TARGETS FOR THE NEXT GENERATION OF ALZHEIMER'S DISEASE TREATMENT

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99.6% of Clinical Trials in AD Have Failed

- Billions of dollars and the efforts of over 30,000 talented researchers have been directed toward studying AD since the mid 1980s, yet the only approved drugs are based on concepts from the 1970s.
- With failure, key opinion leaders have chosen to modify rather than abandon a cascade model of AD that puts Aβ or tau as the initiator.
- Here we explore an alternative holistic approach, one that has benefited patients of other age-related chronic disease.

AD is Dementia with Senile Plaques and Neurofibrillary Tangles

- Did Alois Alzheimer lead us astray?
- He did not confuse causality with association.
- The ‘causality’ link developed in the modern era of AD research due to a focus on the structure and composition of the lesions and later the genetics and cell biology, all of which showed the proteins of the lesions are important
- But is linkage causality? Or is it a role that must be revealed?

Is Removing Plaques and Tangles Beneficial?

- Amyloid cascade hypothesizes that all aspects stem from Aβ.
- Tau cascade hypothesizes that while AD might stem from Aβ, tau is the major driver of cell death.
- Major problem is that Aβ and tau are common features of the brain in normal aging and can exist in and outside of neurons without killing them.
- Clinical trials have effectively removed Aβ, yet there was mixed clinical benefit.
- AD patients show variable neuronal loss and atrophy, yet few if any benefited, indicating that removing Aβ earlier is unlikely to be better.

Alternative View of AD Pathology

- The field has now focused on refining cascade hypotheses with greater complexity, or instead rejecting Aβ and tau as irrelevant tombstones.
- A third ground is that lesions reflect the brain's response to the most common chronic injury: aging.
- Aβ and tau are not passive, but rather key elements necessary for continued function of the brain throughout life.
- Deposition of both in AD indicates chronic induction rather than causality, a pattern seen in other amyloidoses.
- Mutations in Aβ or tau metabolism leave the brain more vulnerable due to improper deployment of the response, rather than causality.

How Can Aβ Be Protective?

- Aβ as plaques and intraneuronal oligomers is associated with reduced oxidative damage in AD (sporadic and genetic) and Down syndrome.
- Oxidative damage is the earliest change of AD, and is highest in MCI, decreasing with Aβ.
- Aβ in plaques contains and redox silences copper, preventing it from causing oxidative stress in aging and AD.
- Aβ is a regulated response that alternatively can cause oxidative stress when outside physiological bounds, e.g. mutations and rodent models.

Could Removing Aβ Be Harmful?

- Removing Aβ, especially prior to dementia, could alter the brain's redox balance.
- Aβ and tau are critical responses to aging that must be understood prior to drastic intervention that so far has not benefited patients, and in some cases has become harmful.
- Risk benefit ratio must be considered when applying Aβ therapeutics to asymptomatic individuals.

What Does This Change?

- Aβ accumulation marks a response to the underlying changes of aging rather than pre-AD; Aβ may be a key element of successful aging.
- Gross removal of Aβ is unlikely to show benefit, although modulation of what might be the most critical pathway to successful aging is a viable therapeutic pathway and biomarker.
- Understanding what drives Aβ in aging will provide new therapeutic targets.

Therapeutic Targets

- In aging, levels of Aβ correlate with mitophagy suggesting Aβ is linked to mitochondria dysfunction and sequestering redox active copper that is released through mitochondria turnover.
- Functional mitochondria are required for Aβ toxicity.
- AD may fundamentally be a metabolic syndrome with a brain specific protective response.
- Therapeutic benefit of insulin, leptin, or other metabolic hormones is showing promise.

AD Prevention

- Numerous epidemiological studies support AD linkage to diet and exercise, the primary controllers of metabolism.
- Intervention studies show lifestyle modification significantly reduces AD.
- AD is joining the list of age-related diseases that can be managed through lifestyle and, in the future, therapeutics that modulate key factors: metabolism, Aβ and tau levels.
- Working with rather against the biological response of the aging brain could offer new windows to delay AD much as it has to reduce heart disease: not by curing but rather by reducing the impact.

Summary

- Failure of the amyloid cascade needs to open AD to new ideas and hope, rather than adding complexity to failed ideas that could stall progress for further decades.
- AD is emerging as a chronic illness in which age-related metabolic abnormalities are met by protective responses.
- Holistic interventions are the only demonstrated paths to offer benefit to patients.