Biology, Evaluation and Management of Alzheimer’s Disease
From Research to Clinical Practice

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Clinical Professor of Neurology, Herbert Wertheim College of Medicine, FIU and University of Florida College of Medicine
<table>
<thead>
<tr>
<th>Company</th>
<th>Relationship Description (Name of drug / compound, type of intervention / instrument, etc)</th>
<th>Relationship</th>
<th>Stock and/or ownership rights &gt; $5,000 or 5% interest</th>
<th>Established or potential royalty income</th>
<th>Income in the PAST 12 months of $5,000 or more</th>
<th>Income in the NEXT 12 months of $5,000 or more</th>
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<tr>
<td>Alzheimer's Therapeutic Research Institute</td>
<td>AZD0530 (FYN) in Mild Alzheimer's Disease</td>
<td>Grant / Research Support</td>
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<td>Avid - Eli Lilly &amp; Company</td>
<td>Amyvid™. Use of AV-45 in ADCS Trials</td>
<td>Grant / Research Support</td>
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<td>Avid - Eli Lilly &amp; Company</td>
<td>Tau: Tau Imaging AV 1451</td>
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<td>Eli Lilly &amp; Company</td>
<td>Solanezumab: Anti-Amyloid Trial in Asymptomatic AD (A4 Study)</td>
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<td>Janssen Research &amp; Development, LLC</td>
<td>JNJ-54861911 in Subjects who are Asymptomatic At Risk for Developing Alzheimer’s</td>
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<td>Medical Learning Group</td>
<td>Speaker's Bureau for Eli Lilly &amp; Company</td>
<td>Consultant or Advisor - Paid DIRECTLY</td>
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<td>Merck &amp; Company</td>
<td>MK-8931: MK-8931-019 in Prodromal Alzheimer’s Disease</td>
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<td>Toyama Chemical Co., Ltd.</td>
<td>TCAD/NOBLE: Toyama Chemical (T-8r7MA) in Alzheimer’s Disease</td>
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<td>vTv THERAPEUTICS LLC</td>
<td>TTP488: TTP488-301 for Mild Alzheimer’s Disease</td>
<td>Grant / Research Support</td>
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BACK IN 1952, GASOLINE COST 20 CENTS A GALLON. WHEN YOU PULLED UP TO THE PUMPS, THREE GUYS CAME OUT AND CHECKED YOUR OIL AND YOUR TIRES AND CLEANED YOUR WINDOWS.

THIS MUST BE THAT THING THEY CALL "SENILITY"
Auguste D & Alois Alzheimer

- **First patient described - 1907**
  - 51 year old woman
  - Memory impairment
  - Hallucinations, delusions, paranoia
  - Agitation
  - Disorientation

- **Progression over 5 years**
  - At end - fetal position, incontinent, unresponsive

Alzheimer’s disease Facts

- First described in a younger persons (50’s and 60s) – now known to be the most common cause of dementia in older persons
- ~ 5+ million individuals currently affected in the U.S.
- Alzheimer’s affects 50% of people 85 + years of age.
- By 2050 22+ million people will be affected worldwide
- Medical, monetary, and human resources will be severely strained
- New data suggests Alzheimer’s is the 3rd most common cause of death (Neurology, 2014)
Genetics contribute to susceptibility

- Early onset AD transmitted as a autosomal dominant trait typically <65 y/o age (esp. presenilin 1 mutation on Chromosome 14; (very rarely Chromosome 1 and Chromosome 21 mutations)

- Majority of cases sporadic (not purely genetic) – but genetic factors play significant role (especially apolipoprotein e4)

- **Non-genetic risk factors important**: age – activity, BMI, blood pressure, diabetes, diet, psychosocial factors (e.g., neuroticism, anxiety)
Alzheimer’s Disease

AD More Likely:
- Age
- Female sex
- E4 genotype
- Hypertension
- Diabetes
- Homocysteine
- Cholesterol
- Head trauma
- Family history

AD Less Likely:
- Education
- Exercise
- Brain fitness
- Antioxidant diet
- Heart health
Biology of Alzheimer’s
Normal brain

PLAQUES
Amyloid beta protein

Alzheimer’s disease

TANGLES
abnormal tau protein
Alzheimer’s Disease: Pathology

- Brain atrophy
- Neurofibrillary tangle
- Amyloid plaque

Amyloid Beta protein deposition considered pivotal in Alzheimer's disease process

(Cummings JL, JAMA, May 8, 2002)
Distribution of amyloid and neurofibrillary pathology in Alzheimer’s disease (From Selkoe, DJ, Sci Am, 1991)

(Braak H, Braak E. Neuropathological staging of Alzheimer-related changes. Acta Neuropathol (Berl) 82: 239-259.)
Biomarker Changes During AD Progression

- Amyloid-β accumulation (CSF/PET)
- Synaptic dysfunction (FDG-PET/MRI)
- Tau-mediated neuronal injury (CSF)
- Brain structure (volumetric MRI)
- Cognition
- Clinical function

Clinical Disease Stage:
R.A. Sperling et al. Alzheimer’s & Dementia; (2011) 1-13 [modified]
Prevalence of plaques in HC

(Davies, 1988, n=110)
(Braak, 1996, n=551)
(Sugihara, 1995, n=123)

~15 yrs

Prevalence of AD
(Tobias, 2008)

Prevalence of PiB+ve PET in HC
Imaging and Diagnosis
Biomarkers for Assessment of AD Pathology in the Clinic

- **Structural**
  - Magnetic resonance imaging (MRI)
  - X Ray CT

- **Functional**
  - Fluorodeoxyglucose positron emission tomography (FDG PET)
  - Functional MRI (fMRI)

- **Molecular and biochemical**
  - CSF
  - Amyloid PET
  - Tau PET
  - PET markers of Microglial Activation
### Medial Temporal Atrophy Rating (HP, ERC, PRC)

<table>
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<tr>
<th>Rating</th>
<th>Atrophy Description</th>
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<tr>
<td>2</td>
<td>Mild Atrophy</td>
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<tr>
<td></td>
<td>1. Mild Decrease In Thickness Or</td>
</tr>
<tr>
<td></td>
<td>2. Mild Widening Of Collateral Sulcus Or</td>
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<tr>
<td></td>
<td>3. Both</td>
</tr>
<tr>
<td>3</td>
<td>Moderate Atrophy</td>
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<tr>
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<td>1. Moderate Decrease In Thickness (Even In The Absence Of Widening Of Collateral Sulcus)</td>
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<td>2. Both Moderate Decrease In Thickness And Widening Of Collateral Sulcus</td>
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<tr>
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<td>Severe Atrophy</td>
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<tr>
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<td>1. Severe Decrease In Thickness (Even In The Absence Of Widening Of Collateral Sulcus)</td>
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[Diagram showing brain structure]
MRI Biomarker and AD Progression

(Reduction in Cortical Thickness Associated with Disease Stage and Future Rate of Decline)


FDG-PET in Normal Aging, MCI, AD and FTD

- **NL**
- **MCI**
- **pAD**
- **fTD**

fTD = frontotemporal dementia; pAD = Probable Alzheimer’s disease.

- **AD-Dementia**
- **Cog NL APOE4 carriers**
**[F-18] Amyloid Imaging Tracers**

<table>
<thead>
<tr>
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<th>Flutemetamol$^1$</th>
<th>Florbetapir$^2$</th>
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<tr>
<td><strong>AD</strong></td>
<td><img src="image1" alt="Flutemetamol AD" /></td>
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<tr>
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<td><img src="image3" alt="Flutemetamol NL" /></td>
<td><img src="image4" alt="Florbetapir NL" /></td>
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</table>

- $^4$Chen K et al. *AAIC.* 2012.
Interpreting Amyloid PET Scans

Negative

Positive

APOE4, Age and Amyloid PET

3 year Risk of Progression: Positive vs Negative Amyloid PET Scan

Healthy Controls
(n=183)

MCI
(n=87)

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<tr>
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<th>Neg (n=130)</th>
<th>Pos (n=53)</th>
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<tbody>
<tr>
<td></td>
<td>25%</td>
<td>77% (47/60)</td>
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<tr>
<td>to MCI/AD</td>
<td></td>
<td>to AD dementia</td>
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</table>

<table>
<thead>
<tr>
<th></th>
<th>Neg (n=27)</th>
<th>Pos (n=60)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>29% (8/27)</td>
<td></td>
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<tr>
<td>to AD dementia</td>
<td></td>
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Odds Ratio 4.8

Odds Ratio 14

Rowe C. AAIC 2013.
A Case Study
History and Clinical Presentation

• 54yo RHF with gradually progressive cognitive changes
  • Difficulty with judgment and decision-making
  • Social/interpersonal behavior change (withdrawn)
  • Some difficulty with expressive language (i.e., word finding problems)

• Working as psychologist but having some difficulty approximately one year after symptom onset

• General medical history unremarkable; no history of depression

• Negative family history of dementia

• MMSE 29/30; Neurological exam unremarkable;
Case Study - Question 1

Which clinical syndrome is most compatible with this case’s history and clinical presentation?

A. Mild Cognitive Impairment (MCI)
B. Dementia
C. Other (e.g., Pseudodementia; Subjective Cognitive Disorder)
What further tests would be considered part of a standard dementia workup? (select all that apply)

A. Detailed Neurocognitive testing
B. Structural MRI
C. Labs: CBC, CMP, B₁₂, TSH
D. FDG PET
E. Amyloid PET
F. CSF Abeta and Tau
Case Study – Neuropsychological testing

- General observations
  - Flat affect
  - Good effort on tests

- Impairments in
  - Executive function
  - Abstract reasoning
  - Verbal fluency
  - Naming (mild)

- Relatively preserved
  - Other language abilities
  - Visuospatial abilities
  - Memory
Case #3 – Structural MRI imaging

- Possible left medial prefrontal atrophy; possible posterior parietal atrophy; radiologist was not convinced outside range of normal
Case Study – FDG PET imaging

- Mild bilateral L>R parietal hypometabolism
Case Study - Question 3

What is the clinical diagnosis for this patient?

A. Early Alzheimer’s Disease
B. Non Alzheimer’s Neurodegenerative Etiology
C. Vascular Cognitive Impairment
What are the possible diagnoses now?

A. MCI due to AD
B. MCI due to FTD
C. MCI due to Lewy body dementia
D. Still unclear
Amyloid PET scan: Amyloid Negative
Amyloid PET scan: Amyloid Positive

Aβ positive
Achieving Symptom and Disease Modification in Alzheimer’s Disease
Recommendations for Possible Prevention

- Control Vascular Risk Factors, esp. HTN and DM
- Dental Hygiene
- Cognitive/Social Stimulation
- Physical Exercise
- B complex Vit. (B12 & B6)
- Vitamin C
- Vitamin E in food
- Eat fish
- Use curry (curcumin)

- Antioxidants
  - Beans
  - Berries
  - Grape juice
  - Pomegranate juice
  - Green tea
- Mediterranean diet
- Quality sleep
  - Treat sleep apnea
- Increase socialization
- Control blood glucose
- Treat anemia
Neuroprotection vs. one-time improvement

We are still looking for our first Disease Modifying/neuroprotective agent for AD!
Current and Emerging Treatments and Clinical Trials in Alzheimer’s Disease

- **Cholinesterase Inhibitors:** Donepezil, Rivastigmine & Galantamine
- **NMDA modulators:** Memantine
- **New symptomatic agents:** Nicotinic agonists: MK 7622
- **Disease-modifying agents**
  - **Anti-amyloid:** Solanezumab; Bapineuzemab; Crenezumab
  - **Anti-tau:** Methylthioninium chloride (MTC); Leuko-MTC (TauRx)
  - **Neuroprotective:** Toyoma-817 MA
Trial failed to show clinical benefit. About 17% of cohort found not to have amyloid in the brain. Too little or too late?

* Difference between patients in the placebo group and those in the bapineuzumab group at Week 78 = -0.24 (\(P = 0.003\)).

Approved Secondary Prevention Studies

- A4 study: 3 year double blind, 1000 person, Solanezumab study in cognitively normal person who are florbetapir +ve
- DIAN study: 40 per arm, Solanezumab and Gantenerumab vs placebo in unaffected carriers of dominantly inherited genes
- ApoE 44 study: Cognitively normal, 650 person, double blind, agent to be decided
- Colombian kindred study: PSEN1 Paisa mutation using Crenezumab (from Genentech) in asymptomatic carriers
**Do’s**

- Look for, Recognize and Rx Precipitating Factors: (Infection, Pain, Constipation, Hunger/Thirst, Sensory Deprivation, Medication change, Other Medical Conditions, Change in Physical or Social Environment)
- Reassure, Agree with and Comfort the Patient, “Go with the Flow” (e.g., with delusions, hallucinations) Simplify and make Environment Safe
- Educate Caregiver(s) about Precipitating Factors; Encourage Support Groups
- Use SSRIs (Citalopram, Sertraline) as first line Rx (treats anxiety, irritability and depression)
- Use Non-D2 Antagonist Anti-psychotics (Quetiapine)
- Use D2 Antagonists (e.g., Risperidone) **Use very sparingly**
- Use Anticonvulsants (esp. Lamotrigine) and Buspar as adjuvants to antipsychotics
- Treat Sleep Disorders (with Trazodone, Mirtazapine)
Managements of Behavioral Manifestations of Alzheimer’s

**Don’ts**

- Don’t Confront, Contradict, Offend, Alarm, Challenge or Argue with the Patient (Don’t Say: “I already told you that”; “Don’t you remember”)
- Avoid Loud Noise and Sudden Movements
- Don’t Overstimulate the Patient
- Don’t Emphasize Patient’s Impairments
- Don’t Use Benzodiazepines (e.g., Lorazepam, Temazepam) for anxiety, sleep disorder or agitation - Except for very short term use.
- Don’t Use Anticholinergics (Benadryl, Unisom, Hydroxyzine Amitriptyline, Meclizine, Ditropan)
- Don’t Use Haloperidol (except parentally and for short-term use (in the ER) for very aggressive and violent patients)
In Summary

• A realistic goal is to delay or prevent AD in the Preclinical or Early Clinical Stage, and to prevent progression of established Alzheimer’s

• With a combination of clinical findings and biomarkers we are able to identify those at risk and those who have the disease

• Secondary prevention and delaying/stopping progression may soon become a reality
Have A Nice Day