University and University Hospital Olomouc, Olomouc, Czech Republic

[2]Czech Advanced Technologies and Research Institute (CATRIN), Institute of Molecular and Translational Medicine, Palacký University Olomouc, Olomouc, Czech Republic

Correspondence
Viswanath Das, Institute of Molecular and Translational Medicine, Faculty of Medicine and Dentistry, Palacký University and University Hospital Olomouc, Olomouc, Czech Republic.
Email: viswanath.das@upol.cz

(V. Das); Bluesky: visdas.bsky.social

Funding information
National Institute for Cancer Research and National Institute for Neurological Research - Funded by the European Union - Next Generation EU from the Ministry of Education, Youth and Sports of the Czech Republic, Grant/Award Numbers: LX22NPO5102, LX22NPO5107; Grantová Agentura České Republiky, Grant/Award Number: 23-06301J; Technologická Agentura České Republiky, Grant/Award Number: TN02000109; National Institute for Neurological Research, Grant/Award Number: LX22NPO5107; Infrastructural projects by the Ministry of Education, Youth and Sports of the Czech Republic, Grant/Award Numbers: CZ-OPENSCREEN–LM2023052, EATRIS-CZ–LM2023053, BBMRI-LM2023033, Czech-BioImaging-LM2023050,LM2018129; Project SALVAGE (supported by OP JAK, with cofinancing from the EU and the State Budget), Grant/Award Number: CZ.02.01.01/00/22_008/0004644

Abstract

Alzheimer's disease (AD) imposes substantial personal, social, and economic burdens, yet current therapies provide only modest slowing of clinical decline. Recent approvals of amyloid-targeting antibodies confirm target engagement but also expose the limitations of single-target strategies in a disease shaped by interacting processes, including amyloid pathology, tau aggregation, neuroinflammation, vascular dysfunction, and metabolic disturbances. These limitations suggest that therapeutic approaches should target multiple pathways rather than isolated lesions. Over the past two decades, cancer therapy has shifted toward rational combinations, multi-target interventions, drug repurposing, and adaptive trial designs. Several of these principles are directly relevant to AD. Recent studies, including work showing that combinations of approved anticancer agents can reverse AD-related network dysfunction across multiple brain cell types, suggest that repurposing oncology drugs for neurodegeneration is biologically plausible. An added advantage is that repurposing builds on existing safety, pharmacokinetic, and clinical experience, which may reduce development time and cost. In this *Perspective*, we discuss how oncology-informed repurposing strategies, combined with biomarker-based enrichment, system-level pharmacology, and adaptive platform trials, could support more integrated therapeutic development for AD. We also consider practical translational and regulatory issues, including expectations for demonstrating combination benefit, managing drug–drug interactions, and navigating intellectual property pathways. Together, these cross-disciplinary strategies offer a realistic path toward treatments that can produce durable, population-level benefits.

KEYWORDS
Alzheimer's disease, amyloid-beta, drug repurposing, oncology, systems biology, tau

Highlights

- Amyloid-targeting monoclonal antibodies such as lecanemab and donanemab validate the amyloid hypothesis but provide only modest clinical benefit, limited by safety risks and failure to address downstream mechanisms.

- Alzheimer's disease (AD) arises from interconnected processes including tau aggregation, neuroinflammation, vascular dysfunction, and metabolic failure, underscoring the need for systems-level therapeutic approaches.
- Oncology offers a translational blueprint for AD through drug repurposing, multi-target therapies, and adaptive trial designs that overcome the limitations of single-target interventions.
- Repurposed oncology drugs, such as letrozole and irinotecan, have shown proof-of-concept for "network correction" by reversing AD-associated gene expression changes and restoring function in preclinical models.
- Epidemiological evidence of an inverse cancer–AD relationship highlights shared mechanisms that can be exploited therapeutically but remain underutilized in current AD research.

1 | EVOLVING THERAPEUTIC STRATEGIES FOR ALZHEIMER'S DISEASE (AD)

AD affects more than 55 million people worldwide and is projected to exceed 130 million by 2050,[1] imposing a growing personal, societal, and economic burden. In 2025, dementia-related costs in the United States alone reached USD 781 billion, driven not only by direct health care and long-term care expenses but also by extensive unpaid caregiving, which accounts for nearly half of total costs and often requires more than 60 h of care per week.[2,3] Despite this escalating impact, current therapies only modestly slow cognitive decline and do not halt disease progression.[2,4] This limited impact reflects continued reliance on single-target interventions such as amyloid beta (Aβ) clearance, despite the multifactorial nature of the disease. Recently, Li and colleagues demonstrated that combining two U.S. Food and Drug Administration (FDA)–approved cancer drugs, letrozole and irinotecan, reversed AD-related network dysfunction across multiple cell types.[5] This proof-of-concept highlights the potential of system-level approaches and provides a timely rationale for reframing AD therapy.

2 | LIMITS OF AMYLOID-TARGETING THERAPIES AND LESSONS LEARNED

Despite decades of investment, Aβ-targeting therapies for AD have produced only modest benefits. Their limited clinical gains and significant safety trade-offs highlight the need for alternative approaches. The approvals of lecanemab and donanemab validate the amyloid hypothesis, but their clinical impact remains limited. In the CLARITY AD trial, lecanemab slowed a decline in cognition and daily function by −0.45 points over 18 months compared with placebo,[6,7] a difference below the minimal clinically important thresholds for many patients. Donanemab showed similar results, with a 0.67–0.70 point advantage at 76 weeks.[8]

2.1 | Safety and practical limitations

These marginal effects are coupled with notable safety risks. Both drugs are linked to amyloid-related imaging abnormalities (ARIA), including edema (ARIA-E) and hemorrhage (ARIA-H). For lecanemab, infusion reactions and ARIA were relatively common, particularly among individuals who were apolipoprotein E (APOE) ε4 carriers.[9] Post-marketing studies report serious adverse events, including fatal cases.[10] Comparable risks have been documented with donanemab, leading to treatment discontinuations and rare fatalities.[8–10] Reviews and meta-analyses consistently conclude that although these agents lower the Aβ burden and modestly slow cognitive and functional decline, their overall benefits remain limited and are counterbalanced by risks.[11]

2.2 | Biological constraints and trial-design challenges

The modest efficacy of amyloid-targeting therapies reflects the underlying biology of the disease. Aβ accumulation begins long before symptoms appear and often plateaus by the time of clinical presentation, thereby limiting the benefit of late interventions.[12] Even among amyloid-positive individuals, positron emission tomography studies reveal significant interindividual differences in cortical and striatal Aβ burden, demonstrating substantial biomarker heterogeneity within trial-eligible groups.[13] Moreover, Aβ clearance has a minimal effect on downstream processes, such as tau pathology, neuroinflammation, and synaptic dysfunction.[14,15] Despite an expanding pipeline of tau-directed therapies, ranging from antibodies to antisense oligonucleotides and small molecules, progress remained limited as of early 2025.[16] AD's heterogeneity—spanning tau, vascular, inflammatory, and metabolic pathways—further underscores the need for

strategies beyond single-target interventions (Figure 1). *APOE* ε4 carriers show substantially faster decline, ≈1.5 × faster on Clinical Dementia Rating-Sum of Boxes (CDR-SB) and 1.1–1.4 × faster on Mini-Mental State Examination (MMSE), introducing predictable genotype-linked heterogeneity in AD trial populations.[17]

An evolution of current therapeutic strategies is therefore required. Systems-level approaches aim to target multiple interconnected mechanisms simultaneously, including Aβ, tau, neuroinflammation, mitochondrial dysfunction, and synaptic loss, treating AD as a network disease.[18] These approaches build on earlier network-focused work in AD rather than representing something entirely new. Prior conceptual work has highlighted multi-target and pathway-focused strategies.[19] This perspective aims to bring oncology-derived repurposed agents and cancer–AD biology into a unified framework for network correction. Oncology offers a clear precedent, having moved from single-oncogene targeting to precision medicine, network-level strategies, and combination therapies.[15] Similarly, AD research will need to adopt integrated, multi-mechanism approaches to achieve genuine disease-modifying effects. A summary of these interconnected scientific and translational arguments is presented in Table 1.

3 | ONCOLOGY DRUG REPURPOSING FOR NETWORK CORRECTION IN AD

A promising alternative to single-target strategies is the repurposing of oncology drugs with activity against multiple mechanisms relevant to AD. Many anticancer agents target pathways such as cell cycle regulation and DNA damage responses, with some also affecting proteostasis mechanisms relevant to protein aggregation, which overlap with processes that drive neurodegeneration.

3.1 | Experimental evidence for network correction

Li et al. provide a detailed proof-of-concept for this strategy.[5] Using single-cell transcriptomics, they reconstructed disease-associated gene-expression signatures across neurons, microglia, astrocytes, and oligodendrocyte precursor cells, and then analyzed drug-perturbation datasets to identify compounds capable of reversing these signatures in a cell-type–specific manner. The resulting combination of two U.S. FDA–approved oncology drugs, letrozole and irinotecan, normalized dysregulated pathways related to synaptic function, choles-

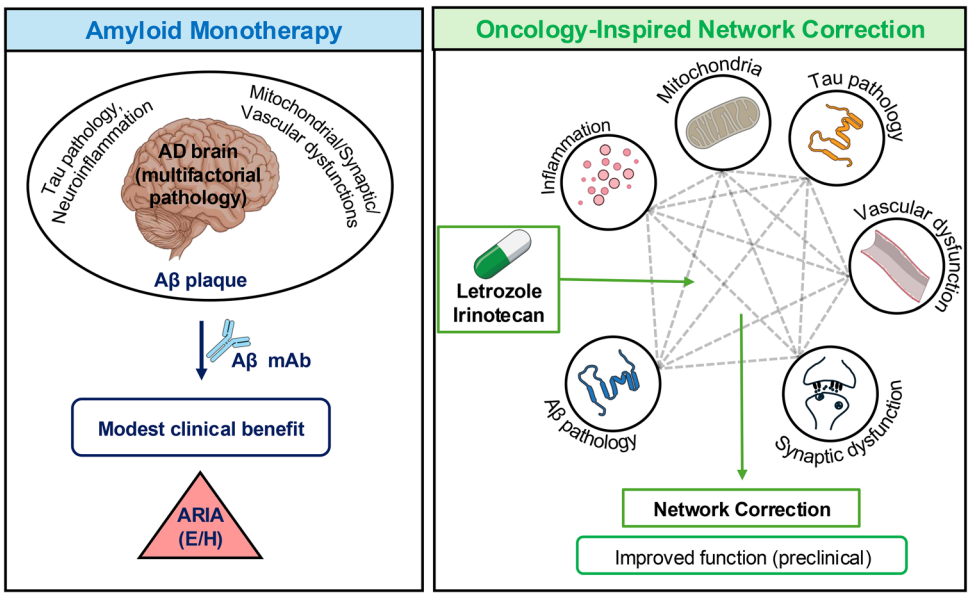

FIGURE 1 From amyloid beta (Aβ) monotherapy to systems-level network correction. Alzheimer's disease (AD) is a multifactorial disorder involving tau pathology, neuroinflammation, synaptic dysfunction, mitochondrial impairment, and vascular abnormalities, with Aβ pathology representing only one component of this broader network. Amyloid-targeting monoclonal antibodies remove Aβ plaques but provide only modest clinical benefits, while also carrying amyloid-related imaging abnormalities (ARIA)–related safety risks. In contrast, oncology-inspired strategies aim to correct network-level dysfunction by repurposing multi-target agents that simultaneously modulate several interconnected pathways. Preclinical work with letrozole and irinotecan illustrates this approach, showing coordinated effects across Aβ, tau, inflammatory, metabolic, mitochondrial, and synaptic pathways that help restore system balance. Icons: NIAID Visual and Medical Arts (BIOART)—*Cytokines* (ID 98), *Brain Lateral* (60), *Mitochondria* (352), *Blood Vessel* (55), *Ceramide Synthase* (73), and *Pill* (407); accessed Oct 7, 2024.

TABLE 1 Summary of key scientific, clinical, and translational arguments supporting an oncology-informed therapeutic strategy for AD, with representative evidence from the current literature.

Theme	AD evidence	Oncology insight	Implication	Ref
Limited impact of amyloid-targeting monoclonals	Lecanemab/donanemab show modest effects; safety risks and ARIA concerns; societal burden	Single-target strategies reached efficacy plateaus in oncology	AD must expand beyond amyloid-only therapies	3,5–11
AD behaves as a network disease	Tau, inflammation, metabolic, and vascular dysfunction are minimally affected by Aβ clearance	Cancer therapy succeeded by embracing pathway interdependence	Multi-node therapeutic approaches needed	12–17
Network logic already exists in AD research	Early multi-target proposals and bottleneck analyses	Oncology shows stepwise evolution from monotherapy → combination → precision	System-level thinking must guide AD	18,19,15
Network correction is experimentally achievable	Letrozole + irinotecan reverse multi-cell-type AD signatures and pathology	Combination regimens target multiple mechanisms simultaneously	Rational multi-target combinations feasible	4
Repurposing accelerates translation	Safety/PK known; computational methods speed selection	Repurposing is standard in oncology	Reduced timelines and cost for AD	20
Regulatory + IP feasibility	Method-of-use, formulation, and FDC protection possible	Oncology combination rules mirror AD needs	Repurposing can be commercially viable	21–23
Drug–drug interaction requirements	AD has not implemented DDI rigor	Oncology mandates PK/PD interaction, synergy, safety lead-ins	AD combinations must adopt similar standards	22,42,47,48
Economics of repurposing	Avoids Phase 1; ~USD 300 M vs billions	Oncology economics prove feasibility	Attractive path for academic + public-sector development	24–25
Cancer–AD inverse epidemiology	Cancer survivors: later onset, better baseline cognition	Meta-analyses show 11% reduced AD incidence	Mechanistic overlap guides target discovery	28,31–34,35
Repeated monoclonal failures	Tau antibodies fail despite target engagement	Oncology moved past single-node interventions	AD should shift to multi-pathway strategies	11,16
Adaptive trial design parallels	Heterogeneous cohorts dilute effects	Oncology uses adaptive arms, enrichment	AD trials should incorporate adaptive and enriched designs	44–46
Rising momentum for repurposing	One-third of AD pipeline involves repurposed agents	Oncology principles already influencing pipelines	Strong foundation for next-generation AD trials	20,26,27

terol metabolism, neuroinflammation, and oxidative stress, reduced amyloid- and tau-associated pathology, and preserved hippocampal neuronal integrity in preclinical models. Beyond supporting the feasibility of repurposing anticancer agents, the study shows that network rewiring across multiple brain cell types can be engineered systematically, providing an experimental template for systems-based precision medicine in AD.

3.2 | Practical considerations in repurposing oncology agents

Repurposing offers practical advantages. Unlike de novo drug discovery, which requires extensive safety evaluation, this approach builds on compounds with established pharmacokinetics (PK) and safety records, enabling shorter development timelines and lower costs.[20] Advanced computational and multi-omics approaches can further accelerate candidate identification by integrating drug databases, patient records, and disease networks.[20] Although generic status may limit commercial incentives, affordability and clinical familiarity make repurposed agents attractive for high-burden conditions like AD.

3.3 | Intellectual property and regulatory considerations for oncology repurposing

From an industry perspective, the feasibility of repurposing hinges on whether meaningful intellectual property and regulatory protection can be secured for an existing molecule in a new indication.[21] Even for generic drugs, exclusivity can be achieved through method-of-use patents covering new indications, dosing strategies, or biomarker-defined subgroups when these elements are central to the AD application.[21] In addition, formulation and delivery patents—such as extended-release, intranasal, or central nervous system–targeted systems—can support product-specific claims when necessary to ensure adequate brain exposure or mitigate adverse effects.[21] Combination-use and fixed-dose combination patents can be granted when data show that each component contributes added therapeutic benefit beyond monotherapy, in line with regulatory expectations for combination products.[21,22] These approaches are compatible with existing regulatory exclusivity pathways, including the United States 505(b)(2) route and the European Union hybrid pathway, which allow off-patent drugs to be incorporated into protected AD products.[21,23]

4 | TRANSLATIONAL SUPPORT FOR REPURPOSING IN AD

Economic analyses suggest that repurposed regimens can shorten development timelines and reduce costs, largely because much of the early safety work has already been completed.[24] Phase 1 in AD typically lasts 12.8 months and represents a significant portion of early-stage expenditure.[25] Avoiding this stage by entering directly into Phase 2 can shorten the development process and reduce costs. Cross-indication analyses estimate development costs for repurposed agents at approximately USD 300 million, compared to USD 0.3–4.5 billion for de novo programs, with AD candidates typically falling at the upper end of this range due to high attrition and lengthy trials.[20] Although combinations still require component-contribution and interaction studies,[22] using known active compounds preserves much of the time and cost advantage of repurposing, particularly when biomarker-enriched or adaptive designs are used.[20]

Repurposed drugs now account for about one-third of the AD pipeline, with many already being tested in Phase 2 and Phase 3 trials.[26] Examples include pioglitazone, sildenafil, and brexpiprazole, which target inflammation, tau phosphorylation, and neurotransmission.[20] These efforts demonstrate that repurposing is a practical and cost-effective approach to expanding AD treatment options.

4.1 | Non-oncology drugs within a systems-level framework

Although this Perspective focuses on oncology-derived agents, several classes of non-oncology drugs also fit within a systems-level framework for AD. Acetylcholinesterase inhibitors such as donepezil, rivastigmine, and galantamine remain the foundation of symptomatic treatment. Other classes are being explored for their effects on specific disease mechanisms, such as the antidiabetic agent, sitagliptin, which targets metabolic and inflammatory pathways, and calcium-channel blockers, such as nimodipine, for cerebrovascular regulation, selective serotonin reuptake inhibitors for neuropsychiatric symptoms and possible neuroprotection, and metabolic modulators like diazoxide, which have emerged from network analyses as potential enhancers of neuronal resilience.[27] These agents demonstrate that multi-pathway targeting is not unique to oncology. In principle, oncology-derived candidates such as letrozole and irinotecan could be paired with selected metabolic or neurotransmitter-modulating drugs to create rational combination regimens for AD.[5]

Against this broader therapeutic landscape, oncology offers some of the most compelling candidates for multi-pathway targeting. Anticancer drugs are designed to act on fundamental cellular processes, many of which are dysregulated in AD. Mechanisms such as cell cycle re-entry, mitochondrial dysfunction, and immune dysregulation directly link the two diseases.[28] Of note, oncology compounds often exert effects across multiple targets, aligning with the systems-level framework required for AD. Together, these features make oncology-informed repurposing both conceptually appealing and increasingly practical for clinical translation. Building on existing safety and dosing data, these agents can advance to AD trials more rapidly than novel compounds. Together with biomarker-guided strategies, this approach offers one of the most realistic paths toward meaningful disease modification (Figure 1).

4.2 | Regulatory incentives and translational support infrastructure

Beyond technical intellectual property (IP) strategies, several regulatory and translational incentives also support the repurposing of drugs. Although repurposed drugs offer limited composition-of-matter protection, multiple regulatory and translational incentives increase their viability for industry. Orphan drug pathways in the EU and United States provide extended exclusivity, reduced fees, and structured engagement for genetically defined or otherwise rare dementia subgroups.[29] The European Medicines Agency (EMA) Repurposing Pilot demonstrates that coordinated scientific advice can clarify the evidence required for off-patent medicines, thereby reducing uncertainty for academic and industry sponsors.[30]

Early-stage translation barriers are reduced by the National Institutes of Health (NIH) and the National Center for Advancing Translational Sciences (NCATS) programs, which provide medicinal chemistry, PK/pharmacodynamic (PK/PD) optimization, toxicology support, formulation and manufacturing expertise, and Phase 1 clinical infrastructure. These programs help academic groups and small companies advance repurposed candidates toward regulatory-ready development more efficiently than would otherwise be possible.[25] The National Institute on Aging (NIA) funding mechanisms further support nonindustry entrants in AD drug development.

Public–private partnerships, such as the AD Neuroimaging Initiative and the Accelerating Medicines Partnership, strengthen biomarker development, trial readiness, and translational infrastructure relevant to repurposed agents.[25] Together, these incentives and support structures make it more feasible to develop repurposed drugs either as standalone therapies or as components of rational combinations for AD.[20]

5 | THE CANCER-ALZHEIMER'S PARADOX: INSIGHTS AND MISSED OPPORTUNITIES

One of the most consistent epidemiological observations in neurology is the inverse correlation between cancer and AD.[28] Individuals with a prior cancer history show better baseline cognition and later AD onset, while progressing at similar rates, indicating that cancer history contributes to baseline variability rather than differences in decline.[31] Meta-analytic and population-level evidence consistently support this inverse association. A pooled analysis of 22 studies covering more than 9.6 million individuals reported an 11% reduction in AD incidence among cancer survivors.[32] Another meta-analysis described reciprocal associations, implicating *APOE* in anti-tumor immunity as a potential mechanistic link.[33] Dementia registries further show that cancer survivors have an 8%–14% lower risk of AD and related dementias.[34]

5.1 | Biological mechanisms underlying inverse risk

Several biological mechanisms may help explain this paradox. Neurons in AD often re-enter the cell cycle aberrantly, triggering apoptosis, whereas cancer cells evade checkpoints to proliferate.[28] This contrast is exemplified by p53 signaling, which promotes apoptosis in AD neurons but is suppressed in cancer cells to sustain proliferation.[28] Metabolic pathways also diverge, with cancer cells relying on the Warburg effect to fuel rapid growth, whereas AD neurons exhibit impaired glucose metabolism.[28] Immune responses follow the same pattern, as cancer progression is driven by immune evasion, whereas AD pathology is amplified by chronic neuroinflammation.[28] Recent evidence on clonal hematopoiesis further strengthens this link. Mutations in *DNMT3A* or *TET2* expand with age and increase the risk of hematologic malignancies, yet are paradoxically associated with a lower risk of AD.[35] These findings suggest that somatic alterations related to cancer can modulate neurodegenerative trajectories.

Despite converging evidence, the translational potential has been overlooked. Most AD drug development remains focused on Aβ-targeting antibodies,[11,36] whereas anti-tau antibodies have similarly underperformed.[16] Several tau monoclonal antibodies, including gosuranemab, semorinemab, tilavonemab, and zagotenemab, were recently discontinued after Phase 2 or 3 trials showed target engagement but no meaningful clinical efficacy.[16] This pattern of repeated failure underscores the limitations of single-target approaches and reinforces the need for multi-mechanism strategies. We previously argued that AD trials should incorporate cancer history and prior therapy into their design.[37] Rather than viewing cancer–AD biology as a confounder, it should be recognized as an opportunity for therapeutic innovation.

Insights from oncology can help identify protective mechanisms and new points of intervention for AD. Overlap in cell cycle regulation, metabolism, and immune function suggests clear biological pathways where oncology drugs might be effectively redeployed. Cancer history may also help in trial stratification by revealing subgroups with distinct underlying biology. If these links are overlooked, the field risks missing a significant therapeutic opportunity. These biological and clinical connections also extend to trial design, where oncology offers a valuable model for building multicomponent treatment strategies in AD.

6 | TRANSLATIONAL AND TRIAL-DESIGN LESSONS FROM ONCOLOGY

Oncology drugs should be integrated into AD pipelines not only for their multi-target activity but also for their translational readiness. Agents such as letrozole and irinotecan reversed AD-relevant gene expression changes, reduced protein aggregation, and improved cognitive performance in preclinical models.[5] These findings demonstrate

how existing PK and safety data from oncology can facilitate the translation of treatments into neurology.

Historical experience in oncology and infectious diseases shows that multidrug strategies often face initial resistance before being accepted once survival benefits are clear. In oncology, early combination chemotherapy for Hodgkin's lymphoma, exemplified by the mechlorethamine, oncovin, procarbazine and prednisone (MOPP) regimen developed by De Vita and colleagues, was initially viewed with skepticism but ultimately demonstrated that drugs with distinct mechanisms could achieve durable remissions and markedly reduce relapse rates.[38] A similar shift occurred in HIV care with highly active antiretroviral therapy, where triple-drug regimens, initially controversial, rapidly became the standard of care by suppressing viral evolution through multi-target blockade and converting HIV from a fatal disease into a chronic condition.[39] These well-established precedents illustrate how multicomponent strategies succeed when single-target interventions plateau, providing a practical historical rationale for pursuing analogous approaches in AD.

This readiness is already reflected in clinical development. Phase 2 trials with immunomodulatory oncology agents, such as lenalidomide, leverage established dosing and safety data accumulated through years of cancer treatment.[28] Kinase inhibitors, originally developed for oncology, are now widely used in autoimmune and inflammatory disorders and are being evaluated in neurological diseases.[40,41] These examples demonstrate how anticancer compounds can be redeployed once mechanisms prove broadly relevant.

Regulatory expectations have also constrained the pace of combination-therapy development outside oncology. The FDA permits the approval of combination regimens, including those whose individual components are not yet approved independently, provided that the combination as a whole demonstrates a favorable benefit–risk profile and, where feasible, that the contribution of each component is characterized in co-development trials and interaction studies.[22] Comparable EMA guidance mandates explicit justification over monotherapy, evidence that the combination improves clinical outcomes, and a thorough evaluation of PK/PD interactions.[42] As recent analyses highlight, unapproved drug combinations are generally confined to controlled clinical trials under strict oversight, and payer coverage decisions can further limit their use even after regulatory clearance.[43] In AD, these requirements impose a substantially higher evidentiary standard for multicomponent regimens.

7 | LESSONS FROM ONCOLOGY FOR AD TRIAL DESIGN

Lessons from oncology trial design are directly relevant to AD. Stratifying cohorts by cancer history may reveal biologically distinct subgroups, consistent with evidence that survivors often exhibit a reduced risk and delayed onset.[44,45] A similar argument was recently made by Harris et al.,[16] who emphasized that tau trials must account for prior anti-amyloid therapy, as previous exposure to anti-amyloid therapy can influence treatment response. Similarly, a history of cancer and prior use of oncology drugs should be recognized as critical stratification variables in AD trials. Current AD trials typically enroll biologically heterogeneous populations and apply single-mechanism interventions broadly, contributing to modest effect sizes and high variability (Figure 2A). Adaptive trial designs, widely adopted in oncology, enable mid-trial modifications such as dose adjustments, arm expansion, or early termination (Figure 2B). These strategies enhance efficiency, reduce costs, and facilitate the identification of responder populations more rapidly (Figure 2B).[46]

Moving toward multicomponent regimens in AD requires careful, systematic evaluation of drug–drug interactions (DDIs) and safety. Preclinical assessment typically integrates in vitro interaction assays with in silico PK/PD modeling, alongside quantitative synergy methods such as isobolograms and dose-equivalence analysis to distinguish additive, synergistic, or antagonistic interactions.[42,47] More recent computational approaches utilize machine-learning models to identify potential DDI risks early in the development process.[48] Clinically, most combination-therapy programs include a Phase 1 or Phase 1b safety lead-in with cautious dose escalation, intensive PK sampling, and predefined stopping rules to detect unforeseen interactions before randomization. Embedding a similar safety lead-in or adaptive dose-finding stage within AD combination trials would provide an essential safeguard for the simplified design proposed in Figure 2B, so that unanticipated safety liabilities do not offset potential network-correcting benefits.

Despite these advantages, repurposed agents in AD often show encouraging early signals but still fail to progress to approval or widespread use. This is usually due to barriers beyond the biological validity of the target.[20] Strengthening IP, for example, by developing a new prodrug, salt form, co-crystal, or fixed-dose combination, can help; however, this requires additional chemistry, manufacturing, and controls work, along with new toxicology studies and clinical bridging.[21] These steps increase cost and development time and introduce additional risk. Many academic-led programs stall after Phase 2 because exclusivity is limited, and Phase 3 trials in AD remain lengthy, expensive, and resource intensive.[25,49]

Additional obstacles also impede translation. Other obstacles include fragmented funding, limited regulatory experience among non-industry sponsors, and trial designs that often fail to generate the payer-relevant evidence necessary for adoption. The EMA Repurposing Pilot further illustrates that even strong scientific cases for off-patent medicines may struggle to attract the engagement of Marketing Authorization Holders, despite structured regulatory support.[30]

Several practical steps can help reduce these risks. For example, developers can pursue method-of-use, formulation, or PK claims through 505(b)(2) or EU hybrid pathways, seek orphan designation where appropriate, and engage regulators early to ensure that studies generate registration-grade data.[23] Stronger partnerships linking programs from the NIH, NIA, and NCATS with disease foundations, philanthropic funders, and later-stage investors, together with adaptive, biomarker-driven trials, could help repurposed agents move toward industry uptake and approval.[20,49]

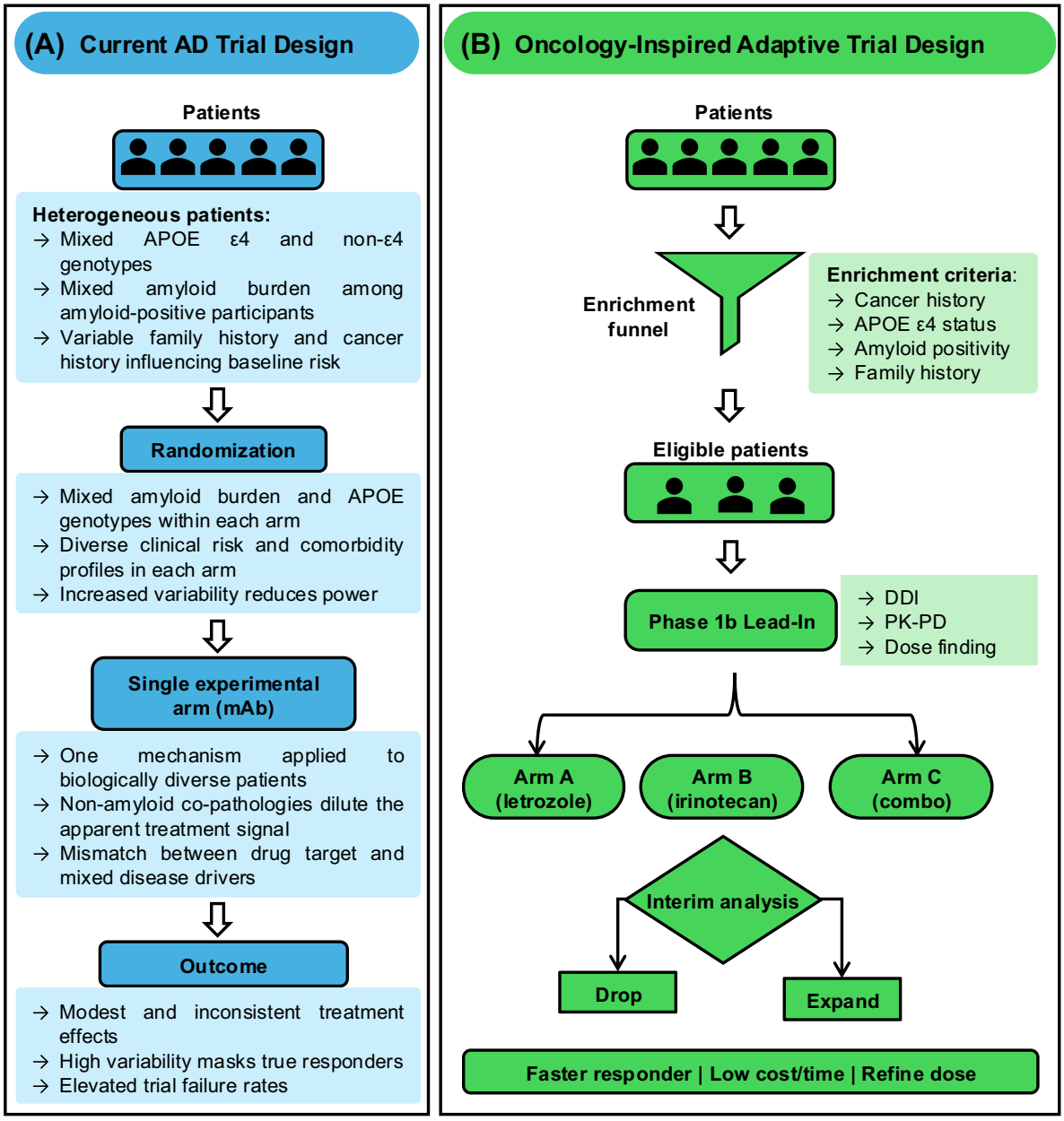

FIGURE 2 Comparison of traditional and oncology-inspired adaptive trial designs for Alzheimer's disease (AD). (A) Current AD trials enroll heterogeneous populations with mixed genetic, biomarker, and clinical risk profiles. Randomization distributes this heterogeneity across arms, and single-mechanism interventions (e.g., monoclonal antibodies) are applied broadly, resulting in modest effects, high variance, and elevated failure rates. (B) The oncology-inspired adaptive designs enrich patients based on biological criteria (cancer history, apolipoprotein E [*APOE*], *APOE* ε4 status, amyloid positivity, and family history) and incorporate a Phase 1b safety lead-in to evaluate drug–drug interactions (DDIs), pharmacokinetic/pharmacodynamic (PK/PD) relationships, and dose finding before randomization. Multiple treatment arms are tested in parallel, and interim analyses expand promising arms, discontinue ineffective ones, and refine dosing. This framework improves efficiency, reduces cost and time, and increases the likelihood of identifying responder subgroups.

Collectively, these examples outline a practical path forward for AD research. By adopting oncology's strategies, multi-target compounds, translationally ready agents, and adaptive trial frameworks, AD drug development can avoid the bottlenecks that have hindered progress. Rather than continuing to rely on single-target monoclonals, the field should draw directly from oncology's successes to implement flexible, systems-level approaches tailored to AD's complexity.

8 | INTEGRATING ONCOLOGY PRINCIPLES INTO FUTURE ALZHEIMER'S THERAPY

A system-based approach is likely essential for meaningful disease modification in AD. The experience with amyloid-only therapies shows that monotherapies cannot change the course of disease at the population level. AD should instead be viewed as a dynamic network

disorder, where restoring system balance offers the best chance of progress.[5]

Oncology provides a model for this shift. By adopting precision medicine, network-level approaches, and rational drug combinations, oncology overcame barriers that once seemed insurmountable. AD research should take a similar path, using multi-target ligands, rational combinations, and repurposed oncology drugs. Evidence from epidemiology, mechanistic studies, and policy converges on a simple conclusion: oncology-informed repurposing provides both the tools and the rationale to reshape AD drug development.

Adaptive frameworks and stratification by clinical and biological features, including cancer history, can identify responder groups that traditional trials overlook.[44–46] Family history strongly shapes baseline AD risk: having one affected first-degree relative increases risk by ~1.7×, whereas families with multiple affected first-degree relatives or multigenerational clustering show substantially higher risks, in some cases approaching 3–4×.[50] Adding biomarkers for amyloid, tau, and inflammation can further refine these approaches by linking patient selection to disease mechanisms, thereby enhancing the accuracy of treatment decisions.

Moving beyond the "magic bullet" model will allow therapies to better reflect AD's complexity. The priorities now are to test network-correcting strategies, broaden the use of repurposed oncology drugs, and redesign AD trials for greater efficiency and precision. Adopting this broader framework could help turn mechanistic insights into more durable benefits at the population level (see Outstanding Questions).

9 | OUTSTANDING QUESTIONS

- How can oncology drugs that are being repurposed for AD be integrated into existing development pipelines, given the much longer disease course, different endpoints, and distinct regulatory expectations in neurodegeneration?
- Which properties of oncology drugs—such as their effects on inflammation, protein homeostasis, metabolism, or cell-cycle control—are most likely to be relevant in AD, and how should these candidates be selected for follow-up experiments?
- Which types of biomarkers, including transcriptomic profiles, immune-state markers, or indicators of clonal hematopoiesis, could realistically be used to identify AD subgroups that might benefit from oncology-informed treatments?
- How should adaptive trial designs be adjusted for AD, where disease progression is slow, biomarker changes are less predictable, and early treatment effects are harder to measure than in cancer trials?
- To what extent do a history of cancer or cancer-associated biological states influence AD risk, baseline cognitive performance, or treatment response, and should these factors be considered routinely in trial stratification or randomization?
- Which regulatory routes, such as 505(b)(2) in the U.S. or EU hybrid applications, are most practical for repurposing off-patent oncology drugs for AD, while still ensuring patient safety, transparency, and equitable access?
- Can combination therapies in AD realistically achieve meaningful multi-pathway modulation across amyloid, tau, inflammation, and metabolism, and what preclinical benchmarks should be met before advancing such combinations into clinical trials?
- How can DDI risks be evaluated early and systematically for AD combinations, and what quantitative tools are needed to ensure safe and effective dosing before pivotal trials?

AUTHOR CONTRIBUTIONS

Viswanath Das drafted and edited the manuscript. Both authors contributed to the conceptual development, and approved the final version of the work.

ACKNOWLEDGMENTS

This work was supported in part by infrastructural projects CZ-OPENSCREEN (LM2023052), EATRIS-CZ (LM2023053), BBMRI (LM2023033), and Czech-BioImaging (LM2023050, LM2018129); the National Institute for Cancer Research (EXCELES, LX22NPO5102) and National Institute for Neurological Research (EXCELES, LX22NPO5107) funded by the European Union Next Generation EU from the Ministry of Education, Youth and Sports of the Czech Republic; project TN02000109 (Personalized Medicine: From Translational Research into Biomedical Applications), co-financed with state support of the Technology Agency of the Czech Republic as part of the National Centres of Competence Program; project SALVAGE (CZ.02.01.01/00/22_008/0004644), supported by OP JAK with co-financing from the EU and the State Budget; and the Grant Agency of the Czech Republic (#23-06301J). This work did not receive direct project-specific funding. and was supported through fundings as listed in the Acknowledments.

CONFLICT OF INTEREST STATEMENT

The authors declare no financial or non-financial competing interests related to this work. All views expressed are solely those of the authors. Any author disclosures are available in the supporting information.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article because no datasets were generated or analyzed during the current study.

ETHICS STATEMENT

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

CONSENT STATEMENT

Patient consent was not required for this perspective article.

EDITORIAL LANGUAGE ASSISTANCE

The manuscript was reviewed using Grammarly software for language, grammar, and clarity. The authors take full responsibility for all scientific content, analyses, and interpretations.

ORCID

Viswanath Das https://orcid.org/0000-0001-5973-5990
Marián Hajdúch https://orcid.org/0000-0002-4834-908X

REFERENCES

1. Nichols E, Steinmetz JD, Vollset SE, et al. Estimation of the global prevalence of dementia in 2019 and forecasted prevalence in 2050: an analysis for the Global Burden of Disease Study 2019. *Lancet Public Health*. 2022;7:e105-e125. https://doi.org/10.1016/S2468-2667(21)00249-8
2. Mudrazija S, Aranda MP, Gaskin DJ, Monroe S, Richard P. Economic burden of Alzheimer disease and related dementias by race and ethnicity, 2020 to 2060. *JAMA Netw Open*. 2025;8:e2513931-e2513931. https://doi.org/10.1001/jamanetworkopen.2025.13931
3. Cavaco MA, Jang SR, Olsen C, Bodnar C, Ferko N. Global societal burden of Alzheimer's disease by severity: a targeted literature review. *Neurol Ther*. 2025;14(5):1797-1826. https://doi.org/10.1007/s40120-025-00815-w
4. Barroeta I, Videla L, Carmona-Iragui M, Fortea J, Rafii MS. Current advances and unmet needs in Alzheimer's disease trials for individuals with Down syndrome: navigating new therapeutic frontiers. *Alzheimers Dement*. 2025;21:e70258. https://doi.org/10.1002/alz.70258
5. Li Y, Pereda Serras C, Blumenfeld J, et al. Cell-type-directed network-correcting combination therapy for Alzheimer's disease. *Cell*. 2025;188(20):5516-5534. https://doi.org/10.1016/j.cell.2025.06.035
6. Honig LS, Sabbagh MN, van Dyck CH, et al. Updated safety results from phase 3 lecanemab study in early Alzheimer's disease. *Alzheimers Res Ther*. 2024;16:105. https://doi.org/10.1186/s13195-024-01441-8
7. van Dyck CH, Swanson CJ, Aisen P, et al. Lecanemab in early Alzheimer's disease. *N Engl J Med*. 2022;388(1):9-21. https://doi.org/10.1056/NEJMoa2212948
8. Sims JR, Zimmer JA, Evans CD, et al. Donanemab in early symptomatic Alzheimer disease: the TRAILBLAZER-ALZ 2 randomized clinical trial. *JAMA*. 2023;330:512-527. https://doi.org/10.1001/jama.2023.13239
9. Xing X, Zhang X, Wang K, et al. Post-marketing safety concerns with lecanemab: a pharmacovigilance study based on the FDA Adverse Event Reporting System database. *Alzheimers Res Ther*. 2025;17:15. https://doi.org/10.1186/s13195-024-01669-4
10. Zimmer JA, Ardayfio P, Wang H, et al. Amyloid-related imaging abnormalities with donanemab in early symptomatic Alzheimer disease: secondary analysis of the TRAILBLAZER-ALZ and ALZ 2 randomized clinical trials. *JAMA Neurol*. 2025;82:461-469. https://doi.org/10.1001/jamaneurol.2025.0065
11. Wang H, Pan J, Zhang M, Tan Z. Re-evaluation of the efficacy and safety of anti-Aβ monoclonal antibodies (lecanemab/donanemab) in the treatment of early Alzheimer's disease. *Front Pharmacol*. 2025;16:1599048.
12. Raket LL, Cummings J, Moscoso A, Villain N, Schöll M. Scenarios for the long-term efficacy of amyloid-targeting therapies in the context of the natural history of Alzheimer's disease. *Alzheimers Dement*. 2024;20:6374-6383. https://doi.org/10.1002/alz.14134
13. Chhatwal JP, Schultz SA, McDade E, et al. Variant-dependent heterogeneity in amyloid β burden in autosomal dominant Alzheimer's disease: cross-sectional and longitudinal analyses of an observational study. *Lancet Neurol*. 2022;21:140-152. https://doi.org/10.1016/S1474-4422(21)00375-6
14. Yiannopoulou KG, Anastasiou AI, Zachariou V, Pelidou S-H. Reasons for failed trials of disease-modifying treatments for Alzheimer disease and their contribution in recent research. *Biomedicines*. 2019;7(4):97. https://doi.org/10.3390/biomedicines7040097
15. Zhang J, Zhang Y, Wang J, Xia Y, Zhang J, Chen L. Recent advances in Alzheimer's disease: mechanisms, clinical trials and new drug development strategies. *Signal Transduct Target Ther*. 2024;9:211. https://doi.org/10.1038/s41392-024-01911-3
16. Harris GA, Hirschfeld LR, Gonzalez MI, Pritchard MC, May PC. Revisiting the therapeutic landscape of tauopathies: assessing the current pipeline and clinical trials. *Alzheimers Res Ther*. 2025;17:129. https://doi.org/10.1186/s13195-025-01775-x
17. Qian J, Betensky RA, Hyman BT, Serrano-Pozo A. Association of APOE genotype with heterogeneity of cognitive decline rate in Alzheimer disease. *Neurology*. 2021;96:e2414-e2428. https://doi.org/10.1212/WNL.0000000000011883
18. Peng Y, Jin H, Xue Y, et al. Current and future therapeutic strategies for Alzheimer's disease: an overview of drug development bottlenecks. *Front Aging Neurosci*. 2023;15:1206572. https://doi.org/10.3389/fnagi.2023.1206572
19. Kabir MT, Uddin MS, Mamun AA, et al. Combination drug therapy for the management of Alzheimer's disease. *Int J Mol Sci*. 2020;21(9):3272. https://doi.org/10.3390/ijms21093272
20. Cummings JL, Zhou Y, Van Stone A, et al. Drug repurposing for Alzheimer's disease and other neurodegenerative disorders. *Nat Commun*. 2025;16:1755. https://doi.org/10.1038/s41467-025-56690-4
21. Recino A, Rayner MLD, Rohn JL, et al. Therapeutic innovation in drug repurposing: challenges and opportunities. *Drug Discov Today*. 2025;30:104390. https://doi.org/10.1016/j.drudis.2025.104390
22. Guidance for industry—Codevelopment of two or more new investigational drugs for use in combination 2013. https://www.fda.gov/files/drugs/published/Codevelopment-of-Two-or-More-New-Investigational-Drugs-for-Use-in-Combination.pdf
23. Ravula JD, Nirogi R, Janodia MD. Review on 505(b)(2) drug products approved by USFDA from 2010 to 2020 emphasizing intellectual property and regulatory considerations for reformulations and new combinations. *J Pharm Sci*. 2023;112:2146-2175. https://doi.org/10.1016/j.xphs.2023.04.004
24. Cummings JL, Goldman DP, Simmons-Stern NR, Ponton E. The costs of developing treatments for Alzheimer's disease: a retrospective exploration. *Alzheimers Dement*. 2022;18:469-477. https://doi.org/10.1002/alz.12450
25. Cummings J, Reiber C, Kumar P. The price of progress: funding and financing Alzheimer's disease drug development. *Alzheimers Dement Transl Res Clin Interv*. 2018;4:330-343. https://doi.org/10.1016/j.trci.2018.04.008
26. Cummings JL, Zhou Y, Lee G, et al. Alzheimer's disease drug development pipeline: 2025. *Alzheimers Dement Transl Res Clin Interv*. 2025;11:e70098. https://doi.org/10.1002/trc2.70098
27. Funari A, De Smaele E, Paci P, Fiscon G. Prioritizing repurposable drugs for Alzheimer's disease using network-based analysis with concurrent assessment of long QT syndrome risk. *Biotechnol Rep*. 2025;47:e00909. https://doi.org/10.1016/j.btre.2025.e00909
28. Das V, Miller JH, Alladi CG, et al. Antineoplastics for treating Alzheimer's disease and dementia: evidence from preclinical and observational studies. *Med Res Rev*. 2024;44:2078-2111. https://doi.org/10.1002/med.22033
29. European Medicines Agency. Scientific advice and protocol assistance 2016. (accessed November 26, 2025). https://www.ema.europa.eu/en/human-regulatory-overview/research-development/scientific-advice-protocol-assistance
30. European Medicines Agency. EU repurposing pilot. 2025. https://www.ema.europa.eu/en/documents/report/eu-repurposing-pilot_en.pdf
31. Fowler ME, Triebel KL, Cutter GR, Schneider LS, Kennedy RE. Progression of Alzheimer's disease by self-reported cancer history in the Alzheimer's disease neuroimaging initiative. *J*

Alzheimer's Dis. 2020;76:691-701. https://doi.org/10.3233/JAD-200108
32. Ospina-Romero M, Glymour MM, Hayes-Larson E, et al. Association between Alzheimer disease and cancer with evaluation of study biases: a systematic review and meta-analysis. *JAMA Netw Open*. 2020;3:e2025515–e2025515. https://doi.org/10.1001/jamanetworkopen.2020.25515
33. Zheng G, Xu M, Dong Z, Abdelrahman Z, Wang X. Meta-analysis reveals an inverse relationship between Alzheimer's disease and cancer. *Behav Brain Res*. 2025;478:115327. https://doi.org/10.1016/j.bbr.2024.115327
34. Ma L, Tan ECK, Goudey B, Jin L, Pan Y. Unraveling the bidirectional link between cancer and dementia and the impact of cancer therapies on dementia risk: a systematic review and meta-analysis. *Alzheimers Dement*. 2025;21:e14540. https://doi.org/10.1002/alz.14540
35. Bouzid H, Belk JA, Jan M, et al. Clonal hematopoiesis is associated with protection from Alzheimer's disease. *Nat Med*. 2023;29:1662-1670. https://doi.org/10.1038/s41591-023-02397-2
36. Chundu UC, Thiriveedhi SR, Bhatti C, et al. A systematic review of the efficacy and safety of anti-amyloid monoclonal antibodies in Alzheimer's disease. *Cureus*. 2025;17:e85377. https://doi.org/10.7759/cureus.85377
37. Das V, Hajdúch M. Randomizing for Alzheimer's disease drug trials should consider the cancer history of participants. *Brain*. 2023;146:e75-e76. https://doi.org/10.1093/brain/awad177
38. Falzone L, Salomone S, Libra M. Evolution of cancer pharmacological treatments at the turn of the third millennium. *Front Pharmacol*. 2018;9:1300. https://doi.org/10.3389/fphar.2018.01300
39. Iheagwara C, Ezulike S, Anja M, Okobi OE. The latest trends and evolution of HIV medication management: a systematic review. *Cureus*. 2025;17:e91933. https://doi.org/10.7759/cureus.91933
40. Attwood MM, Fabbro D, Sokolov AV, Knapp S, Schiöth HB. Trends in kinase drug discovery: targets, indications and inhibitor design. *Nat Rev Drug Discov*. 2021;20:839-861. https://doi.org/10.1038/s41573-021-00252-y
41. Latham BD, Geffert RM, Jackson KD. Kinase inhibitors FDA approved 2018–2023: drug targets, metabolic pathways, and drug-induced toxicities. *Drug Metab Dispos*. 2024;52:479-492. https://doi.org/10.1124/dmd.123.001430
42. Clinical development of fixed combination medicinal products—Scientific guideline | European Medicines Agency (EMA) 2009. (accessed November 25, 2025). https://www.ema.europa.eu/en/clinical-development-fixed-combination-medicinal-products-scientific-guideline
43. Daval CJR, Kesselheim AS. Authority of medicare to limit coverage of FDA-approved products: legal and policy considerations. *JAMA Intern Med*. 2023;183:999-1004. https://doi.org/10.1001/jamainternmed.2023.3961
44. Nudelman KNH, Risacher SL, West JD, et al. Association of cancer history with Alzheimer's disease onset and structural brain changes. *Front Physiol*. 2014;5:423. https://doi.org/10.3389/fphys.2014.00423
45. Yarchoan M, James BD, Shah RC, et al. Association of cancer history with Alzheimer's disease dementia and neuropathology. *J Alzheimer's Dis*. 2017;56:699-706. https://doi.org/10.3233/JAD-160977
46. Cummings J. "Landscape of phase 2 trials in Alzheimer's disease": perspective on adaptive trials. *J Alzheimer's Dis*. 2024;98:859-861. https://doi.org/10.3233/JAD-240145
47. Tallarida RJ. Quantitative methods for assessing drug synergism. *Genes Cancer*. 2011;2:1003-1008. https://doi.org/10.1177/1947601912440575
48. Xia Y, Xiong A, Zhang Z, Zou Q, Cui F. A comprehensive review of deep learning-based approaches for drug-drug interaction prediction. *Brief Funct Genomics*. 2025;24:elae052. https://doi.org/10.1093/bfgp/elae052
49. Ballard C, Aarsland D, Cummings J, et al. Drug repositioning and repurposing for Alzheimer disease. *Nat Rev Neurol*. 2020;16:661-673. https://doi.org/10.1038/s41582-020-0397-4
50. Cannon-Albright LA, Foster NL, Schliep K, et al. Relative risk for Alzheimer disease based on complete family history. *Neurology*. 2019;92:e1745-e1753. https://doi.org/10.1212/WNL.0000000000007231

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Das V, Hajdúch M. Oncology drug repurposing as a blueprint for Alzheimer's therapy. *Alzheimer's Dement*. 2026;12:e70231. https://doi.org/10.1002/trc2.70231