Alzheimer’s Disease: Current Treatments and Future Directions

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Disclosures

Dr. Ahern has carried out clinical research studies in the area of Alzheimer’s Disease in association with the following entities:

- Alzheimer’s Disease Cooperative Study – UC San Diego (ADCS-NIA)
- (Arizona) Alzheimer’s Disease Core Center (ADCC) – NIA
- Avid Radiopharmaceuticals
- Bayer
- Eisai
- Elan
- Glaxo-Smith Kline
- Hoffman-LaRoche
- Janssen
- Lilly
- Medivation
- Merck
- Merck
- ONO
- Parke-Davis
- Pfizer
Definitions
Dementia may be defined in two ways:

1) A progressive deterioration in mental function that interferes with activities of daily living appropriate for one’s age and background

2) A progressive deterioration in mental functions, involving two or more areas of deficit
   - memory
   - language
   - visuospatial skills
   - calculation
   - apraxia & agnosia
   - abstract reasoning & judgment
   - behavioral comportment, etc.

The persistence of the deficit(s) differentiates dementia from delirium.
Types of Dementia

- There are many causes of dementia, some treatable, others not.

- All dementias are **not** Alzheimer’s Disease.
Alzheimer’s Disease
Epidemiology

- This is the most commonly diagnosed form of dementia
  - approximately 50% of newly-diagnosed dementia cases will be AD

- Estimated to affect 4 million people in the U.S. alone

- The East Boston Study suggested that 47% of individuals over 85 may have AD

- Risk Factors
  - Age
    - although aging per se causes neither dementia nor AD
  - Family history
    - h/o AD in 1st degree relative increases odds of developing AD three- to fourfold
  - Head Injury
    - h/o severe head injury with LOC doubles risk of developing AD
Control & AD Brain
Clinical Presentation

- It usually presents in the 6th through 8th decades with an insidious and steady decline in cognitive function, usually starting with problems in:
  - memory
  - language
  - orientation & judgment

- It then progresses over a 2-20 year period, to ultimately involve all areas of mental function

- Death usually results from intercurrent illness
# Stages of AD

<table>
<thead>
<tr>
<th>STAGE</th>
<th>1&lt;sup&gt;st&lt;/sup&gt; – Early</th>
<th>2&lt;sup&gt;nd&lt;/sup&gt; – Middle</th>
<th>3&lt;sup&gt;rd&lt;/sup&gt; – Late</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMSE (0 – 30)</td>
<td>20 – 25</td>
<td>10 – 19</td>
<td>&lt; 9</td>
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</table>

<table>
<thead>
<tr>
<th>COGNITIVE</th>
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</thead>
<tbody>
<tr>
<td><strong>Memory</strong></td>
</tr>
<tr>
<td>Poor recall of new information</td>
</tr>
<tr>
<td>Distant memories lost</td>
</tr>
<tr>
<td>Increasing memory loss and confusion</td>
</tr>
<tr>
<td>Problems recognizing friends and family members</td>
</tr>
<tr>
<td>Untestable</td>
</tr>
<tr>
<td><strong>Language</strong></td>
</tr>
<tr>
<td>Anomia</td>
</tr>
<tr>
<td>Mild loss of fluency</td>
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<tr>
<td>Worsening anomia, paraphasias</td>
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<tr>
<td>Poor comprehension &amp; repetition</td>
</tr>
<tr>
<td>Problems with reading, writing, working with numbers</td>
</tr>
<tr>
<td>Near-mutism</td>
</tr>
<tr>
<td><strong>Visuospatial</strong></td>
</tr>
<tr>
<td>Misplacing objects</td>
</tr>
<tr>
<td>Difficulty driving</td>
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<tr>
<td>Getting lost</td>
</tr>
<tr>
<td>Perceptual-motor problems (such as trouble getting out of a chair or setting the table)</td>
</tr>
<tr>
<td>Untestable</td>
</tr>
<tr>
<td><strong>Other</strong></td>
</tr>
<tr>
<td>Shortened attention span</td>
</tr>
<tr>
<td>Difficulty organizing thoughts and thinking logically</td>
</tr>
<tr>
<td>Inability to learn new things or to cope with new or unexpected situations</td>
</tr>
<tr>
<td>Untestable</td>
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</tbody>
</table>
## Stages of AD

<table>
<thead>
<tr>
<th>STAGE</th>
<th>1\textsuperscript{st} – Early</th>
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<tr>
<td>MMSE (0 – 30)</td>
<td>20 – 25</td>
<td>10 – 19</td>
<td>&lt; 9</td>
</tr>
<tr>
<td><strong>BEHAVIORAL</strong></td>
<td>Mood and personality changes</td>
<td>Hallucinations, delusions, paranoia</td>
<td>Hallucinations, Delusions</td>
</tr>
<tr>
<td></td>
<td>Irritability</td>
<td>Irritability-Aggression</td>
<td>Aggression</td>
</tr>
<tr>
<td></td>
<td>Depression</td>
<td>Restlessness, agitation, anxiety, tearfulness, wandering - sundowning</td>
<td>Wandering</td>
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<tr>
<td></td>
<td>Agitation</td>
<td>Loss of impulse control (shown through sloppy table manners, undressing at inappropriate times or places, or vulgar language)</td>
<td>Weight loss</td>
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<tr>
<td></td>
<td>Insomnia</td>
<td></td>
<td>Groaning, moaning, or grunting</td>
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<tr>
<td></td>
<td>Loss of spontaneity and sense of initiative</td>
<td></td>
<td>Increased sleeping</td>
</tr>
<tr>
<td><strong>FUNCTIONAL</strong></td>
<td>Difficulty with complex tasks</td>
<td>Some supervision required</td>
<td>Requires constant care</td>
</tr>
<tr>
<td></td>
<td>Inability to handle finances</td>
<td>Difficulty with self-hygiene, dressing, meal preparation</td>
<td>Cannot dress or feed self</td>
</tr>
<tr>
<td></td>
<td>Poor judgment leading to bad decisions</td>
<td></td>
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<tr>
<td><strong>NEUROLOGICAL</strong></td>
<td>Frontal release signs</td>
<td>Frontal release signs</td>
<td>Muteness</td>
</tr>
<tr>
<td></td>
<td>Mild extrapyramidal signs</td>
<td></td>
<td>Incontinence</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Difficulty swallowing</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Rigidity → quadriparesis-inflexion</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Loss of gait with or without myoclonus</td>
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<tr>
<td></td>
<td></td>
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<td>Seizures</td>
</tr>
</tbody>
</table>
Preclinical AD (MCI)
Mild to Moderate AD
Severe AD
Pathology

- There are 3 histopathological hallmarks in AD:
  - senile plaques
  - neurofibrillary tangles
  - neuronal granulovacuolar degeneration

- Association cortex in the parietal, temporal, and frontal lobes, is particularly affected

- Loss of cholinergic activity reflects degeneration of forebrain cholinergic systems, especially the nucleus basalis of Meynert

- In addition, serotonergic neurons in the median raphe and adrenergic neurons in the locus coeruleus lead to deficits in serotonin and norepinephrine, respectively
Amyloid Plaques
&
Neurofibrillary Tangles
**Fig. 1.** The amyloid cascade hypothesis. Amyloid precursor protein (APP) is cleaved either by α-secretase resulting in sAPPα, which might have a neuroprotective role, or by β-amyloid cleaving enzyme (BACE) and then γ-secretase to yield Aβ. The larger Aβ42 peptides are more prone to self-aggregate and are thought to be more pathogenic. A variety of known and putative genetic and environmental influences influence steps in the pathway to result in more Aβ42 generation. Abbreviation: AD, Alzheimer’s disease.
(Abnormal) Amyloid Formation 2
(Abnormal) **Amyloid Formation 3**

![Beta-Amyloid Plaque](image-url)
Fig. 2. The tau and tangle hypothesis. Tau binding to microtubules is disrupted by phosphorylation, directly by mutations that alter function, and by mutations that alter isoform expression. Decreased tau binding to microtubules might result in increased free tau which, under the appropriate conditions, will self-aggregate to form insoluble paired helical filaments. Loss of tau binding is predicted to result in loss of microtubule function. The process of tau aggregation in the absence of mutations is not known but might result from increased phosphorylation, protease action or exposure to polyanions, such as glycosaminoglycans. Abbreviations: GSK-3, glycogen synthase kinase 3; FTD, fronto–temporal degeneration.
Genetic Testing
<table>
<thead>
<tr>
<th>Chromosome</th>
<th>Product</th>
<th>Clinical Implication</th>
</tr>
</thead>
<tbody>
<tr>
<td>19</td>
<td><strong>Apolipoprotein E</strong> (ApoE)</td>
<td>Associated with late-onset familial AD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Associated with sporadic cases of AD in the over-60 age group</td>
</tr>
<tr>
<td>21</td>
<td><strong>Amyloid Precursor Protein</strong> (APP)</td>
<td>Trisomy 21 – AD in Down’s patients</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Linked with familial AD – several mutations at this locus in members of families with h/o AD onset at a relatively young age</td>
</tr>
<tr>
<td>14</td>
<td><strong>Presenilin 1</strong></td>
<td>Linked to an early-onset form of AD</td>
</tr>
<tr>
<td>1</td>
<td><strong>Presenilin 2</strong></td>
<td>Linked to the “Volga-German” families who have unusually high incidence of AD</td>
</tr>
</tbody>
</table>
Apolipoprotein E
The Link Between APOE and Alzheimer’s Disease

First reported in 1993, the APOE-ε4 allele is considered a major risk factor for AD

- The APOE genetic test determines which 2 alleles the patient has inherited (1 from mother and 1 from father)

  ε2 - may be protective against SDAT (in Caucasians)

  ε3 - no contribution (wild-type allele)

  ε4 - increases predilection to SDAT
      - 0 ε4 - 66%
      - 1 ε4 - 81%
      - 2 ε4 - 94%

- Individuals with 2 copies of ε4 have an average age of onset before 70
- Individuals with no copies of ε4 have an average age of onset later than 85
Amyloid Imaging
Tau Imaging
T807: Low Probability Subjects vs. MCI, mild AD & severe AD (MMSE= 26, 21, 7) (80-100 min p.i.)

Increasing tracer retention with increasing severity of symptoms; overall very little white matter binding

Increasing Severity

Healthy

Mild MCI
β-Amyloid⁺
MMSE<26

Mild AD
β-Amyloid⁺
MMSE=20-21

Severe AD
MMSE>7

58 yo
69 yo
86 yo
72 yo

*β-Amyloid in MCI and "mild AD" was detected & measured by Amyvid-PET (R. Shankle)

* T807 and T808 are investigational imaging agents and no indications have been approved by the FDA or other regulatory agencies. Future availability cannot be guaranteed. The clinical information contained herein is for informative purposes only and not to be construed as an endorsement for these products.
Current Treatments for Alzheimer’s Disease
Cholinergic Deficit Hypothesis
The loss of cholinergic neurons in the brain is one of the major characteristics of Alzheimer’s disease.

This has led to the so-called “cholinergic deficit hypothesis” and various strategies aimed at reversing this deficit, including:

- **Precursor administration**
  - choline, phosphatidyl choline (lecithin)

- **Inhibition of acetylcholinesterase (AChE), the enzyme responsible for the breakdown of acetylcholine**
  - tacrine, donepezil, rivastigmine, galantamine, etc.

- **Administration of direct-acting agonists**
  - milameline, xanomeline
Nucleus Basalis of Meynert
Actions of Acetylcholine and Acetylcholinesterase
ACTION OF ACETYLCHOLINE

Acetylcholinesterase degrades acetylcholine

Acetylcholinesterase inhibitors block acetylcholinesterase

Acetylcholinesterase Inhibitors
## Features of Acetylcholinesterase Inhibitors

<table>
<thead>
<tr>
<th>FEATURE</th>
<th>GALANTAMINE (Reminyl/Razadyne)</th>
<th>RIVASTIGMINE (Exelon)</th>
<th>DONEPEZIL (Aricept)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enzymes inhibited</td>
<td>Acetylcholinesterase</td>
<td>Acetylcholinesterase and Butyrylcholinesterase</td>
<td>Acetylcholinesterase</td>
</tr>
<tr>
<td>Selectivity for isoforms of acetylcholinesterase</td>
<td>No</td>
<td>Yes – GI</td>
<td>No</td>
</tr>
<tr>
<td>Plasma half-life (hours)</td>
<td>7</td>
<td>1.5</td>
<td>70</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Hepatic CYP450 and Glucuronidation</td>
<td>Target enzymes</td>
<td>Hepatic CYP450 and Glucuronidation</td>
</tr>
<tr>
<td>Elimination</td>
<td>Kidney</td>
<td>Kidney</td>
<td>Kidney</td>
</tr>
</tbody>
</table>
Namenda (Memantine)
The NMDA Receptor

Channel Blockers
- Mg<sup>2+</sup>
- Memantine

Antagonists
- APV
- Mrz 2/576
- Ifenprodil (2B)
- Zn<sup>2+</sup>

Agonists
- Glutamate
- NMDA

Coagonists
- Glycine
- D-serine

Modulator
- Polyamines

Alternative splicing
Glycosylation site
Newer Treatments for Alzheimer’s Disease
Conceptual Approaches to the Treatment of Alzheimer’s Disease

1) Treatment of Cognitive Symptoms
2) Treatment of Behavioral Signs and Symptoms
3) Slow the Rate of Decline of Cognitive Function
4) Delay the Onset of Illness
5) Prevention of the Disease Altogether
## AD Therapy: Future

**Recent Failures**

<table>
<thead>
<tr>
<th>Category</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevention strategies</td>
<td>NSAIDs, Estrogen, Gingko Biloba</td>
</tr>
<tr>
<td>Immunotherapy</td>
<td>Active and Passive</td>
</tr>
<tr>
<td>New cholinesterase inhibitors</td>
<td>Huperzine A, Phenserine, Dimebon</td>
</tr>
<tr>
<td>Cholesterol lowering agents</td>
<td>Atorvastatin, Simvastatin</td>
</tr>
<tr>
<td>Anti-aggregation agents</td>
<td>Tramiprosate (<em>Alzhemed</em>), others</td>
</tr>
<tr>
<td>Gamma secretase modulators</td>
<td>Tarenflurbil (<em>Flurizan</em>), others</td>
</tr>
<tr>
<td>Gamma secretase inhibitors</td>
<td>LY-450139, MK-0249</td>
</tr>
<tr>
<td>Neuroprotection</td>
<td>Divalproex Sodium, Lithium</td>
</tr>
<tr>
<td>Chelating agents</td>
<td>Clioquinol</td>
</tr>
<tr>
<td>Diabetic medications</td>
<td>Insulin sensitizers (rosiglitazone, pioglitazone)</td>
</tr>
<tr>
<td>sRAGE inhibitors</td>
<td>TTP/Pfizer</td>
</tr>
<tr>
<td>Serotonin agonists</td>
<td>Xaliproden, others</td>
</tr>
<tr>
<td>GnRH agonist</td>
<td>Leuprolide</td>
</tr>
</tbody>
</table>
Figure 9 AD: course, prevention, and treatment strategies.
Fig. 1. The amyloid cascade hypothesis. Amyloid precursor protein (APP) is cleaved either by α-secretase resulting in sAPPα, which might have a neuroprotective role, or by β-amyloid cleaving enzyme (BACE) and then γ-secretase to yield Aβ. The larger Aβ42 peptides are more prone to self-aggregate and are thought to be more pathogenic. A variety of known and putative genetic and environmental influences influence steps in the pathway to result in more Aβ42 generation. Abbreviation: AD, Alzheimer’s disease.
Future AD Treatments: Beta and Gamma Secretase Inhibitors

- β-secretase and γ-secretase are two proteases that cleave amyloid precursor protein, producing amyloid beta-peptide
- Early γ-secretase studies indicate predictable reduction of Aβ
- β- and γ-secretase inhibitors would block the production of beta-amyloid, which presumably would slow or halt the progression of the disease.

- Phase II/III trial of Merck MK-8931 - an inhibitor of β-secretase
- Phase II/III trials with Lilly LY450139 (hydroxylvaleryl monobenzocaprolactam), a γ-secretase inhibitor, have been stopped
Future AD Treatments: Aggregation Inhibitors

Active Trial
- Eisai BAN 2401
  - Inhibits aggregation of amyloid fibrils into amyloid plaque

Failed
- Tramiprosate aka Alzhemed (Neurochem)
  - Inhibits Aβ fibrillization and reduces soluble Aβ
  - No further development by Neurochem – will sell as nutraceutical
- D005 (Elan)
  - Scyllo-inositol is a specific stereoisomer of the cyclic sugar alcohol inositol, occurring naturally in coconut palm, dogwood flowers and oak bark.
  - Can inhibit aggregation of Aβ in transgenic mice, improves many AD-like phenotypes and protects from cognitive decline.
  - Is being investigated as an agent to reduce agitation/aggression in AD.
Future AD Treatments: Immunotherapy

• AN-1792 (“the Alzheimer’s vaccine”) was a synthetic form of the 42 amino acid beta amyloid (Aβ) peptide
• It promotes clearance of the toxic Aβ peptide by generation of anti-Aβ antibodies
• Thirteen months subsequent to immunization, virtually all of the mice treated with AN-1792 had no detectable amyloid deposits in their brains

• In a Phase 1 safety study, AN-1792 was administered (multiple dosage regimens) to more than 100 patients with mild to moderate AD. It was safe and well-tolerated.

• A Phase IIa clinical trial of 360 subjects stopped because of 18 cases of encephalitis, paralysis or death (US, UK, France); 5 deaths in the treatment group
• Autopsy data reveals diminution of plaques but no effects on tangles or synapse loss
• 5 year follow-up of titer positive subjects reveals a significant reduction in long term care placement
**Figure 20** Amyloid “vaccine” reduces plaque burden and memory loss in transgenic mouse models of AD.
Future AD Treatments: Immunotherapy

Passive Immunization

- Passive immunization is now being investigated
  - polyclonal IVIG (Baxter)
  - monoclonal antibody Bapineuzamab (Elan/Wyeth)
  - monoclonal antibody Solanezumab (Eli Lilly)

- Subjects with mild to moderate AD will undergo infusions
  - schedule depends on the compound
  - outcomes will include CSF markers, pharmacokinetics, and efficacy measures

- Other companies developing compounds include Eisai and Novartis

Update:

- IVIG, Bapineuzamab, and original Solanezumab trials failed
- Solanezumab is currently being ‘resurrected’, but given to mild/moderate stage patients
Active Immunization

- Active immunization back in development
- These will look at smaller amyloid fragments as immunogens
- Companies include Pfizer/Elan/Wyeth (AAC-001) and Novartis/Cytos (CAD106)

Update:
- Pfizer/Elan/Wyeth (AAC-001) trial halted after interim analysis
- It is not clear whether Novartis/Cytos (CAD106) will continue
If Aβ antibodies are present they bind to Aβ and prevent further plaque formation.

Aβ is sticky and coaleses forming plaques. Antibody binding to Aβ in plaques results in clearance.

Aβ–containing plaques interfere with neuronal function.

Amyloid precursor protein is cleaved (arrows) and Aβ is produced.
Figure 9  AD: course, prevention, and treatment strategies.
Future AD Treatments: Early Treatment

Reiman and Tariot – PS1/Columbia

- Investigating the administration of antibody Crenezumab to large cohort of Presenilin 1 Alzheimer family in Medellin, Columbia
- If trial is successful, it will be the 1st time that AD has been prevented.
  - Will still have to see if this works in typical late-onset AD
- If trial fails, it will bring into question the veracity of the Amyloid Hypothesis

ADCS – A4 Trial

- Investigating the administration of antibody Solanezumab to subjects who are at risk of developing AD, but who have not yet done so
Future AD Treatments: Insulin

Craft – Inhaled Insulin

- Suzanne Craft et al (Intranasal Insulin Therapy for Alzheimer Disease and Amnestic Mild Cognitive Impairment: A Pilot Clinical Trial Study, Arch Neurol 2012) reported on administration of intranasal insulin on cognition, function, cerebral glucose metabolism, and CSF biomarkers in patients with aMCI & Mild AD

- Insulin has a number of important functions in the central nervous system:
  
  - Brain insulin receptors are densely localized in the hippocampus, the entorhinal cortex, and the frontal cortex and are found primarily in synapses, where insulin signaling contributes to synaptogenesis and synaptic remodeling.
  
  - Insulin also modulates glucose utilization in the hippocampus and other brain regions and facilitates memory at optimal levels in normal metabolism.
  
  - Insulin dysregulation may contribute to the pathophysiology of AD.
    - Insulin levels and insulin activity in the central nervous system are reduced in AD.
    - Insulin has a close relationship with the β-amyloid peptide. Insulin modulates the levels of Aβ and protects against the detrimental effects of Aβ oligomers on synapses.
Future AD Treatments: Insulin

Craft – Inhaled Insulin – Cont’d

- 30 placebo, 36 – 20 IU insulin, 38 – 40 IU insulin
  - 20 IU of insulin improved delayed memory (P < .05), and both doses of insulin (20 and 40 IU) preserved caregiver-rated functional ability (P < .01).
  - Both insulin doses also preserved general cognition as assessed by the ADAS-cog score for younger participants and functional abilities as assessed by the ADCS-ADL scale for adults with AD (P < .05).
  - Cerebrospinal fluid biomarkers did not change for insulin-treated participants as a group, but, in exploratory analyses, changes in memory and function were associated with changes in the Aβ42 level and in the tau protein–to–Aβ42 ratio in cerebrospinal fluid.
  - Placebo-assigned participants showed decreased fludeoxyglucose F 18 uptake in the parietotemporal, frontal, precuneus, and cuneus regions and insulin-minimized progression.

- SNIFF (Study of Nasal Insulin to Fight Forgetfulness) – ADCS
  - 250 patients with aMCI & Mild AD; 12 mos double-blind > 6 mos open label
Future AD Treatments: Tau / Neurofibrillary Tangles

Tau / Neurofibrillary Tangles

- Much of the research over the past 5-10 years in terms of strategies to affect the Alzheimer Disease pathophysiological processes has involved β-amyloid.
- Tau oligimers and fibrils, leading to neurofibrillary tangles have been less investigated.
- Promising avenues of research include:
  - Preventing tau aggregation
  - Targeting microtubule stabilization
  - Targeting tau folding
  - Targeting tau phosphorylation
  - Tau-based immunization approaches
Conclusions

Therapy for Alzheimer’s Disease is moving in two (complementary) directions:

1) A transition from ‘symptomatic’ treatment (cholinesterase inhibitors, memantine) to an actual attack on the disease process proper (clearing/preventing amyloid plaques)

2) A realization that by the time Alzheimer’s Disease presents itself in its full-blown form, ‘the horse may already be out of the barn’.

   • Therefore, trials are being aimed at patients with Mild AD / MCI, rather than Mild-Moderate AD.

   • An even bolder theme is to try to prevent the disease from taking hold in the first place. In essence, this can be likened to vaccinating against polio.

Finally, even if the amyloid hypothesis is wrong, an awareness of same will allow researchers to move on toward different conceptualizations of the disease, and hopefully, new & effective treatments.
Patient Populations include:
Mild Cognitive Impairment
Mild/Moderate Alzheimer’s Disease

Therapeutic Agents:
Immune Therapies (infusion)
Oral Agents

For Further Information, call the Neurology Clinical Research Office at:
626-4296