The Future of R&D in Alzheimer's Disease

New investigational drugs with high selectivity for amyloid-β oligomers and the use of pharmacodynamic biomarkers in Phase 1 trials to enable early go/no-go decisions are changing the R&D landscape

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Earlier this year, the failures of two high-profile, anti-amyloid-beta (Aβ) monoclonal antibodies (mAbs) in late-stage clinical trials have sharpened the focus on two key issues that currently dominate the quest to establish effective treatments for Alzheimer's disease (AD): the need to develop drugs that are highly selective for the Aß conformation known to be the pathogenic cause of AD (ie, soluble neurotoxic Aβ oligomers [AβOs]) and the need to employ emerging AD biomarkers to dramatically transform clinical trial design and enable cost-effective, earlier go/no-go decisions on investigational therapeutics.

Selective Targeting

The inability of any disease-modifying therapeutic based on the Aβ hypothesis to demonstrate efficacy in clinical trial subjects with AD has caused doubts about its validity. The recent failures of two anti-Aβ mAbs, aducanumab (Biogen/Neurimmune) and crenezumab (Roche/AC Immune), after two large, long, and costly Phase 3 clinical trials each, have amplified those doubts. However, despite decades of R&D costing billions of dollars, the Aβ hypothesis has not yet been adequately and rationally tested because none of the failed drugs selectively targeted the pathogenic Aβ conformation. They targeted irrelevant species, such as plaque Aβ for aducanumab and Aβ monomers for crenezumab, which are present in AD brains at concentrations that dwarf that of AβOs.

The causal role of Aβ in AD is firmly established by very strong scientific evidence. No plausible alternative hypothesis refutes the genetic evidence showing that amyloid precursor protein (APP), PSEN1, and PSEN2 mutations cause familial and early-onset AD in virtually all carriers. Other genetic findings abound, such as the occurrence of early-onset, AD-like dementia in Down's syndrome (trisomy 21, caused by an additional copy of the APP gene located on chromosome 21), the protection against AD conferred by a rare inherited APP gene variant that decreases production and aggregation of Aβ, and the increased AD risk conferred by the ApoE4 allele, which decreases brain clearance of Aβ. Furthermore, a large body of scientific and clinical data supports the role of Aβ in sporadic AD.

Discoveries of other factors associated with AD have been presented as alternative causes of the disease, including viruses, bacteria, metal intoxication, medical conditions such as diabetes, and others. However, rather than contradict the Aβ hypothesis, they supplement it as risk factors that regulate the expression of AD risk genes and Aβ processing genes. Notably, any alternative hypothesis of AD pathogenesis would need to account for the cytotoxicity, pathophysiology (including Aβ pathway activation and the formation of plaques), and disease progression findings consistent with the natural history of AD.

Since the 1990s, it has been known that Aβ plaque is not toxic (or minimally neurotoxic) and incapable of causing the massive neuronal cell death found in AD. By the late 1990s, soluble AβOs were identified as the neurotoxic Aβ species and the causative agent in AD. The Aβ hypothesis was revised in 2001-2002 to reflect the emerging concept that soluble AβOs, not Aβ plaque, cause AD. Despite clear indications more than 15 years ago that targeting Aβ plaque would not be an effective strategy, therapeutic R&D did not shift to targeting AβOs. To date, not one of the many anti-Aβ mAbs tested in Phase 2 or 3 clinical trials was designed or optimised to selectively target soluble AβOs.

Non-selective targeting of Aβ, or targeting the wrong Aβ conformation, has implications for both efficacy and safety in an anti-Aβ mAb. Aβ monomers are nontoxic. Targeting and achieving high levels of monomer binding may occur

mAb therapeutic		Aβ conformations recognised				Status
	Isotype	Monomer	Oligomer	Fibril	ARIA-E	
Bapineuzumab	IgG1	Yes	Yes	Yes	High	Discontinued; severe adverse events
Solanezumab	IgG1	High	Weak	No	Low	Phase 3: trial halted; unlikely to demonstrate benefit in prodromal AD; monomer distraction
Gantenerumab	IgG1	Weak	Yes	Yes	High	Phase 3 (very early AD); possible cognitive benefit; adverse events may limit
Crenezumab	IgG4	Yes	Yes	Yes	Low	Phase 3: two trials halted after no cognitive benefit in interim analysis
Ponezumab	IgG2	Yes	No	No	None	Discontinued; no cognitive benefit
BAN2401	IgG1	Weak	Yes	Yes	Low	Phase 2; cognitive benefit and dose response
Aducanumab	IgG1	No	Yes	Yes	High	Discontinued; two Phase 3 trials unlikely to meet primary endpoints. Maximum dose was restricted to reduce potential for ARIA-E adverse events
PMN310	IgG4	No	Yes	No	*	Preclinical; *ARIA not anticipated owing to lack of plaque binding and IgG4 isotype

Table 1: Aβ target specificities of monoclonal antibodies explain failures and potential for success in AD
Source: Adapted and modified from (1)

at the expense of AβO binding and reduce efficacy, which is known as off-target distraction. Similarly, fibrillar Aβ (plaque) is nontoxic. Targeting plaque results in off-target distraction, and it can also cause adverse effects known as amyloid-related imaging abnormalities-oedema (ARIA-E) and ARIA-haemorrhage (ARIA-H). Oligomers, specifically soluble low molecular weight AβOs, are the pathogenic cause of AD and thus represent the desired target. In addition to the Aβ target, the immunoglobulin G isotype (IgG) of the mAb drug may be important for avoiding toxicity. IgG4 antibodies appear to be less likely than IgG1 antibodies to cause vasogenic oedema/ARIA-adverse effects and are expected to have better safety profiles. Table 1 shows that Aβ target specificities can predict efficacy and adverse effects (1).

“The development of drugs that selectively target AβOs has been limited by lack of investment, technical challenges, and understanding of pathophysiologic mechanisms of AβO toxicity”

Aβ protein misfolding results in the formation of AβOs, which act as Aβ seeds for the self-propagation of toxic structures (via a corruptive protein templating mechanism) that spread throughout the brain by prion-like mechanisms. Recently, it was shown that amyloid pathology can be passed between humans through proteopathic Aβ seeds present in surgically transferred material. This finding shows how the small quantities of soluble AβOs present in the brain self-propagate and spread (eg, soluble toxic aggregates of tau, like AβO). The development of drugs that selectively target AβOs has been limited by lack of investment, technical challenges, and understanding of pathophysiologic mechanisms of AβO toxicity.

"Monitoring of early clinical stage intervention requires the availability of pharmacodynamic biomarkers that allow the verification of effective target engagement by a drug candidate"

Reducing Cost and Risk in Clinical Trials

AD drug development programs based on traditional clinical trial design during the past 10-15 years have required completion, or near completion, of larger, longer, and more costly Phase 2 and Phase 3 trials before efficacy (and in some cases, toxicity) outcomes can be determined. Resources are wasted, and valuable time is lost on the testing of drugs that eventually demonstrate no efficacy. Fortunately, the clinical research community is on the cusp of a new era, made possible by highly sensitive blood-based biomarkers that will enable screening for AD at earlier stages in the disease and efficient monitoring of disease intervention in clinical development.

Fluid biomarker	Cerebrospinal fluid assay	Ultrasensitive blood-based assay
$A\beta_{40}$, $A\beta_{42}$	Yes	Final validation work underway
Tau	Yes	Under development by multiple labs
Neurofilament light (NfL)	Yes	Yes, requires final validation
Neurogranin	Yes	Under development
SNAP-25	Yes	Under development
YKL-40	Yes	Under development

Table 2: Emergence of new, highly informative fluid-based central nervous system biomarkers

Monitoring of early clinical stage intervention requires the availability of pharmacodynamic biomarkers that allow the verification of effective target engagement by a drug candidate. Pharmacodynamic biomarkers bridge the gap between the proposed mechanism of action based on data from testing in preclinical models and data obtained from human clinical trials. The objective is to significantly shorten the required clinical development period before making a decision about the potential value of an investigational asset. Positive biomarker findings would provide validation supportive of continued or expedited development. Negative findings would provide rationale for early discontinuation, preventing unproductive investment, wasted resources, and lost time.

Table 2 lists prominent emerging fluid-based neurological disease biomarkers, all of which have been associated with AD. Findings from a recent longitudinal study confirm that plasma

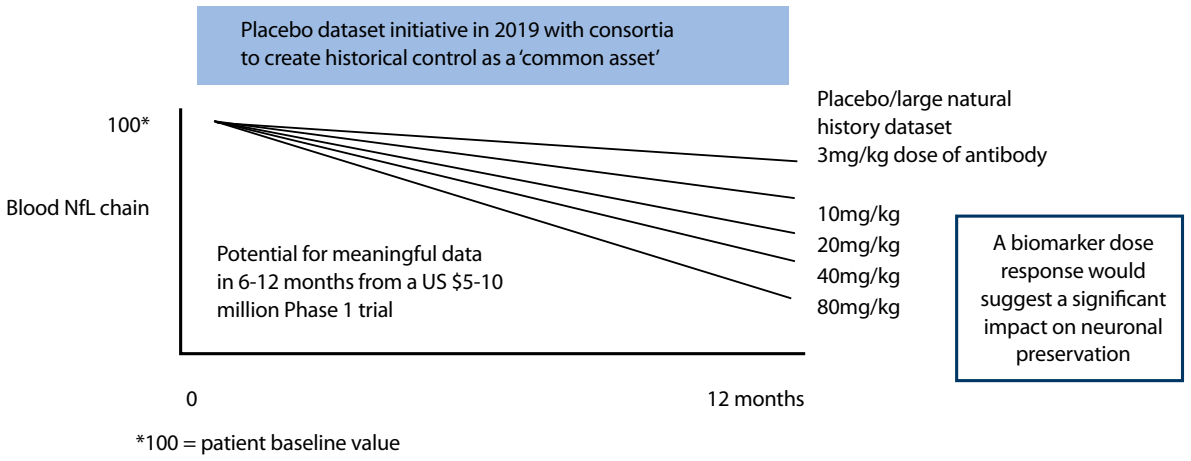

Figure 1: Hypothetical Phase 1 biomarker readout

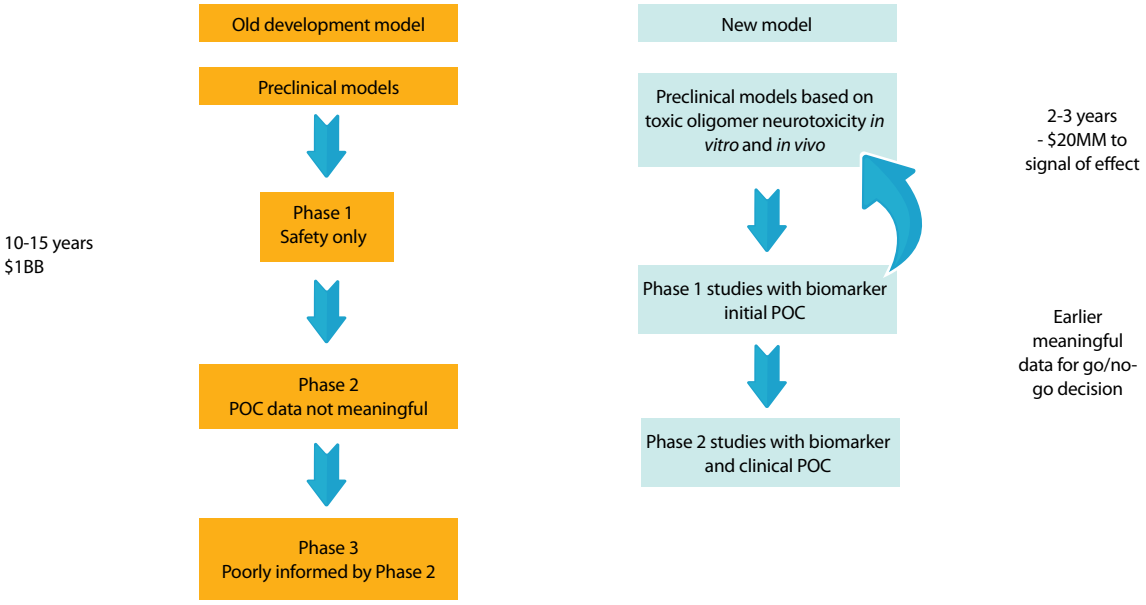

Figure 2: New AD drug development paradigm reduce cost and risk while increasing success rate

NfL is associated with hallmarks of AD (3). That is, longitudinal increases in plasma NfL levels were associated with changes in established measures of neurodegeneration in AD. These findings suggest that noninvasive plasma NfL monitoring can be used to track neurodegeneration in patients with AD and monitor efficacy in early-stage (Phase 1) clinical trials of disease-modifying drug candidates. Figure 1 shows a hypothetical example of a Phase 1 biomarker readout for a drug candidate. In this example, a dose response effect on plasma NfL levels is observed, suggesting the drug candidate is slowing neurodegeneration and preserving neurons.

The schematic in Figure 2 shows the accelerated feedback loop after Phase 1 is completed. Biomarker evidence, or lack of evidence, of proof of concept from the human trial is compared to the preclinical data supporting the efficacy concept, enabling an early evaluation of the drug candidate's performance and value.

Selectively hitting the low molecular weight soluble AβO target – the right target in AD – is the critical requirement for effectively treating the disease. The transformation of clinical trial design to include biomarker data will facilitate an earlier validation of efficacy, accelerated development of promising compounds, and earlier stage discontinuation of candidates that previously would fail only after long and costly Phase 3 trials.

References

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About the authors

Dr Neil Cashman is a Physician and Scientist recognised worldwide as one of the leading researchers pioneering the emerging fields of prion biology and protein misfolding disease, in particular, Alzheimer's disease and amyotrophic lateral sclerosis. His research has attracted more than US $50 million in funding, including grants from the National Institutes of Health. Neil is a past recipient of the Jonas Salk Prize for biomedical research and current Fellow of the Canadian Academy of Health Sciences.

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