Will we have a drug for Alzheimer's disease by 2030? – the view from Pharma

Simon Lovestone, Disease Area Stronghold lead for neurodegeneration, Janssen-Cilag

Husseini K Manji, Global Therapeutic Area Head, Neuroscience, J&J

Conflict of interest

SL is an employee of Janssen-Cilag Ltd. Within the past three years he has performed consultancy for SomaLogic, Eisai, Merck and Lilly, has held direct grant funding from Astra-Zeneca and EU funded public-private partnership research funding through IMI with multiple EFPIA companies. He retains an academic position at the University of Oxford, is a founding director of Cristal Health and is a named inventor on patents for biomarkers held by KCL and the University of Oxford

HKM is an employee of Johnson and Johnson

Funding

No funding related to this work

Introduction

Recent years have seen serial trial failure with compounds developed for Alzheimer's disease modification [1]. These hugely costly negative trials have led to some companies exiting from one of the world's most pressing unmet medical needs. Whilst we acknowledge the challenge of successful drug development in this area, we are confident of eventual success; the question is when that success will come and what can we do to hasten progress.

When will we have a disease modification therapy for Alzheimer's?

Given the timelines of development, for a disease modification compound to reach market by 2030, it would have to be in at least early clinical development today. The question then becomes twofold; first which of the compounds identified by Cummings et al [2] in their annual review of drugs in clinical trials are most likely to succeed, and second, might we see development of further symptomatic therapies, potentially deliverable in a shorter timeframe. In early 2019 Cummings et al identified 132 compounds in trials, of which over 70% were proposed as disease modifying agents. In late phase the largest proportion of these trials were for compounds targeting the generation, aggregation or clearance of amyloid plaques but in earlier phases there was more target diversity. Given the cessation of multiple trials of amyloid agents, it is already clear that next year's report will include a greater proportion of trials targeting tau.

Will today's disease modification compounds fare better than previous approaches?

The growing diversity of drugs in clinical trials is encouraging; although the Alzheimer's disease drug development pipeline remains sparse, it is at least moving in the right direction. However, when considering the immediate prospect of a drug by 2030, a great deal rests on whether tau will prove a better target than – in the broadest sense – amyloid. There are good reasons to think this is indeed the case. Whilst the evidence for a primary role of amyloid in Alzheimer's disease is overwhelming, most of that evidence comes from genetics. This has been tirelessly reviewed, both in the lead up to trials of agents designed to reduce the generation of beta-amyloid or to clear amyloid deposits, and in the post-mortem following their failure [3, 4]. We will not rehearse this argument here, nor discuss the prospects of success were trials to be completed in the pre-clinical phase of disease rather than prodromal or mild AD. Instead we point out that the relationship between tau pathology and disease is considerably more understood, and arguably more direct, than that between amyloid pathology and disease. In summary, this close relationship derives from more than two decades of research showing that:

- Pathological changes in tau including phosphorylation and aggregation have an unambiguous detrimental effect on neuronal function in preclinical models [5]
- Pathological lesions resulting from tau have a characteristic evolution and spread in the brain and correlate tightly with clinical features including severity [6]
- The onset of tau pathology, as measured by CSF assays and PET imaging, occurs at about the same time as symptoms [7, 8]

Given also the genetic evidence for tau being a driver of neurodegeneration, tau pathology is an excellent target for therapeutic development. The breakthrough in such developments came when it was demonstrated that the characteristic spread of pathology may be a

consequence of inter-neuronal seeding of pathological tau [9]. This enabled the development of tau-directed immunotherapies. It is largely these molecules that constitute the hope that we will have a therapy for AD by 2030. Whilst tau pathology represents a tremendous target for disease modification it remains to be seen whether the window of opportunity represented by extracellular, inter-neuronal spread of tau species that seed pathological aggregation in recipient neurons, is wide enough to deliver a successful therapy. Compounds, including from our own company, are in clinical trials that will deliver an answer to this question within the next ten years.

Increasing our shots on goal

In addition to tau, Cummings et al [2] document other therapeutic approaches now in development. Foremost are compounds that modulate neuroimmune regulation. The importance of the immune system in AD has long been recognized. Indeed, given the gliosis and astrogliosis obvious at post-mortem in end stage disease, this has never been in doubt. However, developing therapeutic programmes has lagged behind those targeting the core lesions of AD, not least because of questions as to whether the immune dysfunction is simply a response or a driver of disease, whether the immune response is primarily protective or contributes to neuronal dysfunction and which of the myriad of possible targets are justified as targets. Again, genetics has provided many, if not all, of the answers to these questions and this is reflected in the growing numbers of immune targets in development. Increasingly powerful data from genome wide association studies and other approaches has demonstrated the role both of common variants in genes and pathways and in rare variants of genes relating to immune function in altering risk of disease. This genetic evidence from AD is supported by that from other neurodegenerative diseases with common pathological features with AD where an immune regulatory gene is causative in some familial instances – the immune modulator progranulin in FTD for instance.

Many questions remain, not least which pathway of immunity to target and, given the significant possibility that the immune role could have both protective and deleterious effects at different phases of disease, when to target it. Nonetheless, the proliferation of immune targets in development is a very positive sign. More is needed though. Although it will be too late for a drug by 2030, the most significant change in the landscape of drug development that will facilitate the delivery of a drug will be the growing signs of diversity of targets in development. This cannot be emphasized enough; to score, we need more shots on goal.

Symptomatic therapies for Alzheimer's disease

Regardless of the fate of disease modification therapy for AD there is, and likely will always remain, a need for symptomatic therapy for disorders causing dementia. Whilst memory loss resulting from cognitive decline is a defining feature of dementia, it is only one of the many symptoms of AD. Collectively termed Behavioural and Psychological Symptoms of Dementia (BPSD) these include mood disturbances including depression, activity related disturbances (such as agitation and wandering as well as anhedonia or lethargy), psychotic symptoms such as visual hallucinations and, often disturbing, delusions, sleep disturbance which may be linked to disruption of circadian rhythms and the phenomenon of increasingly disturbed behavior towards the end of the day ('sundowning')[10] and others. BPSD are common in AD,

incur significant carer distress and are a major influence on the need for both domiciliary professional care and for residential care. A large proportion of compounds currently in development are targeted for neuropsychiatric (28%) or cognitive (11%) symptoms [2] and as trials for symptomatic therapies are typically considerably shorter than those for disease modification then there is a very good chance of an intervention proving efficacious within the coming decade.

What will increase the chances of success ?

Whilst we are hopeful that one of the compounds currently in clinical development will reach patients by 2030, we are impatient for progress and strongly believe that confidence in the current pipeline alone is insufficient. The field has been confident before and lessons must be learnt from previous blows to that confidence. We suggest here three areas where recent progress might suggest those lessons are being learnt and, as a consequence, that progress is becoming more likely.

First, the heterogeneity of pathological process in people with a clinical diagnosis of AD has been increasingly recognized. At the most extreme, up to one fifth of those in clinical trials testing amyloid agents had little or no amyloid pathology. Clearly, even less marked heterogeneity than this hampers efficacy testing in the clinic. The increasing sophistication of biomarkers, including PET, CSF and even blood-based markers indicative of different pathologies is rapidly enabling trials in participants defined on entry by pathological measures. Another powerful and complementary approach to the challenge of heterogeneity is to first perform trials in rare, genetically determined, variants with identical pathology

Second, the primary outcome measure of all disease modification trials – cognition – is vulnerable to considerable daily fluctuation, individual differences in prior performance and cultural and linguistic complications in measurement. Although huge efforts have been made to overcome these difficulties, with considerable success, using cognition as an outcome measure necessitates large and long trials, especially when seeking to intercept in prodromal and preclinical phases of disease. Again, biomarker developments hold out the potential for more rapid decision making for futility or acceleration in phase II, proof of concept studies. Molecular biomarkers suitable for such purposes are with us already and we look forward with anticipation to the development of other biomarkers using digital technologies.

Thirdly, given the resource demands of disease modification trials in AD, we welcome the efforts being made to speed clinical development through platform trials such as the European Prevention of Alzheimer's Disease, networks of trial delivery sites such as through the Global Alzheimer's Platform and the sharing of data for modelling and for biomarker development such as through ADNI, GAAIN, EMIF and other initiatives.

All these measures combined with continued support from governments and funders, as represented for example in the series of summits initiated by the UK and then further developed with the leadership of the World Dementia Council, serve to maintain and accelerate research leading towards the goal of a drug for Alzheimer's disease

Conclusions

In summary, we are confident of eventual success in the development of drugs for Alzheimer's disease. The increasing diversity of targets in discovery phase, the nature of the targets in clinical development and the improvement of clinical trials, especially with the use of biomarkers for screening, selection and increasingly for proof of concept outcomes, all underpin this confidence. Whether success will be reached by 2030 depends on the fate of compounds in clinical trials today. We think such success is probable both for disease modification targeting tau and for symptomatic therapies. However, the decade ahead will also, invariably, bring failure and this will require companies as well as governments to hold their nerve, to learn from such failures and to use this learning to double down on this disease and increase our efforts to find the best targets and to execute the best trials. With confidence then we predict success; we certainly need it as our populations are waiting.

1. Cummings, J.L., T. Morstorf, and K. Zhong, *Alzheimer's disease drug-development pipeline: few candidates, frequent failures*. *Alzheimers Res Ther*, 2014. **6**(4): p. 37.
2. Cummings, J., et al., *Alzheimer's disease drug development pipeline: 2019*. *Alzheimers Dement (N Y)*, 2019. **5**: p. 272-293.
3. Hardy, J., *The amyloid hypothesis for Alzheimer's disease: a critical reappraisal*. *Journal Of Neurochemistry*, 2009.
4. Karran, E. and B. De Strooper, *The amyloid cascade hypothesis: are we poised for success or failure?* *J Neurochem*, 2016. **139 Suppl 2**: p. 237-252.
5. Iqbal, K., et al., *Tau pathology in Alzheimer disease and other tauopathies*. *Biochim Biophys Acta*, 2005. **1739**(2-3): p. 198-210.
6. Braak, H. and E. Braak, *Neuropathological staging of Alzheimer-related changes*. *Acta Neuropathol*, 1991. **82**(4): p. 239-59.
7. Johnson, K.A., et al., *Tau positron emission tomographic imaging in aging and early Alzheimer disease*. *Ann Neurol*, 2016. **79**(1): p. 110-9.
8. Roe, C.M., et al., *Amyloid imaging and CSF biomarkers in predicting cognitive impairment up to 7.5 years later*. *Neurology*, 2013. **80**(19): p. 1784-91.
9. DeVos, S.L., et al., *Synaptic Tau Seeding Precedes Tau Pathology in Human Alzheimer's Disease Brain*. *Front Neurosci*, 2018. **12**: p. 267.
10. Leng, Y., et al., *Association between circadian rhythms and neurodegenerative diseases*. *Lancet Neurol*, 2019. **18**(3): p. 307-318.