Advancements in AD treatment studies: “No one left behind”

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• I will discuss research findings with unapproved implications for diagnosis and treatment of degenerative brain disease

• Contract Research: AbbVie, Alector, Biohaven, Esai, Lilly

• Funded by U01 AG010483, P30 AG028383, R01 HD064993, R01 AG038651, U01 AG024904, R01 AG061111, UH3 NS100606, R01 AG054130, R01 AG061848, R01 AG054029, R01 AG063689, R56 AG060608, R01 AG053798, U19 AG024904, R01 AG057187, R01 NS116058

Your Tax Dollars at Work!
We have now figured out the major sequence of pathologic events responsible for AD.
#1 Amyloid plaques

- Amyloid plaques
- Cell death (tau)
- Brain malfunction (PET)
- Brain shrinkage (MRI)
- Memory loss
- Functional loss

Alzheimer’s Disease Center
at the Sanders-Brown Center on Aging
Aβ modulation: lessons learned & a path forward?

- Aβ vaccine trial halted
- Passive immunization has risk & won’t stop late stage AD
- Antibody epitopes may matter
- Move to an earlier disease stage
- Safer vaccines on the way?
Vaccines are ideal
Targeting prevention is optimal
Older persons often have decreased immune responses
Can we get this right?
We think we can and are moving toward the day when we can protect everyone from AD!

- Over 14 new vaccines have been developed for AD that target amyloid
- All appear safe, but none (as of yet) produce high enough responses in aged persons

Passive immunization

- If you already have the disease, giving antibodies can really help!

- It works for COVID, and we have great data that such approaches may work in AD too!
FDA approval for antibody infusions?

- ENGAGE and EMERGE, tested aducanumab in ~1600 mild AD patients
- The drug removed amyloid plaques from the brain
- The FDA concluded that benefits on slowing cognitive decline were inconclusive and the conditional approval requires an additional study
- ~41% subjects had brain swelling/stroke or bleeding in the brain and 25% of those had symptoms including worsening of cognitive decline

http://science.sciencemag.org/content/366/6471/1298

Two other antibodies (maybe 3) are moving forward as well!
Are these all the same medicines?

Let’s think about how you might catch a rattlesnake?

- You could just grab it in the middle?
- Gives you a bigger target?
- But you might get bit and the rattle would attract others to attack?

- You could grab it by the rattle and tail?
- Keeps the rattle from attracting others to attack also?
- But you might get bit?

- Or you could grab it by the neck, right behind the head?
- Harder to do, but you can’t get bit once you grab the snake?
The antibodies “catch” amyloid in different ways

- They may recognize monomers (safest but least effective in removing plaques)
- They may recognize oligomers (increasing risk, but increasing benefit)
- They may recognize the plaque itself (highest risk, but most likely to remove plaques)

- The higher the risk
- The higher the potential benefit
- Finding the right balance is critical for success
Preclinical Alzheimer’s Disease (pAD)?

- Amyloid plaques are found in many asymptomatic persons
- Amyloid-PET allows us to see this in living persons
- Amyloid plaques occur ~15 years before clinical AD becomes evident

One out of every three persons over the age of 65 years has pAD
These drugs may work best prior to memory loss?

- These are critical studies in the field (NIH & UCI)
- A4 is ongoing and we should see results in the next 1-2 years
- AHEAD is enrolling now!
- “an ounce of prevention, is worth a pound of cure!”
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#2 Tau & tangles

Diagram:
- Amyloid plaques
- Cell death (tau)
- Brain malfunction (PET)
- Brain shrinkage (MRI)
- Memory loss
- Functional loss

Progression over time:
- Alzheimer's
- Normal
- TIME

AD

Legend:
- Orange circle
- AD
- Normal
Tau/Neurofibrillary tangles spread from nerve cell to nerve cell

• 282 clinical trials of tau on clinical trials.gov, with 71 of these currently recruiting
• Yet several early Phase II studies have failed
  • Biogen TANGO, AbbVie AWARE, AC Immune (all n-terminal antibodies)
    • They all decreased CSF tau but no effect on tau-PET or clinical benefit
• Is this again a question of “catching rattlesnakes”?
#3 Metabolic dysfunction

Diabetes is a disease marked by high blood sugar levels. Over time, high blood sugar can damage blood vessels, nerves, kidneys, eyes, and other organs, leading to complications and health issues. Metabolic dysfunction plays a crucial role in the progression of Alzheimer's disease (AD).

Diabetes affects the body's ability to control blood sugar levels, which can lead to long-term health problems. Understanding the connection between diabetes and Alzheimer's disease is essential for early detection and effective treatment.
• Hypercholesterolemia may drive AD through dysregulation of metabolic pathways

• ApoE is the major AD risk gene for AD and functions as a regulator of lipid transport

• Insulin resistance drives Aβ through negative effects on IDE (prevents clearance)

• Insulin resistance drives Aβ through activation of BACE (increases production)

• Insulin resistance drives tau pathology through GSK-3β hyperphosphorylation of tau
• GLP-1 agonists increase insulin production
• Effects on brain insulin and AD pathology look promising
• Known cardiovascular risk reduction may also exert an effect on cerebrovascular disease
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#4 Brain atrophy

- Memory loss
- Brain shrinkage (MRI)
- Brain malfunction (PET)
- Cell death (tau)
- Amyloid plaques

Functional loss

TIME

Alzheimer's

Normal
Structural MRI changes predict incipient AD 5 years before clinical cognitive decline

Brain atrophy in AD may be worsened by “hardening of the arteries”

Variance in Atrophy

- Age
- Hippocampal Atrophy (AD)
- White Matter Hyperintensities
Vascular damage can heal and reverse!

- **Regression of WMH is a reality!**
- **If it were due to contraction of irreversible ischemic injury or to resolution of inflammation, we would see associated atrophy.**
- **Instead, we see preservation of brain volume and improvement on cognitive scores, suggesting that such lesions are truly reversible.**

Al-Janabi et al., Brain Sci. 2019 Jul 19;9(7)
SPRINT-MIND shows that controlling HTN can prevent MCI

**QUESTION** Does intensive blood pressure control compared with standard control reduce the occurrence of dementia?

**CONCLUSION** This randomized clinical trial of adults with hypertension found that intensive systolic blood pressure (SBP) control (target <120 mmHg) did not significantly reduce the risk of probable dementia.

**FINDINGS**

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<tr>
<th>PRIMARY OUTCOME: Adjudicated probable dementia</th>
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<tbody>
<tr>
<td><strong>Intensive control</strong></td>
</tr>
<tr>
<td>149 patients (7.2 cases/1000 person-years)</td>
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<tr>
<td>Hazard ratio: 0.83 (95% CI, 0.67-1.04)</td>
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| **Standard control**                          |
| 176 patients (8.6 cases/1000 person-years)   |

**SECONDARY OUTCOME: Adjudicated MCI**

<table>
<thead>
<tr>
<th><strong>Intensive control</strong></th>
<th>287 patients (14.6 cases/1000 person-years)</th>
<th>Hazard ratio: 0.81 (95% CI, 0.69-0.95)</th>
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<tbody>
<tr>
<td><strong>Standard control</strong></td>
<td>353 patients (18.3 cases/1000 person-years)</td>
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**SECONDARY OUTCOME: Composite outcome**

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<tr>
<th><strong>Intensive control</strong></th>
<th>402 patients (20.2 cases/1000 person-years)</th>
<th>Hazard ratio: 0.85 (95% CI, 0.74-0.97)</th>
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<tr>
<td><strong>Standard control</strong></td>
<td>469 patients (24.1 cases/1000 person-years)</td>
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- The HR for dementia did not improve with SBP≤120 mmHg
- The ARR was 0.015 for both MCI & the composite outcome with a NNT = 65
#5 Mild cognitive impairment
Mild Cognitive Impairment (MCI) predicts conversion to dementia.

MCI → AD 12%/yr

Control → AD 1-2%/yr

Will exercise help in MCI?

Exercise reduces risk of dementia in a dose-dependent fashion!


BDNF released by exercise is like “Miracle-Grow” for your brain!

Lazarov et al, Trends Neurosci. 2010 Dec;33(12):569-79
It’s not just about drugs, it’s also about lifestyle!

Based on the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER)

POINTER will explore combination therapy simultaneously targeting physical exercise, a healthy diet, cognitive stimulation, and self-monitoring of heart health risk factors

Ngandu et al., 2015, Lancet VOLUME 385, ISSUE 9984, P2255-2263
#6 Alzheimer’s disease
Case Report: Patient followed longitudinally (>20yrs) with neurocognitive testing, MRI, & autopsy

Neurocognitive test scores: MMSE

[Graph showing MMSE test scores from age 77 to 98 with MMSE scores dropping significantly after age 91, labeled "AD diagnosis age 97" and "MCI diagnosis age 92".]
**LATE**

- **L** = Late-onset
  - Usually > 80 years
- **A** = Age-related
  - Age is #1 risk
- **T** = TDP-43
  - Protein aggregate
- **E** = Encephalopathy
  - Dementia
TDP43 relationships to dementia
Genetic linkage to HS-aging?
How can we stop these K+ channels?

- Nicorandil protects from death OR 0.65 [95% CI: 0.51-0.84]
- Sulfonylureas are linked to HS-aging OR 2.19 [95% CI: 1.04–4.63]

Safety and Modulation of ABCC9 Pathways by Nicorandil for the Treatment of Hippocampal Sclerosis of Aging (SMARt-HS)
NIH R01AG061111 funded
ClinicalTrials.gov Identifier: NCT04120766
AD: a brain destroyed

- We can’t fix a brain that is so damaged
- Reversing AD is many years in the future
- We may be able to slow or stop the disease at an earlier stage
- We may even be able to prevent AD within this very decade
The end-stage of dementia...

- Joan is 82 years old and is in the end-stage of dementia
- She no longer walks, talks or engages in the world around her
- She frequently moans and grimaces as if she is in pain
- All we can do is keep her comfortable and be there for her as this disease slowly takes her life

- It’s impossible to know what she is feeling...
- We can give her opiates and benzodiazepines to make her more comfortable, but then she is less aware and cannot even smile when her son gently kisses her forehead
- There must be more we can do?
Cannabinoids?

12-week, phase 2, multicenter, randomized, double-blind, parallel-group, placebo-controlled study
150 hospice-eligible agitated AD patients from 15 USA sites over a 2-year period
A total daily dose of 8 mg of THC and 400mg of CBD dissolved in digestible oil will be administered 3 times per day
Following the 12-week randomized phase, all participants are eligible for a 6-month open-label extension
• Why would you participate?
• To go beyond standard treatments rather than just rolling over and giving up!
• For the generations to come!

Cummings et al., 2017