

## Update on Alzheimer's Disease Research





### Outline

- What is Alzheimer's Disease (AD)?
- Risk factors for AD
- Brain health
- How research has changed diagnosis
- Current FDA treatments for AD
- Current research projects
- What can you do to advance AD research?



### What is Alzheimer's Disease?

- Alzheimer's is a type of dementia that causes problems with memory, thinking and behavior
- Microscopic changes in the brain begin long before the first signs of memory loss
- Alzheimer's is progressive and degenerative
- Hallmarks of the disease pathology are plaques and tangles
- Greatest risk factor is age



### Plaques and Tangles

- Plaques and tangles tend to spread through the cortext as Alzheimer's progresses
- **Plaques** are deposits of a protein fragment called betaamyloid that build up in the spaces between nerve cells.
- **Tangles** are twisted fibers of another protein called tau that build up inside cells.





### Alzheimer's Disease (AD)





### What is Dementia?

- Not a normal part of aging
- Characterized by problems with:
  - Thinking
  - Language
  - Memory
  - Judgment
  - Reasoning
- Problems get in the way of how life was once lived (impaired activities of daily living)
- Many biological causes of dementia





UCLA Health

### **Staggering Statistics**

- 5.3 million Americans with Alzheimer's Disease (AD)
- 1 in 3 older Americans has AD or another form of dementia
- 6<sup>th</sup> leading cause of death in the U.S.
- The only cause of death in the top 10 that cannot be prevented, cured, or even slowed



### AD is an Increasing Crisis



UCLA Health

Alzheimer's Facts and Figures 2011.

### Alzheimer's Disease Diagnosis

- Definite: autopsy or biopsy confirmation
- <u>Probable</u>: meet various criteria; rule out other causes; impaired memory and one other cognitive impairment; impaired activities of daily living
- <u>Possible</u>: meet criteria above but potential confounder (e.g. stroke)



### Risk Factors for Alzheimer's Disease

- Age
- Genetics
  - Family history: Persons with a family history of disease are at ~1.5 times greater risk

### • APOE gene

- We all have this gene, it helps make proteins that carry cholesterol in the bloodstream
- 3 common variations
  - ApoE ε2 decreases risk
  - ΑροΕ ε3
  - ApoE ε4 increases risk



### Brain Health

The Heart/ Brain Relationship

- Your brain accounts for 2% of your total body weight
- Your brain uses 20% of your blood oxygen/sugar
- If your brain does not get enough blood, brain cells can die





## Cardiovascular Conditions Increase Risk for Alzheimer's disease

- Cardiovascular disease
- Hypertension
- Stroke
- Diabetes
- High cholesterol



# Lowering your risk for and controlling these conditions can lower your risk for AD



### Dieting Away from Dementia

### • Barberger-Gateau et al

- Daily consumption fruits and vegetables reduced risk for allcause dementia
- Weekly consumption of fish associated with reduced risk for AD



### Fish Consumption and AD

### AD Risk





Morris et al. Arch Neurol 2003.

### Mediterranean Diet Lowers Risk for Cerebral Infarct

#### **Infarct Risk**



UCLA Health

Scarmeas et al. Ann Neurol 2011.

### Mediterranean Shopping List

- **Fish** (omega-3 fatty acids; salmon, herring, mackerel, other cold-water fish)
- Fruits and vegetables

   (antioxidants and antiinflammatories; leafy greens like kale, spinach, Brussels sprouts, and collard greens, deeply hued produce like eggplant, bell peppers, tomatoes, blue berries, strawberries, and blackberries



• Olive oil (monounsaturated fat;

• Nuts (FDA recommends 1.5

extra virgin)

### **Dietary Factors**

Antioxidants

- Vitamin E oils, nuts, fortified cereals (400 IU)
- Vitamin C citrus fruits (500 IU)
- Foliate leafy green vegetables (spinach), citrus fruits
- Cruciferous vegetables broccoli, cauliflower
- Resveratrol red wine
- DHA- omega-3 fatty acid (400 mg)

Others

- Curcumin curries (anti-oxidant, anti-inflammatory)
- Soy Isoflavones hormone-like compound

### Cognitive Activity in Older Persons

- Cognitively inactive persons over the age of 65 are 2.6 times more likely to develop AD
- Social network size modifies the association between disease pathology and cognitive function
  - Assuming equal pathology, a person with a greater social network will have better cognitive function



## 30 Minutes of Moderate Exercise is Recommended for Adults

### % American adults who get the recommended 30 minutes of moderate exercise most days of the week





Hillman CH, et al., Nat Neurosci. 2008;9:58-65. Colcombe S, Kramer AF. Psychol Sci. 2003:14:125-130.

### Frequent Exercise Lowers Risk for:

- Diabetes
- Hypertension
- Obesity



### Being active is good for you!

- Many data support the importance of physical activity and its ability to lower risk for dementia
- Framingham Study
  - Moderate to heavy physical activity is associated with a reduced risk for dementia



### **Exercise Decreases Risk for Dementia**



Larson EB, et al. Ann Int Med. 2006;144:73-81.

### Head Trauma (Traumatic Brain Injury)

- Persons who experience head trauma are more likely to develop AD later in life
  - May interact with genotype
  - •Injury may increase A $\beta$  production
  - •Recovery may increase  $A\beta$  production



### Keep a Healthy Brain

- Stop aging
- Choose the right parents (genes)
- Eat a healthy (Mediterranean) diet
- Control hypertension and high cholesterol
- Keep your mind active
- Get regular exercise
- Protect your brain (wear a helmet)



# Research Has Changed Alzheimer's Disease Diagnosis

- Increased confidence
- Ability to diagnose earlier
- Biomarkers of Alzheimer's disease
  - Protein analysis of cerebrospinal fluid
  - Magnetic resonance imaging measures of brain volume
  - Molecular neuroimaging (PET scans)



## Amyloid Positron Emission Tomography (PET)

 "Amyvid is a radioactive diagnostic agent for Positron Emission Tomography (PET) imaging of the brain to estimate β-amyloid neuritic plaque density in adult patients with cognitive impairment who are being evaluated for Alzheimer's Disease (AD) and other causes of cognitive decline"

 Does not equate to Alzheimer's diagnosis



### FDA Approved AD Treatments

- Aricept® (donepezil)—all stages
- Razadyne® (galantamine)—mild to moderate
- Exelon® (rivastigmine)—mild to moderate
- Namenda® (memantine)—moderate to severe
- Namzaric® (memantine and donepezil)- moderate to severe
- None are approved in people with mild cognitive impairment or normal memories
- None have been shown to slow the course of Alzheimer's disease



### Clinical Goals of Disease Modification



UCLA Health

Cummings JL. Alzheimer's & Dementia. 2006;2:263-271.

## Current Research Toward Disease-Modifying Therapies

- Treatments that prevent or reduce the formation of Aβ and amyloid plaques
- $\bullet$  Treatments that removed A  $\beta$  and amyloid plaques from the brain
- Treatments that reduce tau (the protein in neurofibrillary tangles)
- Neuroprotective strategies



### Moving Earlier More Efficiently

• AD is an insidious neurodegenerative disorder



UCLA Health

Sperling R et al. Alzheimer's & Dementia. 2011

### **Functional Imaging**

### Fluorodeoxyglucose PET









### What is a Clinical Trial

- Biomedical or health-related research studies in human beings that follow a pre-defined protocol
  - Observational
  - Interventional



### Many Types of Research Studies





- Telephone interviews
- In-person interviews
- Cognitive testing

- Blood tests
- MRI
- PET scans
- Lumbar
  - punctures

- Lifestyle interventions
- Pills
- Infused medications
- Surgeries



### Phases of Drug Discovery

Preclinical	Phase I	Phase II	Phase III
Development	Development	Clinical Trials	Clinical Trials
<ul> <li><i>In vitro</i> studies</li> <li>Animal studies</li> </ul>	<ul> <li>Pharmacokinetic studies - dosing</li> <li>Healthy young human subjects</li> </ul>	<ul><li>Initial human patient studies</li><li>Safety</li></ul>	<ul> <li>Large multicenter trials</li> <li>Human patients</li> <li>Clinical efficacy</li> </ul>

www.fda.gov. http://www.neurochem.com/PR196.htm. Risner ME, et al. Pharmacogenomics J 2006;6:246-254.



### Randomized Control Trials



### Patient Eligibility

- Inclusion Criteria: Factors that the patient must demonstrate to participate in the study
  - •Ex. Demonstrate a disease state for X years
  - •Ex: Be within certain age limits
- Exclusion Criteria: Factors that, if the patient demonstrates, they are not able to participate
  - •Ex: Other diseases besides that being studied
  - •Ex: Taking too many other medications



### Informed Consent

- A detailed but understandable explanation of the risks, procedures, and requirements of study participation
  - May require caregiver signature
  - Should not be needed immediately



### Randomization

- The assignment to different treatment groups should be a random process
- Not controlled or influences by the investigator or the subject
- Ensures that inherent differences between groups do not bias results



## Blinding

- Unblinded study: both the investigator and the subject are aware of whether they are receiving active drug or placebo
- Single blind study: the subject is not aware of whether they are receiving active drug or placebo
- Double blind study: neither the investigator of the subject is aware of whether they are receiving active drug or placebo
- Blinding prevents biasing of results



### **Risks/ Discomforts**

- Potential for unpleasant, serious, or in rare cases lifethreatening side effects
- No guarantee that new treatment is more effective than previous treatments
- More time/ visits to physician
- Unknown risks
- No decision regarding placebo/ active treatment

### Benefits of Participation

- Active role in own healthcare
- Access to new treatments before they are widely available
- Expert medical care at academic institutions
- Help others by contributing to medical research
- Should be free of charge, and in some cases, subjects may receive compensation for participation



### Local Clinical Trial Resources

- Easton Center for Alzheimer's Disease Research at UCLA
   •310-794-6039 www.eastonAD.ucla.edu
- West Los Angeles VA Clinical Neurosciences Research Laboratory Kagan Institute for Clinical Trials at UCLA
  - •310-478-3711 x42386 Theresa.Narvaez@va.gov
- Kagan Institute for Clinical Trials at UCLA
  - •310-794-6191
- www.nia.nih.gov/alzheimers
- clinicaltrials.gov



### A4 Study

- Individuals ages 65-85 who may be at risk for Alzheimer's disease, but who show no signs of the disease.
- The study aims to prevent the memory loss associated with Alzheimer's disease (AD).
- PET scan will be used to determine whether a potential participant has increased amyloid.
- The goal of the A4 study is
  - to slow possible AD-related damage in the brain and delay symptoms of memory loss
  - To test whether decreasing amyloid with the investigational treatment will slow memory loss associated with amyloid buildup



### CONNECT Study

- Test whether an experimental drug will slow the progression in mild-stage Alzheimer's disease
- PET imaging will evaluate whether the drug is effective in slowing cognitive decline
- 55-85 years old
- Diagnosed with mild Alzheimer's disease
- Have a study partner
- 52 week study



### Merck

Study of A Beta Secretase Inhibitor in Prodromal Alzheimer's Disease

- Tests whether an experimental drug can help slow the progression of Alzheimer's Disease
- Drug reduces level of beta amyloid by blocking the activity of an enzyme called beta secretase
- Oral medication
- Phase 3 study
- 50-85 years old
- Diagnosed with early Alzheimer's Disease
- Have a study partner
- 2 year trial



### Current Clinical Trials at the Mary S. Easton Center at UCLA

- A4
- CONNECT
- Merck
- For more information please contact

Celine Ossinalde at (310) 794-6191 or cossinalde@mednet.ucla.edu

• Potential participant pool (list of people interested in participating in clinical trials)



### Summary

- Alzheimer's Disease is the most common form of dementia
- There are lifestyle risk factors for Alzheimer's disease
- There are 5 current FDA-approved treatments for Alzheimer's disease, but none slow or prevent it
- Research is actively pursuing better treatments and diagnostic tools
- Researchers need your help!



### Contact

- Mary S. Easton Center for Alzheimer's Disease Research at UCLA
- 310-794-6039
- www.eastonAD.ucla.edu
- www.nia.nih.gov/alzheimers
- clinicaltrials.gov

