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EDITORIAL

Recent Alzheimer's disease research highlights

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As co-editors of *Alzheimer's Research and Therapy* we would like to highlight several of the major translational research advances that have occurred over the past year, during which a tremendous amount of superb science relevant to the study of Alzheimer's disease (AD) has been published. Our selection is, of course, influenced by our own biases, and selecting particular advances to highlight was challenging. Nevertheless, many major scientific questions relevant to developing better therapies and diagnostics for AD remain. The advances we have chosen to highlight represent evolving areas of research in AD that raise as many questions as they answer, but offer some promise that may help us to reach our shared goal of translating research advances into real advances that benefit patients.

Better cellular models of Alzheimer's disease?
For many years the lack of truly faithful cellular and animal models of AD has imposed some limitation on what can be inferred from these experimental models. With the technological advances demonstrating that human fibroblasts can be converted into pluripotent stem (iPS) cells and subsequently into neurons, and the promise of this technology to provide new cellular models of human neurodegenerative disease, it was only a matter of time for this technology to be applied to the study of AD.

Over the past year, the first of what are likely to be a plethora of studies examining culture models of AD based on neuronally differentiated iPS cells derived from familial and sporadic AD patients and Down syndrome were published. The first of these demonstrated that fibroblasts from familial AD patients with presenilin 1 or 2 mutations showed altered processing of amyloid β

protein precursor (APP) and increased production of total amyloid β protein (Aβ) with increased relative production of Aβ42 [1]. The second included neuronally differentiated iPS cells from reprogrammed fibroblasts of two APP gene duplication carriers, two patients with sporadic AD and two controls [2]. In the neuronally differentiated iPS cell lines from familial and one of the two sporadic AD patients, there was higher secretion of Aβ40. A further finding in these three AD cell lines provided a suggestion of interactions with mechanisms of tau pathology: higher levels of phospho-tau and active glycogen synthase kinase (GSK)3β. The third and most recent paper conducted similar studies using neuronally differentiated iPS cells from Trisomy 21 patients [3]. When differentiated, these cells showed increased production of Aβ42, increased phospho-tau and perhaps most interesting, the accumulation of Aβ42 aggregates.

Although the alterations in APP and Aβ observed were largely anticipated, based on previous data from human fibroblasts and other biological samples [4], the alterations in tau and GSK3β activity are somewhat surprising. Even more surprising was the demonstration of extracellular Aβ42 aggregates in long-term iPS Trisomy 21 neuronal cultures. Indeed, no previous culture system to date has reproducibly produced such plaque-like aggregates. If this is reproducible and confirmed to result in a plaque-like structure, it may be possible to utilize such cells to more precisely understand plaque formation under physiologic culture conditions.

Of course with any new technology there remain a number of concerns, and it is not clear whether issues of scale and reproducibility will enable this technology to totally overcome limitations of studying a degenerative brain disease in a culture dish. Though the consistency of the findings across the three studies is reassuring, they still only report on the phenotypes of a handful of cell lines from those at risk for AD. One future application that will be very intriguing is whether iPS cell technology may offer a way to obtain insights into biological mechanisms of genes implicated as risk modifiers in late onset AD [5,6]. Hopefully, such future studies will be conducted with appropriate experimental blinding and sufficient power to ensure that the results obtained are widely reproducible.

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Insights into the mechanistic basis for the regional distribution and spread of AD pathology

Classic postmortem studies have framed the characteristic progression and regional distribution of tau and Aβ pathology in the brain. In AD, tau pathology characteristically spreads from the entorhinal cortex into limbic and association cortices as AD evolves [7]. Several studies that have appeared this year provide mechanistic insights into the distribution and spread of tau pathology [8,9].

The microtubule associated protein tau has traditionally been thought to be a cytoplasmic protein. It has been known for some time that soluble tau can be detected in CSF, but its presence in a body fluid was attributed to leakage from dead or dying cells [10]. More recent data from both cell culture studies and *in vitro* microdialysis suggest that tau and tau aggregates can be constitutively secreted from cells [11]. Moreover, there is evidence that extracellular tau aggregates can seed intracellular aggregation. Two papers published in the last year suggest that tau secretion and subsequent seeding of aggregation can occur *in vivo* and account for the progression of tau pathology *in vivo* [8,9]. Both of these papers describe studies using transgenic mice expressing the fronto-temporal dementia-associated tau P301L mutant in the entorrhinal cortex, and both demonstrated that tau pathology begins in the entorrhinal cortex in these mice but spreads along anatomically connected networks, possibly through synaptic connections. These data are important conceptually as they provide further evidence that tau pathology in AD may spread through a prion-like conformation-dependent templating reaction mediated by release of tau aggregates from one cell and subsequent internalization by a neighbouring cell. They also provide an explanation for the potential efficacy of anti-tau immunotherapy [12]. Although it is possible that anti-tau antibodies modulate tau pathology by somehow entering neurons and altering tau aggregation, these data would suggest that some anti-tau antibodies may block spread of tau pathology from one cell to another by targeting the extracellular tau transmitted from one cell to another.

Does epigenetic modification offer new insights for developing treatment strategies?

The role of epigenetic mechanisms, that is, the ability of non-genetic factors to cause genes to express themselves differently without changing their underlying DNA structure, is becoming apparent in an ever increasing number of biological and medical fields and may offer insights into why therapeutic strategies targeting amyloid pathology have been unsuccessful to date. An elegant study reported recently in *Nature* provides evidence that Aβ may constrain the expression of some memory- and learning-related genes [13]. After these have been 'switched off' by Aβ they cannot be 'switched on' again just by removing the Aβ. This process seems to be mediated via a histone deacetylase, HDAC2, which the authors have shown to be activated in brain tissue from both transgenic mouse models, where it reduced synaptic density and memory function, and human AD sufferers. They went on to show that inhibiting HDAC2 restored synaptic plasticity and improved some aspects of memory, although it did not boost the number of surviving neurons in the mice. The pathway is a complex one that also involves the glucocorticoid receptor, GR1.

The implied possibility of reversing pathology, in contrast to slowing decline, is an exciting one but needs further evaluation. HDAC inhibitors are already used or being explored in a number of conditions, for example, oncology, and some pharmaceutical companies are exploring their potential in AD. However, we also need to understand whether such drugs might affect other important but unrelated aspects of genetic function. Roles of epigenetic mechanisms in aging and AD are likely to be a strong focus of future translational research.

Towards Alzheimer's disease prevention

Over the past few years the challenges of disease modification in symptomatic patients have become increasingly apparent. Preclinical studies almost invariably show diminishing efficacy with increasing pathology at initiation of treatment. There have been several failed phase III clinical trials with disease modifying agents, though many of these agents were suboptimal with respect to potency, therapeutic window, or brain penetrance. Moreover, even phase II studies with more optimal disease modifying agents fail to show evidence for significant efficacy.

Thus, a clinical highlight of the past year has been a renewed emphasis on designing and implementing more appropriate clinical trial methodology for evaluating disease-modifying treatment in AD. Editorials and reviews have emphasized that disease-modifying treatment in established AD at the stage of dementia may be too late - the greatest benefit could come from preventing the chain of events that leads to neurodegeneration and irreversible structural changes in the brain [14-17]. Biomarkers exist that are able to identify AD pathology, particularly amyloid deposition, long before cognitive decline begins, and sensitive cognitive tests and paradigms using functional magnetic resonance imaging are showing alterations even during what has been termed 'preclinical AD' [16] and the 'asymptomatic at risk' individual [18] and new diagnostic research criteria have been proposed by two working groups.

Treatment trials are at an advanced level of planning in two groups of people at risk for AD. Programmes to clinically identify and characterize carriers of mutations in the presenilin or APP genes, and also systematic initiatives that aim to assess and evaluate biomarkers

during these presymptomatic stages are under way. The Alzheimer Prevention Initiative [17] has planned a clinical trial in a large population of presenilin 1 E280A mutation-carriers in Colombia, whose natural history and transition from asymptomatic through early symptoms and cognitive deficits to overt dementia has been precisely mapped in a landmark 15 year follow-up study [19]. The international Dominantly Inherited Alzheimer Network group has enrolled and characterized people with different APP and presenilin mutations [20] and is planning an intervention clinical trial in at risk carriers who test positive for amyloid biomarkers. Another initiative more closely relevant to sporadic AD proposes to identify amyloid carriers among elderly subjects who are not cognitively impaired and study their outcomes, using cognitive and imaging measures, over a period of two years [16].

In summary, this has been an exciting year for all of us working to improve treatment for people with AD. Greater understanding of the underlying pathological mechanisms, gained from research using transgenic animals and new stem cell-based technologies, have revealed possible novel therapeutic strategies targeting the underlying pathologies, that is, both Aβ and tau pathology. These developments are complemented by the move to identify pre-dementia AD and improve trial design. Together they provide hope for the future.

Abbreviations
Aβ, amyloid β protein; AD, Alzheimer's disease; APP, amyloid β protein precursor; GSK, glycogen synthase kinase; HDAC, histone deacetylase; iPS, induced pluripotent stem;

Competing interests
DG serves on data and safety monitoring boards for clinical trials for Janssen and Elan Pharmaceuticals and for Balance Pharmaceuticals. He is a consultant for Elan Pharmaceuticals, Phloronol, Inc., and United BioSource. TG has served on advisory boards related to preclinical studies for Janssen, Novarits, Bristol-Myers Squib and Elan Pharmaceuticals. He has received sponsored research grants from Lundbeck and Myriad Pharmaceuticals in the past. GW has served on advisory boards to a number of pharmaceutical companies, including Jannsen, Shire Pharmaceuticals, Lundbeck, Cambridge Neurodiagnostics and Roche. He is a consultant to TauRx. DG, TG and GW are Editors-in-Chief of *Alzheimer's Research & Therapy* and receive an annual honorarium.

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