

PERSPECTIVE

Active immunotherapy and alternative therapeutic modalities for Alzheimer's disease

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Abstract

As knowledge of Alzheimer's disease (AD) progression improves, the field has recognized the need to diversify the pipeline, broaden strategies and approaches to therapies, as well as delivery mechanisms. A better understanding of the earliest biological processes of AD/dementia would help inform drug target selection. Currently there are a number of programs exploring these alternate avenues. This meeting will allow experts in the field (academia, industry, government) to provide perspectives and experiences that can help elucidate what the pipeline looks like today and what avenues hold promise in developing new therapies across the stages of AD. The focus here is on Active Immunotherapies and Alternative Therapeutic Modalities. This topic includes active vaccines, antisense oligomers, and cell-based therapy among others, and highlights new clinical developments that utilize these modalities.

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1 | INTRODUCTION

Patients with Alzheimer's disease (AD) continue to grapple with disappointing clinical trials, exemplified by the numerous failures of compounds to slow progression of this devastating disease. These failures have prompted renewed calls for the pursuit of novel treatment approaches and innovative strategies for delivering therapeutics to the brain. At the same time, a continued technological evolution in methods for studying the brain is uncovering new AD disease mechanisms and novel ways to treat AD, for example, with cellular regenerative, immunological, and gene therapy approaches.

The number of people living with dementia worldwide is now estimated to exceed 50 million.¹ The likely escalation in this number as the global population expands and ages increases the imperative to harness technological innovations to treat AD. With this in mind, the Alzheimer's Association's Research Roundtable focused its May 2019 meeting on alternative therapeutic modalities, including active immunotherapy, in development for neurological diseases. This meeting was designed to explore some of the successes and failures in treatment development across disease types and consider the application of the results of these studies to the development of more efficacious AD treatments. Modalities discussed included active vaccines, antisense oligonucleotides (ASOs), gene therapy and gene editing, biotherapeutics engineered to cross the blood-brain barrier (BBB), targeted protein degradation, and cell-based therapies.

One reason for broadening the scope of the Roundtable beyond AD is that the focus of these technologies on rare, monogenetic disorders (e.g., microtubule-associated protein tau (MAPT) mutations in frontotemporal dementia), may also be applied to complex polygenic and sporadic (idiopathic) forms of AD. Rare, genetic, rapidly advancing disorders provide potential advantages to mitigate some of the challenges of clinical development, including quicker readouts, higher risk tolerance among affected persons and their families, more uniform populations, and well-defined phenotypes. The knowledge gained from developing treatments for these disorders may provide strategies for treating more slowly progressive and heterogeneous diseases such as AD. This will require overcoming barriers including a more complete understanding of the underlying AD biology (in contrast to monogenetic, diseases) and challenges related to participant selection and stage of disease (eg, asymptomatic, mild, moderate, and so on) at intervention for clinical trials. For example, rigorous selection of patients and the stage of disease at intervention has played an important role in the successful development of oncology treatments, including the now nearly mandatory use of combination therapy, and may serve as a model for AD drug development. For AD, combination therapy in a trial may mean the use of marketed drugs focused on symptomatic improvement with investigational drugs usually but not always focused on slowing disease progression; however, combination therapy with more than one investigational drug should also be considered.

2 | SCIENTIFIC FRAMEWORK AROUND ALTERNATIVE THERAPY DEVELOPMENT FOR AD

2.1 | Genetic-associations in AD: Amyloid and beyond

Two factors appear to have guided the development of novel disease-modifying therapeutics in AD: novel treatment modalities that involve genetic modulation mechanisms (e.g., antisense oligos (ASO), ribonucleic acid (RNA) interference, viral vector delivery of therapeutic genes) and the increase in potential therapeutic targets led by the revolution in genomics, particularly sequencing of the human genome, and the emergence of genome-wide association studies (GWASs) and next generation sequencing (NGS). Before these technologies became available, scientists had already determined that mutations in the genes for the amyloid precursor protein (APP), presenilin 1 (PS1), and presenilin 2 (PS2) cause familial, early onset AD,² whereas a common polymorphism in the apolipoprotein E (APOE) gene, known as APOE ϵ 4, is linked to late-onset AD. GWAS and NGS studies subsequently identified at least 45 risk genes or loci that are associated with developing AD.³ Pathway analysis from a recent GWAS meta-analysis of late-onset AD risk-loci implicated genes related to amyloid beta (A β), tau processing, innate immunity, and lipid metabolism as key determinants of AD risk.⁴ Thus both early and late-onset AD were independently associated with amyloid processing, while new targets for potential intervention have appeared.

Another useful way of categorizing these risk genes and gene products that help guide therapeutic development is by functional domain: those that trigger, accelerate, or execute the loss of neurons. A β appears to *trigger* a cascade of events that ultimately results in dementia, whereas tau, through the formation of neurofibrillary tangles, appears to be an *executioner* that may directly and more proximally cause neurodegeneration and dementia. Acting upon triggers and executioners are molecular pathways that may accelerate progression of AD through innate immune activation,⁵ lysosomal dysfunction, and changes in lipid metabolism.⁶

2.2 | Engineering brain delivery

Development of novel and effective therapies for AD requires analysis of why recent experimental trials have failed. Likely factors include an incomplete understanding of the complex neurobiological basis of AD and/or inadequate delivery of therapeutic agents to their intended targets in the brain, which is protected from exposure to agents in the circulatory system by the BBB. Multiple strategies have been proposed for crossing or bypassing the BBB. For example, direct delivery of therapeutics to the brain via intrathecal (IT) delivery has been used to deliver idursulfase to the cerebrospinal fluid (CSF) for the treatment of Hunter syndrome, and tripeptidyl peptidase 1 to the CSF for the treatment of CLN2 (Batten disease).⁷ Another approach,

receptor-mediated transcytosis, shuttles potentially therapeutic molecules to the brain by linking them to a vector such as transferrin receptor (TfR) in brain vasculature, to be transcytosed across the BBB. Although the BBB is a major concern, target engagement alone may be insufficient, as has been demonstrated in trials of beta secretase (BACE) inhibitors, which engaged their targets but did not provide the anticipated efficacy benefits.

2.3 | Biomarker-driven development

The successful development of new central nervous system (CNS) therapeutics is greatly benefited by biomarkers in the blood, CSF, or brain that confirm or at least predict with high confidence target engagement in the brain. Biomarkers might also demonstrate engagement of pathways that are believed to contribute to the neurodegenerative process. Biomarkers of reduced neuronal loss and/or function are also in development and may potentially better correlate with long-term outcomes. Successful clinical trials also require accurate selection of the appropriate participants, which can often be facilitated through biomarker-based, patient phenotyping. Patient-phenotyping biomarkers are also essential for adaptive clinical trials and for developing precision medicine therapy approaches.

3 | ACTIVE IMMUNOTHERAPY

In 1999, Dale Schenk and colleagues demonstrated in mice that a vaccine directed at the $A\beta_{42}$ peptide reduced $A\beta$ pathology,⁸ and subsequent studies showed that the vaccine also improved cognitive performance.⁹ These and other findings led to a clinical trial of the anti- $A\beta$ vaccine AN-1792 in mild to moderate AD. The trial was suspended in 2002 after several participants developed meningoencephalitis, and subsequent studies showed that 6% of participants treated with AN1792 developed this type of brain inflammation.¹⁰ AN1792 appears to have elicited a T-helper cell 1 (Th1)-mediated response in some subjects, which stimulated a pro-inflammatory reaction. Continued follow-up with trial participants has provided important information about the effects of active vaccination against $A\beta$. Neuropathological studies have shown, for example, marked variability in the extent of $A\beta$ clearance in the brain but little correlation between plaque removal and progression to dementia.^{11,12} Some participants continued to express high levels of anti-AN1792 antibodies and remained plaque free for many years, demonstrating a long duration of efficacy in terms of $A\beta$ clearance, although they still progressed to severe dementia possibly due to continued spread of tau pathology.¹³ Whether active immunization against $A\beta$ could prevent AD is yet unknown. A better understanding of how to avoid a T cell-mediated autoimmune response has helped fuel development of many immunotherapy approaches against pathological proteins in AD and other neurodegenerative diseases.

Clinical development of five second-generation active $A\beta$ immunotherapies was presented by industry representatives and discussed at the Roundtable. The status of each of these is summarized below:

- CAD106 (Novartis) was designed using a short $A\beta$ peptide to induce $A\beta$ -specific antibodies without activating $A\beta$ -specific T cells.¹⁴ Multiple Phase 1-2 studies in participants with mild AD demonstrated a strong and persistent antibody response against plaques and oligomers with initial evidence of CNS activity and no major safety issues.¹⁵⁻¹⁷ CAD106 is now being tested in cognitively unimpaired older adults homozygous for $APOE\epsilon 4$ in the Alzheimer's Prevention Initiative's Generation Study 1 (NCT02565511). The study, conducted in major countries globally, allows that subjects who were receiving active immunotherapies be included in the study, as long as antibody titers are documented to be below serological responder threshold. This approach was accepted by the Health Authorities.
- ACI-24 (AC Immune) also uses a short $A\beta_{1-15}$ peptide anchored to a liposome and adjuvant, which is designed to elicit a strong antibody response without activating $A\beta$ -specific T cells.¹⁸ A Phase 1-2 ascending dose study in mild-to-moderate AD demonstrated safety at all doses with no study-related severe adverse events, no signs of CNS inflammation, no observed T cell activation, and a dose-dependent anti- $A\beta$ IgG response at the two highest doses. Although the study was not powered for efficacy end points, a tendency for a reduction in brain amyloid at the two highest doses and a positive trend on cognition and function were also observed.
- UB311 (United Neuroscience) comprises two $A\beta_{1-14}$ peptides fused to T-helper cell peptides and has been shown in a Phase 1 study to elicit a strong antibody response against $A\beta$ without stimulating a cytotoxic T cell response.¹⁹ In a Phase 2a study in mild-to-moderate AD, it was shown to be safe and well tolerated. Exploratory end points suggested a slowing of cognitive decline, a reduction in brain amyloid, and improvements in brain network connectivity.
- A deoxyribonucleic acid (DNA)-encoding $A\beta_{42}$ vaccine uses the full-length $A\beta_{1-42}$ trimer injected into the skin, where its expression triggers an immune response in regional lymph nodes, including antibodies against many epitopes and induction of regulatory T cells but no increase in inflammatory $CD4^+$ T cells.²⁰ In mouse models, the vaccine reduced brain amyloid and tau and demonstrated a possible positive trend in spatial learning.²¹ In large mammals including rhesus monkeys, immunization via a gene gun led to high levels of anti- $A\beta$ antibodies with no inflammatory or cellular immune response.²² A first-in-human study is planned once a good manufacturing practice (GMP)-grade vaccine becomes available.
- Lu AF20513 (Lundbeck) is a trimer of $A\beta_{1-12}$ fragments separated by sequences of tetanus toxin epitopes. The construct is designed to induce a "non-self" T cell response in people that have pre-existing memory T cells, thus breaking self-tolerance to $A\beta$ and enabling a strong humoral anti- $A\beta$ response. In mouse models, Lu AF20513 induced a strong IgG response, cleared CNS $A\beta$, slowed the formation of plaques, and improved performance on a novel object recognition task.^{23,24} A Phase 1 study (NCT02388152) showed that the vaccine was well tolerated at all doses tested; however, titers were much lower than what was seen in animal models. The company concluded that it was too risky to move forward given the lack of a translational understanding of the low titer levels in humans and the lack

of a biomarkers to demonstrate both target engagement and downstream effects thereof.

4 | ALTERNATIVE THERAPEUTIC MODALITIES

4.1 | Oligonucleotide therapies

Oligonucleotide therapies use short, chemically or nucleic acid-modified DNA or double-stranded RNA sequences to target RNA transcripts and modulate the expression of proteins.²⁵ Three types are currently in clinical development: steric-blocking antisense oligonucleotides (ASOs) that modulate translation of messenger RNA (mRNA); splice-modulated ASOs that recruit ribonuclease H (RNase H) to cleave mRNA and thus downregulate genes and expression; and small interfering RNAs (siRNA) oligonucleotides that interact with other proteins to form the RNA-induced silencing complex (RISC) and then cleave mRNA, thus downregulating gene activity.²⁶ Oligonucleotides do not cross the BBB in healthy adults and thus require direct injection into the CSF.

In 2016, nusinersen (Spinraza) became the first approved ASO for a CNS disorder and the first disease-modifying treatment for spinal muscular atrophy (SMA), a rare autosomal-recessive neuromuscular disorder and the leading genetic cause of infant mortality.²⁷ Two other ASO therapeutics approved for neurological disorders target genes in the periphery and do not cross the BBB: Eteplirsen for Duchenne muscular dystrophy (DMD) and inotersen for familial amyloid polyneuropathy.

For example, DeVos et al. have used ASOs to target MAPT mRNA, reverse tau pathology and seeding, prevent neuronal loss, and extend survival in mice that express mutant human tau.²⁸ A Phase 1–2 clinical trial of this strategy in humans is currently underway in early AD (IONIS-MAPT_{Rx} – NCT03186989). Schoch et al. have also used exon-skipping ASOs to reduce the form of tau (4R tau, which has four rather than three repeat domains) thought to induce tau aggregation²⁹ in mice expressing normal and mutant human tau.

RNAi-based therapeutics are also in development for CNS disorders. By optimizing the chemical architecture of siRNAs targeting *HTT* mRNA, for example, Khvorova et al. demonstrated the widespread distribution of an *HTT* siRNA in mouse and marked reduction in the production of the toxic huntingtin protein throughout the brain including caudate and putamen.³⁰ Although these approaches are relatively easy to re-engineer for other monogenic targets, applying it to complex polygenic disorders such as AD may require a combinatorial approach against multiple targets.

4.2 | Gene therapy and gene editing

Two gene therapy products have been approved for rare monogenic CNS disorders: voretigene neparvovec (Luxturna) for the treatment of a rare form of retinal dystrophy in 2017 and onasemnogene abeparvovec-xioi (Zolgensma) for the treatment of SMA in 2019. Unlike ASOs, which often require repeat dosing to sustain the treat-

ment effect, gene therapy aims to correct the underlying genetic defect with a single treatment. Most gene therapies currently in development use one of several serotypes of adeno-associated viruses (AAVs) as delivery vectors.³¹ These viruses have proven to be safe and effective and do not readily integrate into the genome of the target cell, thus reducing the potential for oncogenesis. Serotypes vary with respect to their capsid, which results in different tissue specificities, transduction efficiency, and antigenicity.³² Preclinical studies suggest that by optimizing the capsid, delivery method, and vector genome design (eg, by using different promoters), vectored antibodies can be delivered to specific cells in the CNS of mice via intravenous dosing and can achieve cell-specific or ubiquitous antibody expression. This drawback has been lessened by direct delivery of AAV gene therapies to brain, and pretreatment of patients with immune-suppressing drugs.

AAV gene therapy is also in development to deliver the *APOE ϵ 2* gene to *APOE ϵ 4* homozygotes. *APOE ϵ 4* is the strongest genetic risk factor for AD,³³ whereas *APOE ϵ 2* appears to be protective.³⁴ Converting *APOE ϵ 4* homozygotes to *APOE ϵ 2/APOE ϵ 4/APOE ϵ 4* heterozygotes could theoretically cancel out the harmful effects of the *E4* allele.³⁵ Crystal and colleagues have developed an AAV vector to deliver the *APOE ϵ 2* gene with a promoter that, delivered intracisternally in non-human primates enabled widespread expression of *E2* throughout the CNS, suppressed A β levels, and did not induce any vector-related inflammation or pathology at autopsy. A Phase 1 trial is underway.

Gene editing offers yet other approaches to gene therapy for the treatment of AD. For example, a clustered regularly interspaced short palindromic repeats-associated protein 9 (CRISPR/Cas9) strategy was used to selectively edit the DNA encoding the C-terminus of APP in a manner that reduced A β production in human induced pluripotent stem cell (iPSC) neurons and mouse brains. AAV9 was used to deliver the CRISPR/Cas9 machinery to the brain.³⁶ An alternative and potentially more efficient editing strategy called base editing³⁷ enables the direct targeting of a single DNA base, converting an adenosine (A) to guanine (G) or a cytosine (C) to thymidine (T) without introducing the double-strand DNA breaks required for CRISPR/Cas9 editing, which can result in random insertions and deletions. Base editing enables a diverse array of treatment strategies, including gene correction, regulation, silencing, reprogramming, and multiplex editing. In mammalian cell models, base editing was used to convert *APOE ϵ 3*, which presumably would lower AD risk.³⁸ One significant barrier of gene editing for CNS disorders is the challenge of efficiently delivering the editing components to the relevant cells in the CNS.

Modulation of the formation of mRNA from pre-mRNA by endogenous splicing also has shown promise as a treatment strategy for genetically based diseases, including tauopathies. Ninety-four percent of all human genes must be spliced. RNA trans-splicing molecules (RTMs) can invade the splicing of a targeted gene and insert any desired exon sequence into the trans-spliced mRNA. RTMs are small, do not require delivery of any enzymes or co-factors, and they do not require mitosis to replace coding sequence, thus enabling gene editing in vivo. Trans-splicing with RTMs can correct mutations that otherwise would appear in the mRNA sequence, and thus affect the

expressed protein. Trans-splicing has corrected the imbalance in 3R:4R tau isoforms associated with tauopathies in AD. This imbalance in mice is associated with cognitive and APP transport deficiencies and arises from 3R overexpression in which exon 10 is spliced out of the tau pre-mRNA. Spliceosome-mediated RNA trans-splicing in this tau mouse model resulted in augmented 4R transcripts and a partial correction of tau mis-splicing, which led to a reduction in tau pathology and less cognitive impairment. Trans-splicing may also be suited to AD by converting APOE ϵ 4 to APOE ϵ 2, an approach that may be superior than adding APOE ϵ 2 to patients with APOE ϵ 4 homozygosity

4.3 | Targeted protein degradation

Many disease-causing proteins are considered undruggable because they lack active sites that can be targeted by small molecules. Tau is one such protein. For this and other proteinopathies, one promising approach is to induce degradation of the target protein. One targeted protein degradation approach uses two-headed small molecules engineered to induce degradation of disease-causing proteins via the ubiquitin-proteasome system. In these **PRO**teolysis **T**argeting **C**himeras (PROTACs),³⁹ one head—the protein ligand binding domain—binds the target protein, while the other head—the ubiquitin ligase recruiting domain (E3 ligase)—tags the protein with ubiquitin, leading to degradation of the protein by the proteasome. A linker region orients the two heads to control protein proximity and enable activity. PROTAC complexes are highly potent and selective with the potential to degrade any unwanted protein rapidly (minutes/hours) and to continue doing so for days to weeks. They have been optimized for oral bioavailability and engineered to cross the BBB.

Small molecule PROTACs/degraders have been used to target a wide variety of proteins, including tau with peptidic⁴⁰ and drug-like small molecules.⁴¹ With their proprietary PROTAC platform, Arvinas, Inc. has engineered molecules that get into the brains of tauopathy rodent models and degrade pathological tau. Using their humanized CNS drug discovery platform consisting of patient-derived iPSCs as genetically accurate, ex vivo models of tauopathy,⁴² recently published studies from Mass General Hospital/Dana-Farber, along with unpublished studies in vivo studies in tauopathy mouse models, have demonstrated efficacy of bifunctional degraders that by controlling protein proximity selectively target tau for ubiquitination by the CUL4^{CRBN} E3 ligase, leading to its rapid and potent degradation. By incorporating unique structural elements from tau positron emission tomography (PET) imaging tracers, it has been possible to selectively degrade pathological conformations of human tau in tauopathy patient neurons without affecting normal tau in neurons from healthy controls.⁴²

“Molecular glues” also promote protein-protein interactions⁴³ and could represent an alternative approach to target specific proteins for degradation. These small molecules, a number of which have been found in nature, bind to a protein such as an E3 ubiquitin ligase and modify it so that can recruit a new protein, such as a pathogenic protein, thus tagging it for degradation by the proteasome.

4.4 | Cell therapies

In preclinical models, multiple types of stem cells—hematopoietic stem cells (HSCs), neural stem cells (NSCs), embryonic stem cells (ESCs), iPSCs, and mesenchymal/stromal cells (MSCs)—have shown promise as potential treatments for CNS disorders, although clinical development remains in its early stages.⁴⁴ For example, hematopoietic stem cells transduced with a lentiviral vector delivering the *N*-sulfolglucosamine sulfohydrolase (*SGSH*) gene and genetically engineered for enhanced monocyte expression have been used to correct a deficiency of this enzyme in the devastating lysosomal storage disorder mucopolysaccharidosis IIIA (Sanfilippo syndrome A).⁴⁵ Transduced monocytes are actively transported to the brain, where they differentiate into microglia, delivering the enzyme specifically to the brain. In a vector-bridging study in mice, a GMP version of the vector was shown to be safe and efficacious.⁴⁶

Neuron replacement therapy may make sense for neurodegenerative diseases such as PD where there is a loss of certain types of neurons (ie, dopaminergic, serotonergic, noradrenergic) in a specific location. Fetal cell transplantation of dopaminergic neurons has been shown to result in successful engraftment, restored dopamine signaling, and reversal of symptom⁴⁷; however, quality control issues, adverse effects, and ethical concerns raised by the use of aborted fetuses led investigators to focus instead on human pluripotent stem cells (hPSCs: embryonic [hESC] and induced pluripotent stem cells [iPSCs]). Both kinds of hPSCs are capable of both unlimited proliferation and differentiation into virtually every type of cell in the body. In 2014, investigators in Europe, the United States, and Japan joined forces to advance development of this technology for PD; there are currently several clinical trials in the planning stages.⁴⁸ Although most investigations are planning clinical trials with dopamine neurons derived from unmatched iPSCs or hESCs, iPSC technology offers the possibility of using autologous iPSCs, which would eliminate the need to immunosuppress recipients. The application of hPSCs to treatment of PD opens the possibility that a pluripotent stem cell-based therapy might eventually be useful for AD. In animal models of AD and tauopathy, neural stem cell (NSC) transplantation has been shown to improve cognition, synaptic connectivity, and neuronal survival without altering amyloid or tau pathology.^{49,50} NSCs engineered to express the A β -degrading enzyme neprilysin were effective in removing plaques, but since there was no difference in cognitive improvement between the animals transplanted with non-engineered NSCs, removal of amyloid plaques in this animal model did not make any discernable difference.⁵¹

Allogeneic mesenchymal/stromal stem cells (MSCs) are being tested in a Phase 1 clinical trial in mild AD (NCT02600130). MSCs do not have the unlimited expansion and differentiation capabilities of hPSCs, so their therapeutic potential in AD would derive from pleiotropic mechanisms and their ability to cross the BBB.⁵² Because of their intrinsic properties, MSCs do not require tissue-type matching, and thus immunosuppression is not required in recipients. Allogeneic MSCs can also be derived from adults, thereby obviating ethical concerns regarding fetal tissue use. In rodent models of neurodegenerative diseases

including AD, transplantation of MSCs has resulted in clinical improvement, presumably through anti-inflammatory and pro-regenerative mechanisms, improved immune function, and improved endothelial function.⁵³ Trials in other disease areas including aging frailty have demonstrated a good safety profile for MSCs.^{54,55}

5 | DISCUSSION AND RECOMMENDATIONS

Active immunotherapies have been used in clinical trials in AD for over 10 years. They generally induce persistent antibody titers with high inter-individual variability, requiring corresponding safety monitoring and follow-up with respect to antibody titer levels. Learnings from active immunotherapies might be useful for the upcoming new approaches. One of the main challenges for development of active immunotherapies is the fact that the subjects who participated in the clinical trials were not permitted to enter other clinical trials. This posed ethical challenges for investigators and trial participants. The rationale for exclusion of these participants was most likely related to the meningoencephalitis observed AN1792. Distinction among active immunotherapies, in particular, with respect to the fact that second-generation active immunotherapies were not associated with activation of A β -reactive T cells, or brain inflammation, was never done. Roundtable participants therefore recommend the following to all sponsors: Subjects previously receiving active immunotherapies should not be excluded from the subsequent trials if (a) the active immunotherapy has not been associated with CNS inflammation or any other autoimmune disease, as documented in the respective Investigators Brochure, and (b) antibody response at the last time-point tested has been shown to be below Serological responder threshold or Lower limit of quantification threshold, with the assay and threshold defined by the Sponsor of the active immunotherapy.

Furthermore, Roundtable participants recommend the following to all sponsors of the active immunotherapies: Upfront commitment, in interest of the study participants, to (a) allow investigators to share Investigators Brochure with another sponsor if subject is being screened for another trial, and respective information is required to proceed with screened, and (b) measure antibody titers for subjects receiving active immunotherapy until titers are below Serological responder threshold.

Similar, evidence-based principles should be applied to other novel therapies (eg, cell/gene therapies) that are emerging.

6 | CONCLUSIONS AND NEXT STEPS

Many of the innovative technologies discussed at the Roundtable have already begun to be implemented in other disease areas, particularly in oncology and rare, genetic, and rapidly advancing disorders. Applying these technologies to AD comes with a unique set of challenges and risks, due to its slow progression and heterogeneity. A further complication with AD is that the appropriate target is still not clear, but it seems likely that successful therapies would need to influence A β , tau, or immune responses, and that combination therapy may be necessary.

One of the critical questions that concerns the community is the stage of disease at which some of these novel therapies can be applied, and the uncertainty as to whether a benefit could be shown or not. In many monogenetic CNS diseases, the idea that the earlier a treatment is applied, the greater chance of modifying the disease course appears to be clear.

As such, the risk/benefit relationship of novel therapies in AD may be harder to justify to regulators at early stages of disease progression; however, regulatory agencies have already issued many relevant guidance documents on topics related to therapy development in early AD, combination therapy, and early phase clinical trials of immunotherapies and gene therapies, including safety monitoring, evaluating the immune response to AAV capsids and transgenes, and assessing the immune response and durability of effect. Regulators have also created pathways for fast track, breakthrough therapy, priority review, and accelerated approval of therapies that address unmet medical needs.

Despite the many challenges ahead, Roundtable participants expressed sincere optimism that they can be met. Moreover, they argued that the rapid and successful development of these innovative technologies in other disease areas (eg, genetically targeted therapies in oncology and other neurodegenerative diseases like SMA) provides a roadmap forward for achieving success in treating AD and related dementia.

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CONFLICTS OF INTEREST

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