Alzheimer's disease therapy: a moving target

> "*As unlikely as it is that therapeutic approaches to Alzheimer's disease currently under study will have any meaningful impact on disease progression, we also cannot exclude the possibility of a breakthrough in our lifetimes … Our best hope for such a breakthrough appears to be a multimodality attack on Alzheimer's disease biology.*"

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Pharmacological intervention in Alzheimer's disease (AD) has been the subject of intensive, time consuming and costly investigations in the past 25 years, particularly with the elucidation of the protein constituents of pathological lesions presumed to have pathogenic relevance and therefore be the prime target for reversal [1]. The enthusiasm centered on lesion-based constructs to treat the disease, however, this approach has been tempered in the last 10 years by repeated failures of immunotargeting, including untoward outcomes such as the precipitation of meningoecephalitis, and cognitive measures reported as worse than placebo [2].

Specifically, we have seen proof of concept (i.e., reduction of amyloid-β by immunotherapeutic constructs, or amyloid-β 'clearing') and continued relentless progression of disease. The temptation to 'move the goal posts' as it were, to a prodromal state is predictable. Yet, a renewed view of lesion-based approaches through the original and appropriate scientific prism, that is the acceptance of the null hypothesis until proven otherwise, is in order. Furthermore, a wholesale re-examination of the issue of modern therapy and exploration of alternative approaches is needed.

Several issues are therefore open to questioning and worth examining. First, the concept of familial versus sporadic disease has been addressed only obliquely in the literature. The prevailing underlying premise suggests that when a germline mutation produces a disease phenotype mimicking sporadic disease, the Mendelian condition is the 'familial form' of the sporadic disease [2]. Indeed, this concept is so pervasive that patients with familial AD are excluded from clinical trials, despite the fact that the constructs, animal models and pathogenic cascades were elaborated from pathogenic mutations. Yet it is becoming ever more clear that one should equate familial and sporadic disease only at one's peril when it comes to therapeutic trials of understanding pathogenesis. The similarities and differences in the underlying pathology between familial and sporadic disease are therefore examined in this issue of *Therapy*.

Along these same lines, demonstrable efficacy of therapeutic challenges in experimental animals is often necessary for therapeutic approaches to progress into clinical trials. Nevertheless, animal models are widely regarded as tangential to human disease at best. They typically contain one to several pathogenic mutations that individually are exceedingly rare in humans [3]; the animals develop neuronal loss and neurofibrillary pathology only with great difficulty, and the behavioral/cognitive end points vary from model to model and sometimes experiment to experiment [4]. The case might even be made that modeling human AD is sufficiently complex to basically preclude a relevant model being found at present or at any time in the foreseeable future. In this issue of *Therapy*, two strategies that are ostensibly complementary are explored: immunotherapy and anti-inflammatory therapy. Both are thought to target either an initiating, toxic protein species (e.g., soluble amyloid β or phosphorylated tau) or the deleterious consequence of that toxicity. However, as data indicating that proteins and cascades are part of a host response that is probably beneficial accumulates, the theoretical hurdles of using anti-inflammatory and immunomodulatory therapies increases [5–7]. Nevertheless, given the limited understanding, study and continued review of the issue is clearly warranted and discussed in detail in this issue of *Therapy*.

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Of relatively recent interest, the pleiotropic endocrine hormone leptin has been implicated in AD pathogenesis, and has been suggested as a link between obesity and AD. Leptin has been demonstrated to have a complex array of effects on brain structure and function, including hippocampal neurogenesis, dendritic outgrowth and synaptogenesis, memory consolidation and long-term potentiation via influences on glutamate receptors [8]. The discussion of leptin in this issue of *Therapy* by Dr Tezapsidis is therefore of some prescience [9].

Finally, as AD and age-related cognitive decline affects memory disproportionately, attacking the outcome of memory loss *per se* as a palliative measure has substantial merit, as the only marginally useful therapy available to date is the simple enhancement of neurotransmission via cholinergic agonists [1]. Dr Summers therefore discusses ways to improve memory loss in AD in this issue of *Therapy* [10].

As unlikely as it is that therapeutic approaches to AD currently under study will have any meaningful impact on disease progression, we also cannot exclude the possibility of a breakthrough in our lifetimes, even if by accident. Our best hope for such a breakthrough appears to be a multimodality attack on AD biology, combined with the humble recognition that we are losing the battle to date, and are only beginning to understand the totality of the process.

Dedication

This issue is dedicated to Mark A Smith.

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