Received: 9 July 2020 | Accepted: 28 July 2020 | Published online: 30 September 2020

DOI: 10.1002/trc2.12073

Alzheimer's & Dementia
Translational Research & Clinical Interventions

PERSPECTIVE

Advancing combination therapy for Alzheimer's disease

Stephen P. Salloway[1] | Jeff Sevingy[2] | Kumar Budur[3] | Jan Torleif Pederson[4] | Ronald B. DeMattos[5] | Philipp Von Rosenstiel[6] | Antonio Paez[7] | Rebecca Evans[8] | Christopher J. Weber[9] | James A. Hendrix[10] | Susan Worley[11] | Lisa J. Bain[12] | Maria C. Carrillo[9]

[1] Brown University, Providence, Rhode Island, USA

[2] Prevail Therapeutics, New York, New York, USA

[3] AbbVie Inc., Lake Bluff, Illinois, USA

[4] H. Lundbeck A/S, Valby, Copenhagen, Denmark

[5] Eli Lilly and Company, Indianapolis, Indiana, USA

[6] Biogen, Cambridge, Massachusetts, United States

[7] Grifols, Sant Cugat del Vallès, Barcelona, Spain

[8] Takeda Development Center, Americas, Inc., Cambridge, Massachusetts, USA

[9] Alzheimer's Association, Chicago, Illinois, USA

[10] LuMind IDSC, Burlington, Massachusetts, USA

[11] Independent Science Writer, Bryn Mawr, Pennsylvania, USA

[12] Independent Science Writer, Elverson, Pennsylvania, USA

Correspondence
Christopher J. Weber, Director, Global Science Initiatives, Alzheimer's Association, 225 N. Michigan Ave. 18th floor, Chicago, IL 60601, USA.
E-mail: cweber@alz.org

Abstract

The study of Alzheimer's disease (AD) has led to an increased understanding of the multiple pathologies and pathways of the disease. As such, it has been proposed that AD and its various stages might be most effectively treated with a combination approach rather than a single therapy; however, combination approaches present many challenges that include limitations of non-clinical models, complexity of clinical trial design, and unclear regulatory requirements. The Alzheimer's Association Research Roundtable meeting on May 7–8, 2018, discussed the approaches and challenges of combination therapy for AD. Experts in the field (academia, industry, and government) provided perspectives that may help establish a path forward for the development of new combination therapies.

KEYWORDS
Alzheimer's disease, biomarkers, clinical trials, combination therapy, research roundtable

1 | INTRODUCTION

The Alzheimer's disease (AD) community is committed to achieving the global goal of developing effective treatments for AD by 2025. There is growing recognition, heightened in light of the multitude of negative monotherapy phase-3 studies, that to slow, stop, or reverse AD and attendant symptoms a combination of therapies will be required. Analogs to this approach have been successful in other therapeutic areas, including cancer, infectious disease (eg, human immunodeficiency virus [HIV], tuberculosis), and heart disease.[1] Moreover, evidence from neuropathologic, biomarker, and genetic studies indicates that AD arises from the interaction of multiple

TABLE 1 Rationale for combination disease-modifying therapy for Alzheimer's disease

Multiple complex biological pathways contribute to the disease.
A wide range of druggable targets exist within these pathways.
To achieve a clinically meaningful benefit, it may be necessary to target multiple pathways or the same pathway at two (or more) points.
Monotherapies that by themselves have modest clinical effects may, when combined, produce additive or synergistic effects.
The use of two or more disease-modifying agents may allow for smaller and potentially safer doses of each agent.
A sequence of agents, or combinations may be required across the continuum of disease as the biological mechanisms evolve.
Regulators (Food and Drug Administration) have endorsed the concept of combination therapies and have issued guidance for co-development of two or more new investigation drugs for use in combination.
Clinicians are accustomed to combining therapies for the treatment of many disease conditions.

complex and overlapping pathophysiological pathways, suggesting that complex treatments, including combinatorial approaches, may be needed to effectively treat the disease.

On May 7 and 8, 2018, the Alzheimer's Association Research Roundtable convened a forum of experts from industry, academia, and government agencies to share perspectives on, and discuss ideas about, the current status of combination therapy development and lay out a path forward to advance this approach.

Many factors support the development of combination disease-modifying therapies for AD (Table 1).

2 | BIOLOGICAL RATIONALE FOR COMBINATION THERAPY TO TREAT AD

It is well accepted that a series of pathophysiological changes begin decades before AD symptoms appear and progress in a predictable manner during the asymptomatic and symptomatic phases of disease.[2] The amyloid cascade hypothesis, which was first proposed in 1992, and which continues to be the leading model of AD pathogenesis, points to the deposition of amyloid beta (Aβ) plaques in the brain as the initiating step of AD pathogenesis, which in turn leads to the accumulation of neurofibrillary tangles composed of hyperphosphorylated tau, synaptic and neuronal dysfunction and loss, and cognitive decline.[3,4] Since 1992 the discovery of a wide range of molecular and cellular processes that play a critical role in the development of AD has led experts to revise and expand the original hypothesis.[5-8] Genetic studies also have provided further insight into the complex mechanisms and biological pathways underlying AD, including those involving amyloid precursor protein (APP), tau, immune response and inflammation, lipid transport and endocytosis, synaptic function, cytoskeletal function, and axonal transport.[9] Together these developments have essentially held a magnifying glass to the amyloid cascade hypothesis, and by revealing critical processes occurring upstream, downstream, and in parallel with extracellular Aβ deposition and the intercellular accumulation of hyperphosphorylated tau, have revealed a wealth of potential new drug targets. It is reasonable to assume that drugs designed to address these new targets may have additive or synergistic effects when combined with one another, or with drugs designed to reduce Aβ and tau accumulation.

Although Aβ aggregation may initiate a cascade of events leading to AD, research findings during the past decade suggest that other factors or conditions are necessary for the development of AD-related cognitive decline. A weak correlation between Aβ deposition and cognitive decline, for example, has been demonstrated in studies of individuals with AD as well as in studies of AD-negative individuals.[10,11] Moreover, clinical trials of a series of anti-amyloid monotherapies have resulted in a failure to halt the progression of cognitive decline, even when these agents have been successful in removing amyloid. Both lines of research point to intermediary processes, including but not limited to tau pathology, that may be mechanistically linked to or triggered by Aβ deposition, yet may potentially play a more direct role in cognitive decline.[7,11] Therefore, while recent developments suggest that an anti-amyloid therapy such as aducanumab, when delivered during an earlier stage of AD, may limit cognitive decline to some extent, such an agent might prove more effective when coupled with one targeting a process that has a more direct bearing on cognitive decline.

Although it has been established that tau pathology, which occurs downstream of Aβ deposition, is a primary driver of neurodegeneration and strongly associated with cognitive decline, whether an anti-tau agent alone will prove sufficient to halt the progression of cognitive decline remains unknown. Analyses of tau propagation in the AD brain show that tau propagation occurs in predictable stages and that the stage of tau pathology is strongly correlated with degree of cognitive impairment.[12] However, as with the removal of amyloid, the removal of tau at an advanced stage of disease may have negligible effects on cognitive impairment.[10] Yet, a closer examination of the hyperphosphorylation of tau, the process of tau aggregation and accumulation, and the means by which tau spreads from the entorhinal cortex to the neocortex may point to potential drug targets that, in tangent with the removal of tau, may effectively address cognitive impairment. Tau phosphorylation, for example, is mediated by a number of kinases which may prove to be successful drug targets.[14] Elucidating the conditions under which tau, a normally highly soluble protein undergoes aggregation and the formation of neurofibrillary tangles that contain an insoluble form of tau also will likely reveal new drug targets, which might be exploited most advantageously in combination therapy.[14,15] A greater understanding of the function and behavior of tau under normal physiologic and pathologic conditions also may improve the ability to identify and target tau variants that are most strongly associated with AD.[15]

The rise of amyloid and tau levels long before symptoms emerge suggests the possibility of targeting upstream mechanisms that may be responsible for the failure of protein degradation, through autophagy or other pathways, many of which decline with age. Autophagy may also be involved in the acceleration of tau spreading.[16] Thus, targeting

autophagy or other pathways that help maintain proteostasis may represent a therapeutic strategy for AD.[17] Data from cell and animal studies suggest that Aβ and tau aggregation can also induce mitochondrial dysfunction and oxidative stress[18] and that antioxidants can prevent cognitive decline.[19] However, human trials of antioxidants have thus far failed to demonstrate an effect. Whether the same interventions would add value to a combination approach is an unanswered question.

Studies of AD risk genes also point to a wide range of disease-related processes, such as the defective clearance of Aβ and tau that might be targeted by agents in combination with anti-tau or anti-amyloid agents.[7] These include not only processes that may contribute to AD-related cognitive decline but also those that may be protective against AD. It has been well established that the apolipoprotein E (*APOE*) ε4 allele is the strongest risk factor for late-onset AD, with recent longitudinal imaging studies confirming that compared with non-carriers, ε4 allele carriers have significantly increased amyloid deposition, with accumulation occurring at a more rapid rate and at an earlier age.[20,21]

Adding to the underlying complexity of AD pathobiology are epidemiologic studies that have identified a range of modifiable risk factors for AD—including diabetes, cardiovascular risk factors (e.g., hypertension, obesity, smoking), traumatic brain injury, and lifestyle factors. Research continues to reveal an association between these risk factors and biological mechanisms similar to those identified in genetic studies, such as inflammation, mitochondrial dysfunction, apoptosis, autophagy, and synaptic dysfunction. Vascular disease risk, assessed using the Framingham Heart Study cardiovascular disease (FHS-CVD) risk score, has also been associated with cognitive decline both in the absence of Aβ pathology and synergistically when combined with Aβ burden.[22] The association of vascular disease and cognitive impairment suggests several possible combination therapies and prevention strategies, including pharmaceutical approaches combined with lifestyle modifications such as exercise and nutritional intervention.

3 | DETERMINING WHICH PATHWAYS TO TARGET: THE VALUE OF MOUSE MODELS

Transgenic mouse models have been useful in understanding multiple pathways for AD therapy development and may be valuable in creating a roadmap for determining effective combinations in a clinical setting. To date these models have been useful, for example, in demonstrating the potential value of immunotherapy;[23] in enabling the testing of many approaches to Aβ reduction, including passive Aβ and tau immunization, and the inhibition or modulation of β- and γ-secretases;[24] in testing gene therapy approaches to manipulating *APOE*;[25] and in predicting adverse effects of compounds in development. Through constitutive and conditional gene deletion, genetically engineered mouse models have enabled examination of potential therapeutic targets in proof-of-principle settings with better selectivity, specificity, and efficiency than could be accomplished using small molecule targeting.

However, efficacy observed in mouse models thus far has failed to translate in human experiments.[26] This serious limitation argues not for rejecting mouse models but for using them appropriately and for the development of new models, especially for testing combination therapies and considering multifactorial pathophysiological processes.[27,28] Newer AD models must, for example, address critical differences between murine and human phenotypes and also more closely mimic the gradual progression of disease and disruption of neuronal connectivity that occurs in human brains over the years.[7,28]

Whether mouse models also may be useful in helping to determine which forms of Aβ are toxic and in helping define the critical windows for intervening with multiple therapies that target a variety of mechanisms has yet to be determined. Testing in multiple models may be necessary, because therapies may react differently based on the genetic makeup of the animal. For example, interleukin 10 (IL-10) has been shown to have a beneficial effect in some mouse models but a deleterious effect in others.[29,30] Testing in multiple models would also increase confidence in the selection of a dosing regimen for clinical trials. Non-mouse animal models, human induced pluripotent stem cell models (iPSCs), and human organoids composed of multiple cell types are also being studied and may provide drug-testing systems that are more predictive of drug responses in humans.

4 | DEVELOPING COMBINATION THERAPY IN THE CLINICAL SETTING

Successfully targeting multiple AD pathways will require moving beyond a focus on amyloid and tau accumulation. Among the most advanced approaches so far proposed has been the combination of two amyloid-targeting agents (ie, a beta secretase inhibitor [BACEi] and anti-Aβ monoclonal antibody [mAb]). Other approaches currently under consideration include a BACEi plus anti-tau mAb, an anti-Aβ mAb plus anti-tau mAb, or a BACEi inhibitor plus anti-Aβ mAb plus anti-tau mAb. Other compounds in early stages of development that may be used in combination target tau, glia, and other pathways, including tau modulators and inhibitors, RNA interference and antisense approaches that target tau, microtubule stabilizers, cytokine and chemokine inhibitors, glial phenotype modulators (eg, TREM2, CX3CR1), mitochondrial modulators, free radical inhibitors, and vascular modulators including those that interfere with *APOE* pathways.

The process of selecting interventions likely to have an additive or synergistic effect must involve a consideration of the stage of disease. In the earliest stages of AD (ie, more than 20 years before disease onset), targeting amyloid alone with a monotherapy may prove to be effective. As plaque burden beings to grow (approximately 10 to 20 years before onset), combining an amyloid plaque removal agent with a soluble Aβ production modulator might be indicated; and when biomarkers demonstrate an increase in soluble tau isoform production, a tau production inhibitor might be added. As hypometabolism becomes apparent, multiple drugs may be indicated including those that remove plaque, protect neuronal function, inhibit tau production, inhibit tau seeding, and improve brain perfusion.

There also may be benefits from combining non-pharmaceutical with pharmaceutical interventions. Lifestyle interventions such as exercise and diet, for example, may help reduce the risk of AD. The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) suggested that a multidomain intervention comprising diet, exercise, cognitive training, and vascular risk monitoring could improve or maintain cognitive functioning in at-risk older adults.[31] More recently the Alzheimer's Association has launched the U.S. Study to Protect Brain Health through Lifestyle Intervention to Reduce Risk (U.S. POINTER), a 2-year clinical trial to evaluate whether lifestyle interventions that simultaneously target multiple behavioral modifications can protect cognitive function in older adults at increased risk for cognitive decline. Other interventions, such as neurostimulation and novel approaches using stem cells, CRISPR (clustered regularly interspaced short palindromic repeats) gene editing, and antisense oligonucleotides may one day prove beneficial for preventing or treating AD either as monotherapy or in combination with other treatments. To advance these treatments and determine when they might be most useful across the disease course, study populations need to be better characterized with a wide range of biomarkers to determine, for example, whether there are differential benefits to those with or without pathological markers of AD.

4.1 | Selecting the study population: when to intervene

The overlapping temporal sequence of these various pathways suggests that multi-target combinations may vary by disease stage.[32] For primary prevention, targeting genetic and other modifiable risk factors may be an ideal approach. Once pathology has been triggered, and assuming that cortical tau pathology is dependent on Aβ, treatment targeting Aβ alone (with sequential or combination therapy, ideally involving two or more mechanisms of action) may be sufficient. Once tau pathology has been initiated, both Aβ and tau-directed therapies, possibly in combination with disease-modifying agents directed at other targets, may be necessary. For prodromal or symptomatic AD, combinations, including treatments directed at downstream events and concomitant pathologies, will almost certainly be needed for maximum benefit.

To date most trials of new disease-modifying agents for AD have been conducted with participants taking cholinesterase inhibitors and/or memantine. Trials testing late-stage drugs typically allow participants to continue taking these drugs as long as their treatment has been stable for several months. However, including people not taking these medications as well as those on standard therapy in the same trial is not advised, as these two groups likely represent very different populations; for example, those not on standard therapy are likely to have a more stable course of disease.

The ideal setting for combination therapy is likely to be patients who are currently unimpaired but who show biomarker evidence of AD pathology. For example, a plaque-clearing immune therapy combined with a drug that blocks production could prove effective in this high-risk population and also improve the tolerability and affordability of prevention with long-term use of the oral drug.

4.2 | Designing a clinical trial of combination therapy

Most trials of disease-modifying agents for AD so far have been monotherapy trials that have compared a single active agent with placebo, with or without a background of standard symptomatic therapy. In contrast, combination therapies may be tested in either add-on, combination, or sequential designs. Because a disease-modifying agent for AD has yet to be approved, current add-on designs compare a new agent with placebo in individuals receiving symptomatic therapy. Depending on the stage of disease, there may be benefits to having all participants receive stable background therapy, and stable standard therapy in add-on trials may enable detection of a disease-modifying effect; however, any changes in background therapy will degrade the resolving power of such studies.

Combination trials of unapproved agents are possible but challenging, particularly if neither compound has been well studied. The most efficient type of combination trial would have two arms (ie, the combination versus placebo). However, this type of trial may mask the causes of adverse events and fail to discern synergy or interference. Factorial designs are far more informative. Compared with standard randomized controlled trials that have two or more arms, factorial designs are capable of answering more questions with the same sample size. For example, factorial designs can provide evidence of an additive versus a synergistic treatment effect.

One possible trial design suggested for a proof-of-concept study would enroll 1000 participants in a 2 × 2 factorial design with 250 participants per arm for a 2-year trial. Patients enrolled in this type of trial are randomized to agent A plus placebo, agent B plus placebo, agent A plus agent B, or placebo plus placebo.[33] For a study enrolling participants in the late preclinical or early symptomatic phase (eg, persons with subjective cognitive decline plus biomarker evidence of AD pathology), outcome measures would include biomarkers and cognition.

5 | OPPORTUNITIES TO ADVANCE COMBINATION THERAPY

Clinical trials have traditionally been conducted by building the infrastructure individually for each trial, dismantling it at the end of the trial, and then rebuilding infrastructure for the next trial. Not only is this approach inefficient, but the use of different protocols and different outcome measures limits the ability to analyze results across trials.

5.1 | Adaptive trial platforms

The European Prevention of Alzheimer's Dementia Consortium (EPAD) consists of an adaptive platform with a standing infrastructure for proof-of-concept studies, a single master protocol (including a common institutional review board) with multiple arms, and a shared placebo. The platform is ideal for longitudinal cohort studies including combination therapies, as has been demonstrated in the I-SPY2 (Investigation of Serial Studies to Predict Your Therapeutic Response with Imaging and Molecular Analysis 2) trial of treatments for breast cancer, which has run 14 different arms over 8 years.[34] The platform improves efficiency by running continually with sites ready to go; by sharing a database, monitoring boards, and controls; and through more efficient statistical modeling and analysis. For combination studies, the platform enables the use of factorial designs with biomarker interim analysis to support continuing, dropping, or modifying an arm or the addition of new arms, thus allowing more "shots on goal."

The DIAN (Dominantly Inherited Alzheimer Network) Trials Unit (DIAN-TU), an adaptive platform designed to test multiple AD drugs, is well positioned to test combination therapies. After completing enrollment of two drug arms—solanezumab and gantenerumab—the DIAN-TU launched the Next Generation (NexGen) study to incorporate new drugs, including a BACEi, and potentially combination therapies.[35] Efficiency of combination therapeutics is greatly increased by having multiple drug mechanisms tested in parallel in the same trial. The inclusion of drugs from three different companies also has demonstrated that companies can work together to meet the operational challenges involved in conducting a joint clinical trial.

5.2 | Novel combinatorial approaches

A single therapeutic being developed by Denali Therapeutics targets both Aβ and tau in the brain with a bispecific antibody, which is engineered to bind to transferrin receptors on endothelial cells and thus traverse the blood-brain barrier more efficiently. Using this "antibody transport vehicle" or ATV, researchers have demonstrated the ability to reduce Aβ levels and plaque formation in APP transgenic mice by delivering anti-BACE1 antibodies[36] and have separately demonstrated the ability to decrease tau pathology in a tau transgenic mouse by delivering antibodies against tau.[37] Now, they are engineering a bispecific ATV that targets both Aβ and tau simultaneously. Based on data showing that amyloid accelerates tau propagation,[38] this bispecific antibody may have the potential for synergism.

5.3 | Non-pharmacological interventions

Combining pharmaceutical and lifestyle interventions such as those that target cardiovascular risk factors offers yet another approach with the potential for improved efficacy yet will require a better understanding of the interaction between AD and vascular pathologies and better animal models to study the mechanisms of gene–environment interactions that may lead to cognitive decline and dementia. For example, exercise in combination with antihypertensives and statins is likely to be more effective than exercise or drug treatments alone to ameliorate cardiovascular risk factors such as hypertension and dyslipidemia, which are also thought to increase AD risk.[39] Based on clinical observations and research on the potential role of neurovascular coupling in AD, a trial has been launched—The Exercise and Intensive Vascular Risk Reduction in Preventing Dementia (rrAD study, NCT02913664) that is using a 2 × 2 factorial design to determine the independent and combined effects of aerobic exercise and intensive pharmacological treatments to lower blood pressure and blood lipid levels on neurocognitive function in older adults who have a family history of dementia or subjective memory complaints.

6 | REGULATORY CONSIDERATIONS

Regulators have expressed interest in and support for combination studies and platform trials,[40] and the International Conference of Harmonization (ICH) has established regulatory guidance across countries which touch on potential drug combination scenarios. This guidance suggests that in combination trials, rather than conducting an entire toxicology program on the combination, a bridging study of up to 90 days giving the combination to an appropriate species will likely suffice. For early-stage drugs for which little data are available, the Food and Drug Administration has indicated that the need for toxicity studies on the combination will be based on whether both drugs target the same organ, the possibility of pharmacodynamic or pharmacokinetic interaction, prior experience with the combination in animals or human, and the possibility of biochemical pathway synergy or interaction between drugs or that one drug may alter effectiveness of the other. Conversations with regulators early in the development process can ensure that all parties are aligned on the need for toxicity studies, the timeline, and other issues. If aged mice will be required, extra time will need to be built into the process.

Regulators are particularly interested in seeing data relevant to potential synergy, that demonstrates added value of the combination over each monotherapy, and that addresses the question of whether trials can be conducted with the combination only compared to placebo or if monotherapy arms are needed. Validated biomarkers are critical, including a range of potential downstream markers reflective of AD progression; and biomarkers should be validated in the populations in which they will be used.

From the industry perspective, major challenges in meeting the regulatory requirements are the long treatment exposure time and the large numbers of subjects needed before an assessment can be made of whether the combination is clinically better than monotherapy. Cognitive measures lack the sensitivity to detect subtle changes quickly, especially in early stages of AD. Downstream functional markers are needed to ease this pathway.

7 | SUMMARY

The biological mechanisms underlying AD are multitudinous and interact in complex ways that evolve over the course of the disease. Despite the many yet answered scientific questions relating to the biology of AD, our current understanding points to specific pathways and targets therein. Based on the complexity of the disease, it is unreasonable to predict that a single pharmacological intervention will cure or otherwise bring meaningful clinical benefit across the spectrum of AD, with the possible exception of AD caused by single gene mutations (eg, PSEN1), in which very early intervention may potentially prevent disease onset. The science, as we know it, is compelling: eradicating AD will ultimately require a combination of treatments used concurrently and sequentially. This, together with the urgency of solving the problem, the precedence of using of combination therapies for other diseases, and the existing regulatory framework (albeit dated and written with infectious diseases in mind) for developing combination therapies, makes the unassailable case that the field ought to move expeditiously toward developing clinical candidates in a combination therapy paradigm.

While the rationale is clear, there are barriers that need to be thought through. From the pharmaceutical industry point of view, combination studies are complicated and complex endeavors. Few companies are likely to have clinical candidates within their portfolios that are concurrently characterized and enabled for co-development. Enablement may also require non-clinical characterization of the combination, in addition to the individual clinical candidates. The operational complexity of multi-drug delivery for a large multi-center, multi-national study adds further difficulty and expense. Furthermore, demonstrating additive or synergistic effects along with the contribution of each clinical candidate in the combination to the overall effect, if deemed necessary by regulators and payers, may require factorial design studies that are likely to require study sample sizes much larger than currently used in phase 2 and phase 3 studies. If a combination regimen involves two companies, additional complexities arise related to decision making, project management, data sharing, investigational new drug (IND) possessor-ship, and new drug application/biologic license application (NDA/BLS) filing responsibilities. The cost to health care of not having an effective treatment for AD is potentially crippling and too high to permit these barriers to impede us from developing effective treatments for AD. Partnerships between industry, academia, National Institutes of Health (NIH), and philanthropic stakeholders may provide a solution, both in terms of advancing the science and addressing business-related issues such as intellectual property and data sharing.

Many partnerships and consortia that could support the inclusion of combination trials are already established or being planned. For example, the Alzheimer's Clinical Trials Consortium (ACTC), established in December 2017 by the National Institute on Aging (NIA) and partnering institutions, plans to accelerate recruitment by assembling trial ready cohorts of individuals at high risk for rapid decline but early enough to potentially rescue neurons. The 35-site network will also collaborate with other similar networks such as the Global Alzheimer's Platform (GAP). These networks will provide the infrastructure and resources needed to conduct concurrent studies of different approaches. Including a combination study in their portfolios despite the many challenges and unanswered questions will allow these networks to work through the scientific, regulatory, and practical issues without sacrificing rigor, enabling them to set the stage for more definitive combination studies as was done in the HIV field.

Additional efforts will be needed. Non-clinical "bench-to-bedside" experiments take us a long way to understanding the disease processes underlying AD and potential therapeutic approaches. The burden of testing new compounds in multiple animal models, especially in aged animals with or without comorbidities, is huge and perhaps prohibitive, even for industry, particularly when "treatment effects" observed the models often fail to replicate or to translate into humans. This obstacle might be overcome through a centralized resource to support non-clinical animal studies in a rigorous and consistent manner. NIA has already funded the work of a new consortium—the MODEL AD (Model Organism Development & Evaluation for Late-Onset Alzheimer's Disease) consortium—to build, deeply phenotype, and compare AD animal models. This consortium could facilitate a deeper understanding of the intricacies distinguishing different models and encourage consistency across labs and provide independent, unbiased replication. NIA also has a new funding initiative to increase data sharing from human, animal, and cell-based models, and to leverage the cutting-edge computational analyses of these data for target discovery and validation that should expand future opportunities for combination treatment.

Information is also needed from the "bedside-to-bench" direction. Fortunately, there are several prospective longitudinal observational studies currently underway (ADNI [Alzheimer's Disease Neuroimaging Initiative], DIAN, etc.). These may be considered translational research studies in the "bedside-to-bench" direction that provide descriptive, evidence-based information from AD patients at relevant points in the pathophysiological pathway. Early treatment intervention would appear most appropriate to alleviate individual and family suffering. Only by identifying the pathophysiogical events that actually occur in humans are we able to design treatment intervention strategies likely to be most relevant in patients with AD and other age-related neurodegenerative disorders. Surrogate efficacy biomarkers may be necessary in early stages of disease, as clinical outcomes are unlikely on their own to provide unequivocal evidence to evaluate efficacy across the long continuum of heterogenous preclinical, prodromal, and manifest disease.

ACKNOWLEDGMENTS

The authors thank our contributing speakers and panelists: Edoardo Marcora, PhD; Barbara Stopschinski, PhD; Melissa Murray, PhD; Oskar Hansson, MD, PhD; Joanna Jankowsky, PhD; Kurt Brunden, PhD; Brian Bacskai, PhD; Suzana Petanceska, PhD; Reisa Sperling, MD; Paul Aisen, MD; Eric Reiman, MD; Scott Berry, PhD; Veronica Miller, PhD; Eric Siemers, MD; Randall Bateman, MD; Carole Ho, MD; Roger Lane, MD; Rong Zhang, PhD; Christopher Aluise, PhD; Stacie Weninger, PhD;

Maria Tome, MD, PhD; Takaaki Suzuki, PhD; Maribeth Lazzaro, PhD; Samantha Budd, PhD; Rachelle Doody, MD, PhD; and Eliezer Masliah, MD.

CONFLICTS OF INTEREST

Jeff Sevingy is a full-time employee of Prevail Therapeutics. Kumar Budur is a full-time employee of AbbVie, Inc. and owns stock in the company. Jan Torleif Pederson is a full-time employee of H. Lundbeck A/S. Ronald B DeMattos is a full-time employee and stock holder of Eli Lilly and Company. Philipp Von Rosenstiel is a full-time employee of Biogen. Antonio Paez is a full-time employee of Grifols, Rebecca Evans is a full-time employee of Takeda Pharmaceuticals, and James A. Hendrix is a full-time employee of LuMind IDSC.

REFERENCES

1. Tomaszewski S, Gauthier S, Wimo A, Rosa-Neto P. Combination therapy of anti-tau and anti-amyloid drugs for disease modification in early-stage Alzheimer's disease: socio-economic considerations modeled on treatments for tuberculosis, HIV/AIDS and Breast Cancer. *J Prev Alzheimers Dis*. 2016;3(3):164-172.
2. Bateman RJ, Xiong C, Benzinger TLS, et al. Clinical, cognitive, and biomarker changes in the Dominantly Inherited Alzheimer Network. *N Engl J Med*. 2012;367(9):795-804.
3. Hardy JA, Higgins GA. Alzheimer's disease: the amyloid cascade hypothesis. *Science*. 1992;256(5054):184-185.
4. Hardy J, Selkoe DJ. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. *Science*. 2002;297(5580):353-356.
5. Musiek ES, Holtzman DM. Three dimensions of the amyloid hypothesis: time, space and 'wingmen'. *Nat Neurosci*. 2015;18(6):800-806.
6. Selkoe DJ, Hardy J. The amyloid hypothesis of Alzheimer's disease at 25 years. *EMBO Mol Med*. 2016;8(6):595-608.
7. Karran E, De Strooper B. The amyloid cascade hypothesis: are we poised for success or failure?. *J Neurochem*. 2016;139(Suppl 2):237-252.
8. Long JM, Holtzman DM. Alzheimer Disease: an update on pathobiology and treatment strategies. *Cell*. 2019;179(2):312-339.
9. Lambert JC, Ibrahim-Verbaas CA, Harold D, et al. Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's disease. *Nat Genet*. 2013;45(12):1452-1458.
10. Mesulam MM. Neuroplasticity failure in Alzheimer's disease: bridging the gap between plaques and tangles. *Neuron*. 1999;24(3):521-529.
11. Nelson PT, Alafuzoff I, Bigio EH, et al. Correlation of Alzheimer disease neuropathologic changes with cognitive status: a review of the literature. *J Neuropathol Exp Neurol*. 2012;71(5):362-381.
12. Braak H, Braak E. Neuropathological stageing of Alzheimer-related changes. *Acta Neuropathol*. 1991;82(4):239-259.
13. Sato C, Barthelemy NR, Mawuenyega KG, et al. Tau Kinetics in Neurons and the human central nervous system. *Neuron*. 2018;97(6):1284-1298 e7.
14. Guo T, Noble W, Hanger DP. Roles of tau protein in health and disease. *Acta Neuropathol*. 2017;133(5):665-704.
15. Lippens G, Giant B. Elucidating Tau function and dysfunction in the era of cryo-EM. *J Biol Chem*. 2019;294(24):9316-9325.
16. Avila J, Gomez-Ramos A, Bolos M. AD genetic risk factors and tau spreading. *Front Aging Neurosci*. 2015;7:99.
17. Penke B, Bogar F, Crul T, Santha M, Toth ME, Vigh L. Heat shock proteins and autophagy pathways in neuroprotection: from molecular bases to pharmacological interventions. *Int J Mol Sci*. 2018;19(1):325.
18. Caspersen C, Wang N, Yao J, et al. Mitochondrial Abeta: a potential focal point for neuronal metabolic dysfunction in Alzheimer's disease. *FASEB J*. 2005;19(14):2040-2041.
19. McManus MJ, Murphy MP, Franklin JL. The mitochondria-targeted antioxidant MitoQ prevents loss of spatial memory retention and early neuropathology in a transgenic mouse model of Alzheimer's disease. *J Neurosci*. 2011;31(44):15703-15715.
20. Bussy A, Snider BJ, Coble D, et al. Effect of apolipoprotein E4 on clinical, neuroimaging, and biomarker measures in noncarrier participants in the Dominantly Inherited Alzheimer Network. *Neurobiol Aging*. 2019;75:42-50.
21. Risacher SL, Kim S, Nho K, et al. *APOE* effect on Alzheimer's disease biomarkers in older adults with significant memory concern. *Alzheimers Dement*. 2015;11(12):1417-1429.
22. Rabin JS, Schultz AP, Hedden T, et al. Interactive associations of vascular risk and beta-amyloid burden with cognitive decline in clinically normal elderly individuals: findings from the Harvard aging brain study. *JAMA Neurol*. 2018;75(9):1124-1131.
23. Schenk D, Barbour R, Dunn W, et al. Immunization with amyloid-beta attenuates Alzheimer-disease-like pathology in the PDAPP mouse. *Nature*. 1999;400(6740):173-177.
24. May PC, Dean RA, Lowe SL, et al. Robust central reduction of amyloid-beta in humans with an orally available, non-peptidic beta-secretase inhibitor. *J Neurosci*. 2011;31(46):16507-16516.
25. Hudry E, Dashkoff J, Roe AD, et al. Gene transfer of human *Apoe* isoforms results in differential modulation of amyloid deposition and neurotoxicity in mouse brain. *Sci Transl Med*. 2013;5(212):212ra161.
26. Sasaguri H, Nilsson P, Hashimoto S, et al. APP mouse models for Alzheimer's disease preclinical studies. *EMBO J*. 2017;36(17):2473-2487.
27. Onos KD, Francoeur MJ, Wormwood BA, Miller RL, Gibson BM, Mair RG. Prefrontal neurons encode actions and outcomes in conjunction with spatial location in rats performing a dynamic delayed non-match to position task. *PLoS One*. 2016;11(2):e0149019.
28. Jankowsky JL, Zheng H. Practical considerations for choosing a mouse model of Alzheimer's disease. *Mol Neurodegener*. 2017;12(1):89.
29. Chakrabarty P, Li A, Ceballos-Diaz C, et al. IL-10 alters immunoproteostasis in APP mice, increasing plaque burden and worsening cognitive behavior. *Neuron*. 2015;85(3):519-533.
30. Guillot-Sestier MV, Doty KR, Gate D, et al. Il10 deficiency rebalances innate immunity to mitigate Alzheimer-like pathology. *Neuron*. 2015;85(3):534-548.
31. Ngandu T, Lehtisalo J, Solomon A, et al. A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial. *Lancet*. 2015;385(9984):2255-2263.
32. Kang JH, Korecka M, Figurski MJ, et al. The Alzheimer's disease neuroimaging initiative 2 biomarker core: a review of progress and plans. *Alzheimers Dement*. 2015;11(7):772-791.
33. Evans SR. Clinical trial structures. *J Exp Stroke Transl Med*. 2010;3(1):8-18.
34. Barker AD, Sigman CC, Kelloff GJ, Hylton NM, Berry DA, Esserman LJ. I-SPY 2: an adaptive breast cancer trial design in the setting of neoadjuvant chemotherapy. *Clin Pharmacol Ther*. 2009;86(1):97-100.
35. Bateman RJ, Benzinger TL, Berry S, et al. The DIAN-TU next generation Alzheimer's prevention trial: adaptive design and disease progression model. *Alzheimers Dement*. 2017;13(1):8-19.
36. McConlogue L, Buttini M, Anderson JP, et al. Partial reduction of BACE1 has dramatic effects on Alzheimer plaque and synaptic pathology in APP Transgenic Mice. *J Biol Chem*. 2007;282(36):26326-26334.
37. Yanamandra K, Jiang H, Mahan TE, et al. Anti-tau antibody reduces insoluble tau and decreases brain atrophy. *Ann Clin Transl Neurol*. 2015;2(3):278-288.

38. Pooler AM, Polydoro M, Maury EA, et al. Amyloid accelerates tau propagation and toxicity in a model of early Alzheimer's disease. *Acta Neuropathol Commun*. 2015;3:14.
39. Whelton PK, Williams B. The 2018 European society of cardiology/European society of hypertension and 2017 American college of cardiology/American heart association blood pressure guidelines: more similar than different. *JAMA*. 2018;320(17):1749-1750.
40. Woodcock J, LaVange LM. Master protocols to study multiple therapies, multiple diseases, or both. *N Engl J Med*. 2017;377(1):62-70.

How to cite this article: Salloway SP, Sevingy J, Budur K, et al. Advancing combination therapy for Alzheimer's disease. *Alzheimer's Dement*. 2020;6:e12073.
https://doi.org/10.1002/trc2.12073