alzheimer's research&therapy

EDITORIAL

Progress in Alzheimer's disease research circa 2013: Is the glass half empty or half full?

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These are exciting but challenging times in Alzheimer's disease (AD) research. At many levels, a more detailed picture of the disease is being refined and advanced, but other aspects of the disease remain highly enigmatic. Furthermore, long-hoped-for advances in the development of disease-modifying therapy remain unfulfilled.

Recent areas in which there have been both steady and partially transformative advancements include the following:

- Burgeoning research in biomarkers and imaging that provide windows into the structure, chemistry, and connectivity of the brain, extending from preclinical cases to minimally symptomatic patients to those with dementia [1]. Current and emerging imaging tools and cerebrospinal fluid biomarkers provide methods to better assess risk for dementia and rate of progression. The US Food and Drug Administration (FDA) has recently recognized the promise of these tools by providing new guidance for initial approval pathways in preclinical prevention trials [2]. Several AD prevention trials that are currently under way or soon to be enrolling subjects will critically test the utility of these biomarkers in these pivotal studies and potentially the willingness of the FDA to use surrogate markers in lieu of cognition or functional changes as trial endpoints.
- Basic research advances include the demonstration of circuit dysfunction, connectivity [3], and models of spread of pathologically misfolded proteins (tau, A-beta42, and alpha-synuclein) [4-7] in explaining progression of disease and perhaps offering new avenues for treatment. Better tools to characterize oligomers of pathogenic proteins are helping to clarify their roles in pathological events.
- Genetic research on a large scale in well-phenotyped people has given a booster shot to the amyloid hypothesis of AD. Attenuated risk in Icelandic family members with a rare amyloid precursor protein (APP) mutation provides further evidence of the triggering role of Aβ in AD [8] and further support efforts to lower Aβ prior to its deposition in the brain.
- Two consortia identified TREM2 variants with significant risk for AD [9,10]. This genetic association between a receptor known to regulate microglial/monocyte activation and cytokine release more firmly establishes a genetic connection between innate immunity and AD. Numerous preclinical studies also suggest that various manipulations of innate immunity can modulate Aβ and tau proteostasis and other phenotypes in preclinical models. Collectively these data provide a rationale for further investigating the role of innate immunity in AD and suggest that novel therapeutic approaches could emerge from such studies.

However, these positive advances are tempered by data and observations that provide a sobering look at how challenging it is to translate our enhanced understanding of the disease into therapies that benefit patients:

- The negative or weakly positive results from large phase 3 clinical trials of monoclonal antibody therapies raise questions about how and when to target brain amyloid effectively. Given the enormous costs associated with these trials, will such negative trial data reduce private sector investment in AD?
- Detailed neuropathology studies indicate the high frequency of mixed pathology (AD, vascular lesions, synuclein pathology, and hippocampal sclerosis) that may combine to tip a patient's cognitive abilities into symptomatic dementia [11,12]. Such data raise the possibility that single-target approaches may have limited benefit, especially in symptomatic patients.
- Lack of well-defined treatment targets beyond those that affect the production or clearance of Aβ. Although tau and apolipoprotein E have been studied for decades, translational research to produce druggable targets and candidate compounds is thin. Furthermore, major gaps remain in our knowledge of the various factors downstream of Aβ, connecting Aβ to tau, and those that drive neurodegeneration. All of these

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present formidable obstacles to the development of novel therapeutic approaches to AD.

From a societal perspective, we hope that we are at a tipping point in terms of translating the enhanced public awareness of the disease into enhanced support. Indeed, even in challenging fiscal times, there appears to be increased political interest in recognizing that the enormous public health problems posed by AD appear to be impacting efforts to increase public sector funding and also spur public-private partnership. However, given its economic and societal costs, AD appears to be very much underfunded.

A second issue we should consider is to ensure that efforts to move to primary or secondary prevention do not diminish efforts to develop novel treatments for AD at symptomatic stages. Even if the current prevention trials yield promising results, it will be many more years before a successful prophylactic therapy could be widely deployed. For those at risk of developing AD in the near future and those who currently suffer from the disease, we are morally obligated to try to develop novel approaches that can impact the disease course in people who are showing symptoms of cognitive decline. Even approaches that may be more invasive than researchers are accustomed to, such as deep brain stimulation, gene therapy, or direct infusion of a therapeutic agent into the brain, may be worth considering.

Alzheimer's Research & Therapy takes pride in our open-source coverage of these findings and issues, from original papers to research reviews, commentaries, and thematic series. Our recent news highlights include the following:

- Changes in leadership: Gordon Wilcock is stepping down after years of valuable guidance, input, and collegiality. We are delighted to announce that Philip Scheltens has agreed to take his place as one of the Editors-in-Chief, and we greatly look forward to his enthusiasm and wide-ranging research knowledge, which will help us to grow and improve the journal.
- The journal will be receiving its first Thomson Reuters (ISI) Impact Factor this year and will be indexed in Science Citation Index Expanded, Journal Citation Reports, and Current Contents. This is in addition to the other bibliographic databases that currently include articles published in *Alzheimer's Research & Therapy*, such as CAS, Embase, PubMed, PubMed Central, and Scopus.
- We have set up alliances with several organizations to foster communication and explore new opportunities for interacting with the research community. One such partner is Alzheimer's Disease International, and we look forward to working with them to identify emerging research news and areas of focus. We also have links with Alzforum (www.alzforum.org) and are exploring ways to link webinars or topics that they cover with articles or thematic reviews that appear in *Alzheimer's Research & Therapy*.

This editorial has been written to accompany our annual highlights print issue, featuring a selection of articles already published in the journal in 2013. The issue features a range of article types and research foci that illustrate the scope of the journal, including diverse patient-oriented research [13-16] that highlights the growing translational presence of the journal [17-21]. Collectively, these studies demonstrate the increasing impact of *Alzheimer's Research & Therapy* as a home for high-quality primary research manuscripts but also for reviews, debates, and commentaries that can help to survey and guide the field.

Finally, we would like to thank our Editorial Board for their advice and contributions. We have enlarged the Board recently to include emerging researchers in areas that were not well covered and to broaden our global representation. We thank both the reviewers, without whom we would not be able to maintain the quality of our articles, and those who by submitting their manuscripts are supporting our efforts to make this a premier and respected journal.

Abbreviations

AD, Alzheimer's disease; FDA, US Food and Drug Administration.

Competing interests

DG serves on Data Safety Monitoring Boards for Elan Pharmaceuticals (Dublin, Ireland), Janssen (Beerse, Belgium), and Balance Pharmaceuticals (Santa Monica, CA, USA); is a consultant for Elan Pharmaceuticals; and receives research support from the National Institutes of Health (NIH), the Michael J Fox Foundation, and the Alzheimer's Drug Discovery Foundation. TEG receives research support from the NIH, the Ellison Medical Foundation, the Thome Medical Foundation, ALSA, and the Michael J Fox Foundation. PS receives research support from Alzheimer Nederland (Amersfoort, The Netherlands), ZonMw (The Hague, The Netherlands), Merck (Westpoint, PA, USA), and GE Healthcare (Amersham, Buckinghamshire, UK). DG, TEG and PS are Editors-in-Chief of *Alzheimer's Research & Therapy* and receive an annual honorarium.

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Published: 29 May 2013

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doi:10.1186/alzrt180
Cite this article as: Galasko D, *et al.*: Progress in Alzheimer's disease research circa 2013: Is the glass half empty or half full? *Alzheimer's Research & Therapy* 2013, **5:**26.