Alzheimer's Disease Research
Outline

• What is Alzheimer's disease?
• Why is it important to fund Alzheimer's research?
  • Biomarkers
  • 3rd phase clinical trials
  • Risk factors
  • Hot topics
• My research

Disclosures

• Research Support:
  – Departmental Support
• Consultant/Advisory Boards:
  – None
• Off-Label Discussion:
  – None

Alzheimer's Disease Research
Outline

What is Alzheimer's disease?
1. Alzheimer's Disease & Statistics

- Most common form of dementia (70% of dementia)
- 5.4 million US with AD
- 6th leading cause of death
- Every 6 hours someone dies of AD*
- $200 billion cost in U.S. in 2012
- $33,000/yr per person costs


Alzheimer's Disease

- How many of you know someone with Alzheimer's?
  - 1 in 8 people over 65 have Alzheimer's
(AD) pathology in the brain is profound.

- Atrophy
- Amyloid (tau and Aβ) accumulation

Healthy Neuron

Diseased Neuron

Aβ 40/42 amino acid protein
Generated from precursor protein
Alzheimer's Disease Research Outline

• Why is it important to fund Alzheimer's research?
  • Biomarkers
  • 3rd phase clinical trials
  • Risk factors
  • Hot topics

Alzheimer's Disease Research Outline

• Why is Alzheimer's disease a national/worldwide problem?
In my opinion, part of the differences are due to differences in funding. More scientific and technological advances occur in the other areas with greater funding. http://www.alz.org/alzheimers_disease_facts_and_figures.asp

Alzheimer’s Disease & Statistics

It is clear that there is a funding disparity

National Alzheimer’s Project Act (NAPA, Public Law 111-375)

- A coordinated national plan to overcome the Alzheimer’s crisis
- This will require funding
- Recently, $156 million to NIH for Alzheimer’s (51% for research)
Alzheimer's Disease Research

Outline

• Why is it important to fund Alzheimer’s research?
  • Biomarkers

Biomarkers

Biomarkers can be simply defined as measurable biological characteristics:
- indicators of normal or pathogenic processes in the body,
- tools to track pharmacological responses to therapeutic drugs.

Vanderstichele et al 2012 Neurology 2012 Mar 6;78(10):709-19
**Biomarkers**
Alzheimer’s Disease Neuroimaging Initiative (ADNI).
- Low Aβ, elevated tau-proteins that aggregate. ADNI will resolve this issue. Tau not AD specific (a stroke and trauma).
- Isoprotanes - oxidative stress biomarkers
- Oligomeric Aβ
- YKL-40 produced by astrocytes has no known function but might be a marker of inflammation.
- Visinin-like protein-1 (VILIP-1), markers of neuronal injury
- Ceramides/sphingolipids, markers of neuronal injury.
- methodological challenges in searching for meaningful biomarkers. The ADNI project will address this issue.

**Biomarkers-**
Brain imaging in live patients
Alzheimer’s Disease Neuroimaging Initiative (ADNI).
- Volumetric MRI and regional volume determination - clinical impairment
- FDG Glucose PET ↓
- Amyloid Imaging ↑

**Biomarkers**
- Now there are imaging agents FDDP that detect Aβ and tau - both amyloids.
- Other compounds (PIB) etc only image Aβ.
Biomarkers

Video

http://www.loni.ucla.edu/~thompson/FDDNP/video.html

Alzheimer's Disease Research

3rd phase clinical trials

Clinical Trials 3rd

Metabolism

NAME: AC-1204
OTHER NAMES: caprylic triglyceride, long-chain triglyceride
FDA PHASE: Phase II/III
MECHANISMS: Chronic induction of ketosis to improve mitochondrial metabolism
ROLE IN ALZHEIMER'S DISEASE: AC-1204 increases ketone body production and targets glucose hypometabolism by providing increased ketone bodies as an alternative energy source in the brain.
### Antibody Therapy

**NAME:** ACC-001  
**FDA PHASE:** Phase II/IIa/IIb  
**ROLE IN ALZHEIMER’S DISEASE:** ACC-001 is a short amino-terminal Aβ(1-6) fragment that is derived from the N-terminal B cell epitope of Aβ while avoiding T cell activation. Elan  
**NAME:** Intravenous Immunoglobulin  
**OTHER NAMES:** Gammagard, IVIg  
**FDA PHASE:** Phase III  
**MECHANISMS:** Natural anti-amyloid antibodies may reduce CNS and peripheral Aβ and improve cognition.

Likely some effect on both cognitive and functional efficacy endpoints ADAS-Cog, NTB and CDR-SB

---

### Antioxidants

**NAME:** Alpha-tocopherol  
**OTHER NAMES:** Vitamin E  
**FDA PHASE:** Phase III  
**ROLE IN ALZHEIMER’S DISEASE:** Thought to prevent brain cell damage by destroying toxic free radicals.

---

### Receptors

**NAME:** Azd2650  
**OTHER NAMES:** TC-6683  
**FDA PHASE:** Phase II/IIa/IIb  
**MECHANISMS:** α4β2 nicotinic (nAChR) receptor activator  
**ROLE IN ALZHEIMER’S DISEASE:** Activates neuronal nicotinic receptor, and enhances the release of acetylcholine from the cortex and thereby be memory-enhancing.

**NAME:** Dimebon  
**OTHER NAMES:** 5,6-dimethyl-1-(2-methylpyridyl)-5-ethyl-1,2,3,4-tetrahydro-γ-carboline dihydrochloride, Dimexolon, Latrepirdine, PF-0313519  
**FDA PHASE:** Phase II  
**MECHANISMS:** Has activity as an inhibitor of cholinesterase and NMDA receptors. Inhibits neuronal death, potentially by mitochondrial-mediated inhibition of apoptosis.

---

### Clinical Trials 3rd

**NAME:** Bapineuzab  
**OTHER NAMES:** AAB-001  
**FDA PHASE:** Phase III  
**MECHANISMS:** Designed to bind and remove the Aβ peptide that accumulates in the brain.

**NAME:** Solanezumab  
**OTHER NAMES:** LY2062430  
**FDA PHASE:** Phase III  
**MECHANISMS:** Designed to bind and remove the Aβ peptide that accumulates in the brain.

**NAME:** Intravenous Immunoglobulin  
**OTHER NAMES:** Gammagard, IVIg  
**FDA PHASE:** Phase III  
**MECHANISMS:** Natural anti-amyloid antibodies may reduce CNS and peripheral Aβ and improve cognition.

**NAME:** Docosahexanoic acid (DHA)  
**OTHER NAMES:** Omega-3 fatty acids  
**FDA PHASE:** Phase III  
**MECHANISMS:** DHA is a major component of neuron membranes and has multiple functions, including modulation of presenilin.

**NAME:** AZD1446  
**OTHER NAMES:** TC-6683  
**FDA PHASE:** Phase II/IIa/IIb  
**MECHANISMS:** α4β2 nicotinic (nAChR) receptor activator  
**ROLE IN ALZHEIMER’S DISEASE:** Activates neuronal nicotinic receptor, and enhances the release of acetylcholine from the cortex and thereby be memory-enhancing.

**NAME:** Dimebon  
**OTHER NAMES:** 5,6-dimethyl-1-(2-methylpyridyl)-5-ethyl-1,2,3,4-tetrahydro-γ-carboline dihydrochloride, Dimexolon, Latrepirdine, PF-0313519  
**FDA PHASE:** Phase II  
**MECHANISMS:** Has activity as an inhibitor of cholinesterase and NMDA receptors. Inhibits neuronal death, potentially by mitochondrial-mediated inhibition of apoptosis.

---

**NAME:** Alpha-tocopherol  
**OTHER NAMES:** Vitamin E  
**FDA PHASE:** Phase III  
**ROLE IN ALZHEIMER’S DISEASE:** Thought to prevent brain cell damage by destroying toxic free radicals.

---

**NAME:** Docosahexanoic acid (DHA)  
**OTHER NAMES:** Omega-3 fatty acids  
**FDA PHASE:** Phase III  
**MECHANISMS:** DHA is a major component of neuron membranes and has multiple functions, including modulation of presenilin.

**NAME:** AZD1446  
**OTHER NAMES:** TC-6683  
**FDA PHASE:** Phase II/IIa/IIb  
**MECHANISMS:** α4β2 nicotinic (nAChR) receptor activator  
**ROLE IN ALZHEIMER’S DISEASE:** Activates neuronal nicotinic receptor, and enhances the release of acetylcholine from the cortex and thereby be memory-enhancing.

**NAME:** Dimebon  
**OTHER NAMES:** 5,6-dimethyl-1-(2-methylpyridyl)-5-ethyl-1,2,3,4-tetrahydro-γ-carboline dihydrochloride, Dimexolon, Latrepirdine, PF-0313519  
**FDA PHASE:** Phase II  
**MECHANISMS:** Has activity as an inhibitor of cholinesterase and NMDA receptors. Inhibits neuronal death, potentially by mitochondrial-mediated inhibition of apoptosis.

---

**NAME:** Bapineuzab  
**OTHER NAMES:** AAB-001  
**FDA PHASE:** Phase III  
**MECHANISMS:** Designed to bind and remove the Aβ peptide that accumulates in the brain.

**NAME:** Solanezumab  
**OTHER NAMES:** LY2062430  
**FDA PHASE:** Phase III  
**MECHANISMS:** Designed to bind and remove the Aβ peptide that accumulates in the brain.

**NAME:** Intravenous Immunoglobulin  
**OTHER NAMES:** Gammagard, IVIg  
**FDA PHASE:** Phase III  
**MECHANISMS:** Natural anti-amyloid antibodies may reduce CNS and peripheral Aβ and improve cognition.

**NAME:** Docosahexanoic acid (DHA)  
**OTHER NAMES:** Omega-3 fatty acids  
**FDA PHASE:** Phase III  
**MECHANISMS:** DHA is a major component of neuron membranes and has multiple functions, including modulation of presenilin.

**NAME:** AZD1446  
**OTHER NAMES:** TC-6683  
**FDA PHASE:** Phase II/IIa/IIb  
**MECHANISMS:** α4β2 nicotinic (nAChR) receptor activator  
**ROLE IN ALZHEIMER’S DISEASE:** Activates neuronal nicotinic receptor, and enhances the release of acetylcholine from the cortex and thereby be memory-enhancing.

**NAME:** Dimebon  
**OTHER NAMES:** 5,6-dimethyl-1-(2-methylpyridyl)-5-ethyl-1,2,3,4-tetrahydro-γ-carboline dihydrochloride, Dimexolon, Latrepirdine, PF-0313519  
**FDA PHASE:** Phase II  
**MECHANISMS:** Has activity as an inhibitor of cholinesterase and NMDA receptors. Inhibits neuronal death, potentially by mitochondrial-mediated inhibition of apoptosis.

---
**Clinical Trials 3rd**

**Amyloid binding**

**NAME:** Alzhemed™

**OTHER NAMES:** 3-amino-1-propanesulfonic acid, 3-amino-1-propylsulfonic acid, 3-AP, homotaurine, RC-531, tramiprosate

**FDA PHASE:** Not FDA regulated

**MECHANISMS:** Designed to cross the blood-brain barrier; tramiprosate is an amyloid-β antagonist.

**ROLE IN ALZHEIMER’S DISEASE:** Tramiprosate was designed to prevent amyloid formation and deposition in the brain, and thus modify the course of AD.

**NAME:** ELND005

**OTHER NAMES:** AZD-103, cyclohexane-1,2,3,4,5,6-hexol, myo-inositol, Scylo-inositol

**FDA PHASE:** Phase I/III

**MECHANISMS:** Block accumulation of Aβ oligomers; prevent Aβ oligomer formation

**Neuroprotective**

**NAME:** Resveratrol

**OTHER NAMES:** trans-3,4',5'-trihydroxystilbene

**FDA PHASE:** Phase III

**MECHANISMS:** neuroprotectant

**ROLE IN ALZHEIMER’S DISEASE:** Blass and Gordon (2004) have demonstrated positive effects in AD with an oral preparation of combined glucose, malate and resveratrol.

---

**Alzheimer's Disease Research Outline**

**Risk factors**
Risk Factors

- diabetes
- mid-life hypertension
- mid-life obesity
- Smoking
- Depression
- low educational attainment
- low physical inactivity

http://www.alz.org/aaic/tuesday_1230amC7_news_release_riskfactors.asp

A 25% reduction in Risk Factors could lower Alzheimer's cases by 3 Million in the US

Alzheimer's Disease Research Outline

Hot topics
Hot topics

Brain imaging- discussed previously

Hot topics

PLoS ONE Journal Publishes
Mechanistic Model of Alzheimer's
Disease Endorsing Prana’s PBT2
PBT2: A Novel Alzheimer’s Disease Treatment, The Microtubule-Stabilizing Agent, Epothilons
Reduces Axonal Dysfunction, Neurotoxicity, Cognitive Deficits, and Alzheimer-like Pathology in an Interventional Study with Aged Tau Transgenic Mice

Cherny et al., 2001.

New Attack on Alzheimer’s

Cherny et al., 2001. A novel drug quickly and dramatically improved function and social ability and reduced the amount of plaques in the brain of Alzheimer’s disease, suggesting a new way to battle the disease.

Alzheimer’s is associated with the accumulation of protein fragments called amyloid-beta in the brain. This new research found that administering the cancer drug called Bortezomib cleared this protein in the brains of older mice within days. The study was published Tuesday in the journal Science.

Disclosure: I have no financial or promotional or research disclosures related to these drugs. I am not condoning use of these drugs- I am presenting the scientific literature.

Alzheimer’s Disease Research

Outline

• My research
My research

What is my research?

ASAP Hypothesis

I use mass spectrometry, biochemistry and histochemical assays on human tissues, mouse / invertebrate models and synthetic proteins.

Amyloids as Sensors and Protectors (ASAP hypothesis). Amyloids sense dysfunction (oxidative, metabolic, abnormal synaptic activity, and elevated metals) and respond with misfolding.

Misfolding initiates the unfolded protein response and endoplasmic reticulum stress response. With chronic stress instead of protection we get pathology.

Potential Therapies

With regards to therapeutics, we have demonstrated in vitro efficacy of several drugs.

- Reduction of oxidative stress modification-Hydralazine
- Calcimtric influx inhibitor compound binds amyloid/immages plaques.

- Antidiabetic compound alters amyloid misfolding (manuscript in preparation).

These data are a step towards in vivo studies.
Acknowledgements

Murray lab

Grace Ellis  Sara Falasca
Erica Fang  Candle Forewer
Karen Duong  Hayley Schall  Clarissa Archer

and NIH and departmental funds

TMSIAM Health Science Center