Alzheimer’s disease: Problems of retaining old constructs.
Examples of reasons for and successes of revising concepts of disease subtyping

George Perry, Ph.D.
Chief Scientist, Brain Health Consortium
Semmes Foundation Distinguished University Chair of Neurobiology
The University of Texas at San Antonio (UTSA)
Outline – Revision vs Reconstruction

Revision of AD
• Amyloid Cascade Hypothesis.
• Clinical trials targeting Aβ.
• Revising AD key concepts

Reconstruction
• Alternative view of AD pathology
• Alternative targets in AD
• AD prevention
• Summary
Amyloid Cascade Hypothesis

• By definition, AD patients have Aβ and tau deposits associated with neuronal and glia degeneration.

• Mutations linked to AD all alter Aβ processing from amyloid beta protein precursor (AβPP).

• In cell and animal models, Aβ can kill neurons.

• Hardy and later Hardy and Selkoe proposed Abeta as the initiator and cause of AD (Bauptists).

• Primary alternative is Tau suggested to be critical for neuronal survival (Tauists).

Amyloid-β cascade hypothesis.
Amyloid-β precursor protein (APP) gene expression is followed by consecutive protease processing by β-secretase 1 (BACE1) and γ-secretase complex (PSEN1(presenilin 1), PSEN2(presenilin 2), nicastrin and APH1 (anterior pharynx-defective 1)) releasing the amyloid-β peptide, including pathogenic species Aβ42. Aβ42 undergoes conformational change, assembles into oligomers (2–100 units) and protofibrils (>100 kDa), which are neurotoxic, and ultimately deposits as senile plaques.
Amyloid Cascade Hypothesis

Here is another view of how massive cell loss changes the whole brain in advanced Alzheimer's disease. This slide shows a crosswise "slice" through the middle of the brain between the ears.

In the Alzheimer brain:

- The **cortex shrivels up**, damaging areas involved in thinking, planning and remembering.

- Shrinkage is especially severe in the **hippocampus**, an area of the cortex that plays a key role in formation of new memories.

- **Ventricles** (fluid-filled spaces within the brain) grow larger.

Histochemical detection of plaques in AD
Smith MA, PNAS 1997, 19, 9866
Is removing Plaques and Tangles Beneficial?

• Amyloid cascade hypothesizes all aspects of AD stem from Aβ.
• Tau cascade hypothesizes 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 for decades without killing them.
• Clinical trials have effectively reduced or removed Aβ, yet there was NO clinical benefit.
• Failed Phase III clinical trials based on old constructs.
• AD patients show variable neuronal loss and atrophy, yet NONE benefitted indicating that removing Aβ earlier is unlikely to be better.

Underwood E, Science 2016. doi:10.1126/science.aaf9985
99.6% of Clinical trials in AD have failed

- Billions of dollars and the efforts of over 30,000 talented researchers have directed their efforts to studying AD since the mid 1980s yet the only approved drugs are based on concepts from the 1970s.
- Removal or reduction of Aβ had no or little therapeutic benefit, and definitely not the promised cure.
- 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.

Fig. 2 Distribution by molecular target of amyloid-related clinical trials. Diagram shows selected amyloid-related clinical trials of compounds divided into their molecular target. For Immunotherapies, compounds were subclassified into vaccines and therapeutic antibodies. Small drugs were classified into compounds that interfere with Aβ aggregation, modulators of β-secretase, γ-secretase or α-secretase, or compounds with overall effects on neuronal/brain metabolism.
Clinical trials in Aβ related therapeutic strategies

Fig. 3 Schematic of Amyloid-β therapeutic strategies. Diagram shows selected Aβ related compounds divided into immunotherapies that target N- or C-terminus or epitopes present in high-order oligomers of fibrillar assemblies. Additional compounds intended as Aβ-vaccines or to interfere with Aβ-aggregation into fibrillar aggregates. Compounds in red text are inactive/discontinued in clinical trials. Despite the diversity of Aβ species targeted, clinical trials to date have failed to demonstrate disease modification. Atomic structures from PDB 5OQV and EMB-3851, were modeled with PyMOL and UCSF Chimera.
Clinical trials in secretase therapeutic strategies

• Similar to Aβ-related clinical trials.
• Failure of almost all compounds tested.
• Side effects in clinical trials.
• Major pharmaceutical companies are closing their clinical trials due to poor results.
Clinical trials in Aβ related therapeutic strategies

### Table 1: Some Aβ-targeting therapeutic constructs with completed, terminated, or ongoing clinical trials in phase 2 or phase 3

<table>
<thead>
<tr>
<th>Agent</th>
<th>Target</th>
<th>Status</th>
<th>Findings of trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>A09540</td>
<td>Aβ (Active vaccine)</td>
<td>Recruiting</td>
<td>Phase 2: pending</td>
</tr>
<tr>
<td>A09541 Synonym: Sorbion, Noordg, RO 10670</td>
<td>Aβ (active vaccine)</td>
<td>Recruiting</td>
<td>Phase 2: pending</td>
</tr>
<tr>
<td>Adamantum Synonym: BIB057</td>
<td>Aggregated Aβ</td>
<td>Completed</td>
<td>Phase 3: pending</td>
</tr>
<tr>
<td>Affibody AD02</td>
<td>Aggregated Aβ</td>
<td>Completed</td>
<td>Phase 2: benefit or worse than placebo; limited data available.</td>
</tr>
<tr>
<td>Alphamw Synonym: Vivitron, Trumans매, NC 531, homeostatic, 3-APS</td>
<td>Aβ-glycosylated binding</td>
<td>Completed</td>
<td>Phase 3: no benefit overall; possible benefit for 44 patients</td>
</tr>
<tr>
<td>AN-1792 Synonym: AN-1792</td>
<td>Aβ (Active vaccine)</td>
<td>Terminated</td>
<td>Phase 2: no benefit; Aβ plaque clearing; monocytes depleted in 6%</td>
</tr>
<tr>
<td>Anacoreccept Synonym: JN-56/S69/91</td>
<td>Aβ synthesis (BACE1)</td>
<td>Active, not recruiting</td>
<td>Phase 2: no benefit (questionable benefit at high doses); Aβ reduction on PET.</td>
</tr>
<tr>
<td>BAR2010 Synonym: mAb-6/58</td>
<td>Aβ prion targeting</td>
<td>Active</td>
<td>Phase 2: no benefit; neurovascular complications; reduced Aβ in 4-mice</td>
</tr>
<tr>
<td>Bapiminimab Synonym: AAAB-001</td>
<td>Fibrillar and soluble Aβ</td>
<td>Terminated</td>
<td>Phase 2: no benefit; neurovascular complications; reduced Aβ in 4-mice</td>
</tr>
<tr>
<td>Bevacizumab Synonym: Targeted</td>
<td>Soluble and insoluble Aβ</td>
<td>Terminated</td>
<td>Phase 2: no benefit; neurovascular complications; reduced Aβ in 4-mice</td>
</tr>
<tr>
<td>CAD106 Synonym: Aβ (active vaccine)</td>
<td>Aβ (active vaccine)</td>
<td>Recruiting</td>
<td>Phase 2: no benefit; some neurovascular complications in phase 2.</td>
</tr>
<tr>
<td>CNP520 Synonym: Aβ (active vaccine)</td>
<td>Aβ (active vaccine)</td>
<td>Recruiting</td>
<td>Phase 2: no benefit; some neurovascular complications in phase 2.</td>
</tr>
<tr>
<td>Cerezyme Synonym: MABTS152A, RG7412</td>
<td>Oligomeric and fibrillar Aβ</td>
<td>Active</td>
<td>Phase 3: no benefit; possible benefit at high doses in phase 2</td>
</tr>
<tr>
<td>Elirax Synonym: CT1812</td>
<td>Aβ oligomer receptor (competitive inhibition)</td>
<td>Recruiting</td>
<td>Phase 2: no benefit; some neurovascular complications in phase 2.</td>
</tr>
<tr>
<td>ELN005 Synonym: AZD-103, scyllo-inositol, cyclohexane 1,2,3,4,5,6, benzal</td>
<td>Aβ aggregation</td>
<td>Terminated</td>
<td>Phase 2: no benefit; some neurovascular complications in phase 2.</td>
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<tr>
<td>Ellerheiss Synonym: Es206</td>
<td>Aβ (active vaccine)</td>
<td>Terminated</td>
<td>Phase 2: no benefit; some neurovascular complications in phase 2.</td>
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<tr>
<td>Epigallocatechin gallate (EGCG) Synonym: Sempipho BCG</td>
<td>Aβ synthesis (BACE1)</td>
<td>Terminated</td>
<td>Phase 2: no benefit; increased adverse reactions; no clear reduction in Aβ</td>
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<tr>
<td>E2909 Synonym: Synonym: E2906</td>
<td>Aβ synthesis (BACE1)</td>
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<tr>
<td>EFP5069 Synonym: EFP 0015902</td>
<td>Aβ synthesis (BACE1)</td>
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<tr>
<td>Eflutone Synonym: sertibend, Eflutone, MIP-2669</td>
<td>Aβ synthesis (BACE1)</td>
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<tr>
<td>Gammaprod Synonym: Intravenous immunoglobulin, IVlg</td>
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<td>Gammagen Synonym: Intravenous Immunoglobulin, Human-Albion Combined with Fibrinogen</td>
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<tr>
<td>Gambutacel Synonym: RO4090332, RGI-550</td>
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- **Selected Phase II/III**
- **Completed.**
- **Terminated.**
- **On going.**
AD is dementia with senile plaques and tangles

REVISING OLD CONSTRUCTS

• Did Alois Alzheimer lead us astray? He did not confuse causality with association.

• The link developed with the modern era in AD research that focused 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 instead does Abeta play a critical role in the pathway of aging and cognitive decline separate from causality.
Copernicus revisited: Aβ in Alzheimer’s disease 2001

- The beta-amyloid hypothesis of Alzheimer’s Disease (AD) has dominated the thinking and research in this area for over a decade and a half.

- While there has been a great deal of effort in attempting to prove its centrality in this devastating disease, and while an enormous amount has been learned about its properties (e.g., putative toxicity, processing and signaling).

- Aβ has not proven to be both necessary and sufficient for the development, neurotoxicity, and cognitive deficits associated with this disease. Instead, the few treatments that are available have emerged from aging research and are primarily directed toward modification of acetylcholine levels.

- Clearly, it is time to rethink this position and to propose instead that future approaches should focus upon altering the age-related sensitivity of the neuronal environment to insults involving such factors as inflammation and oxidative stress. In other words “solve the problems of aging and by extension those of AD will also be reduced.”

- This review is being submitted as a rather Lutheran attempt to “nail an alternative thesis” to the gate of the Church of the Holy Amyloid to open its doors to the idea that aging is the most pervasive element in this disease and Ab is merely one of the planets.
How mice immunity is hindering research
The Times--2017

• “The big problem of mouse models of Alzheimer’s is that amyloid deposition is not part of the biology of mice,” George Perry, from the University of Texas at San Antonio, said. “You’re creating a problem that doesn’t exist in that mouse at all. You create the problem, you remove the problem.”

• He likened it to simulating respiratory problems by putting a plastic bag on someone’s head. “It’s easy to cure — you take the plastic bag off the head. But what have you really done?”

• Critical need for better animal models to understand Alzheimer’s disease.
Alternative View of AD Pathology

• The field has now focused on refining cascade hypotheses with greater complexity or instead rejecting Abeta and tau as irrelevant tombstones.

• A third ground, is that lesions reflect the brains response to the most common chronic injury; aging.

• Aβ and tau, are not passive, but rather essential elements necessary for continued function of the brain throughout life. The genetics supports a key role.

• 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.
Alternative targets in AD Pathology

- Changes in last years to alternative targets in AD.
- Tau
- Genetics/epigenetics
- ApoE and lipid neurobiology
- Circuits and synaptic failure
- Cell death processes
- Immunity and inflammation
- Metabolism and bioenergetics
- Vascular etiology
- Neuroendocrinology

**Shifting priorities**
Researchers seeking Alzheimer’s drugs are choosing targets other than β-amyloid and tau, the proteins long thought to be the key to treatments. The bars below reflect the percentage of National Institute on Aging grants for basic research devoted to various topics in 2008 and 2017.
Revising Concepts: How can Aβ be protective?

- Abeta in low concentrations has neurotropic activity
- Abeta has anti-microbial activity
- 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.
- Aβ in plaques contains and redox silences copper preventing it from causing oxidative stress in aging and AD.
- Aβ is a regulated physiological response that alternatively can be detrimental when outside physiological bounds, e.g. mutations and rodent models
Could Removing Aβ be harmful?

• Removing Aβ, especially prior to dementia, could alter the brains 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 become harmful, e.g. removing Abeta from vessels.

• Risk benefit ratio must be considered when applying Abeta 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.
- Oxidative stress and Amyloid-β.
- Gross removal of Aβ is unlikely to show benefit, although modulation of the pathway is a viable therapeutic pathway and biomarker.
- Understanding what drives Aβ in aging will provide new therapeutic targets

Oxidative damage (8OHG, blue) decreases with increased amyloid - β (brown)
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.

• Oxidative stress and Amyloid-β.

• Gross removal of Aβ is unlikely to show benefit, although modulation of the pathway is a viable therapeutic pathway and biomarker.

• Understanding what drives Aβ in aging will provide new therapeutic targets.

X-ray microscopy and STEM of amyloid plaques.
Alteration in iron, copper, and calcium.
Sci Rep, 2016, 6, 24873
Nanoscale, 2017, 9(47), 18634
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 studies support AD reduction through diet, exercise, stress reduction and a reason for living.
• All these factors improve metabolism.
• AD is joining the list of age related diseases that can be managed through lifestyle and for AD future therapeutics that modulate key factors: which will include metabolism, Aβ and tau.
• The same risk factors are seen in heart disease which is effectively treated but not cured by drugs and lifestyle.
• 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.

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 NOW.

• Focus on drugs that alter the Abeta and tau responses can only be effective as we further understand the function of both proteins.