Amyloid PET Scans: Another Expensive Imaging Test We Don’t Need?

Susan Molchan, Peter Whitehouse, Brian Gran and Cory Cronin
Preventing Overdiagnosis, Barcelona
September 21
World Alzheimer Day
Our context - A Changing Story of Alzheimer's

• The Mythical Monster
  • Heterogeneity
  • Age-relatedness

• Alzheimer's Disease Cooperative Study uncooperative (law suits)
• Alzheimer Association fragmenting (chapters leaving)
• Dementia replacing Alzheimer's e.g. WHO Dementia Summit
• Perhaps we are curing ourselves of “cure” Stopping Alzheimer's
• Public health in the ascendancy – “brain health”
Monster in the Mind: The Convenient Un-Truth about Alzheimer’s  - Jean Carper
Mad “Cash Cow” Disease (MCCD)

HEALTH AND SAFETY ALERT Be on the lookout for failures to ask critical and challenging, potentially inflammatory, questions (dysquestionitis) and low levels of passion for circulating deep and heart-felt value concerns (amoralema)

MCCD was formerly thought to be an Alzheimer-like, protein folding disorder characterized by amnesia about the ecological roots of bioethics, but is now also considered a form of frontal lobe dementia characterized by apathy, poor goal setting, bad planning, and occasional social inappropriateness. Its cause relates to unbridled capitalism and unsceptical scientism. Its treatment is Responsible Research and Innovation.
Responsible Research and Innovation

• Technology in a cultural and moral context

• Broader moral scope than American bioethics – European origins

• Starting with social need – grand challenges and wicked problems

• Engaging the whole system, especially citizens and end users

• Taking the long view – e.g. the precautionary principle

• Examining opportunity costs
Changing Trajectory report—save trillions with free magic drug
Institutional Corruption case study
Anti-Amyloid treatment in Asymptomatic AD (A4 Trial)

- ADCS
- Converging evidence from both age and genetic at risk cohorts that the pathophysiological process of AD begins more than a decade before dementia
- Aβ accumulation is thought to be one of the critical factors in the early pathogenesis of AD
- Multiple trial failures at the stage of mild to moderate dementia with anti-Aβ therapies, despite evidence of biological activity
- Need to intervene much earlier to adequately test the amyloid cascade hypothesis
### Aβ Immunotherapies in development.

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<th>Drug Name</th>
<th>Sponsor</th>
<th>Characteristics</th>
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<td><strong>Monoclonal Antibodies</strong></td>
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<td>Gammagard</td>
<td>Baxter; NIH Alzheimer’s Disease Cooperative Study</td>
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<td><strong>Active Vaccines</strong></td>
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<td>AD01/AD02</td>
<td>Affiris</td>
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Leon Flicker Cochran Dementia Group 21\textsuperscript{st} birthday Oxford September 16, 2016

field still making the same mistakes

ARTICLE

doi:10.1038/nature19323

The antibody aducanumab reduces Aβ plaques in Alzheimer’s disease

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Alzheimer’s disease (AD) is characterized by deposition of amyloid-β (Aβ) plaques and neurofibrillary tangles in the brain, accompanied by synaptic dysfunction and neurodegeneration. Antibody-based immunotherapy against Aβ to trigger its clearance or mitigate its neurotoxicity has so far been unsuccessful. Here we report the generation of aducanumab, a human monoclonal antibody that selectively targets aggregated Aβ. In a transgenic mouse model of AD, aducanumab is shown to enter the brain, bind parenchymal Aβ, and reduce soluble and insoluble Aβ in a dose-dependent manner. In patients with prodromal or mild AD, one year of monthly intravenous infusions of aducanumab reduces brain Aβ in a dose- and time-dependent manner. This is accompanied by a slowing of clinical decline measured by Clinical Dementia Rating—Sum of Boxes and Mini Mental State Examination scores. The main safety and tolerability findings are amyloid-related imaging abnormalities. These results justify further development of aducanumab for the treatment of AD. Should the slowing of clinical decline be confirmed in ongoing phase 3 clinical trials, it would provide compelling support for the amyloid hypothesis.
Florbetapir (Amyvid)
C-PIB-PET for the early diagnosis of Alzheimer’s disease dementia and other dementias in people with mild cognitive impairment (MCI) (Review)

Authors’ conclusions Although the good sensitivity achieved in some included studies is promising for the value of 11C-PIB-PET, given the heterogeneity in the conduct and interpretation of the test and the lack of defined thresholds for determination of test positivity, we cannot recommend its routine use in clinical practice. 11C-PIB-PET biomarker is a high cost investigation, therefore it is important to clearly demonstrate its accuracy and standardise the process of the 11C-PIB diagnostic modality prior to it being widely used.
History of Amyloid Imaging Commercialization Strategy (US)

2012 – FDA approves florbetapir (Amyvid)
   - estimates amyloid neuritic plaque density

2013 – CMS – Coverage denied – Insufficient evidence
   The CMS standard: “reasonable and necessary for the diagnosis or treatment of illness”

- Exceptions: CMS will pay for scans to
  (1) to rule out Alzheimer’s in difficult diagnoses;
  (2) to enrich clinical trials

2013 Alzheimer’s Assoc Int’l Conference

2015 IDEAS study design approved by CMS

2016, March: IDEAS begins enrollment –will continue 24 months
Don't allow the government to stand in the way of doctors providing an early and accurate diagnosis.

Half of the more than 5 million Americans with Alzheimer's have never received a formal diagnosis. We know that an early and accurate diagnosis leads to better outcomes and higher quality of life for people with Alzheimer's and their families. Yet the federal government is moving to put up a barrier to those benefits.

Urga policy makers to improve care and provide an accurate diagnosis.

On July 3rd, Centers for Medicare and Medicaid Services (CMS) -- the agency that controls many aspects of the Medicare services you receive -- issued a disappointing draft decision on coverage for a particular type of diagnostic test called brain amyloid imaging (read more). CMS stated they believe there is insufficient evidence that use of this test improves health outcomes for Medicare beneficiaries with dementia or neurodegenerative disease in specific populations.

However, the Alzheimer's Association convened the Amyloid Imaging Taskforce, a group of leading experts in the field, who recommended that for certain situations amyloid imaging should be covered by Medicare immediately to improve the quality of care. One of those situations is when a dementia expert is unsure whether a decline in memory is due to Alzheimer's or some other -- perhaps preventable -- cause.

Thankfully the decision is not yet final. Make your voice heard if you have had firsthand experience with dementia diagnosis and care, for yourself or a loved one. If you and your family experienced challenges in obtaining a diagnosis, or if an accurate diagnosis has allowed you and your family to better plan and manage the disease, please share your experience.
An Accurate “Definitive” Diagnosis of Alzheimer’s Disease

From the protocol

“Helps direct rational pharmacologic therapy”

“. . . leads to a care plan that improves safety and minimizes the risk of preventable complications”

“Establishing the diagnosis in the early stages . . . Enables patients to participate in care planning while they are still able . . .”

“Receiving a definitive diagnosis has a positive psychological impact on most patients who are experiencing symptoms and their caregivers.”

Evidence for these benefits??????
Appropriate use criteria for amyloid PET: A report of the Amyloid Imaging Task Force, the Society of Nuclear Medicine and Molecular Imaging, and the Alzheimer’s Association

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\textsuperscript{j}Society of Nuclear Medicine and Molecular Imaging, Reston, VA, USA
The definition of dementia expert – no conflicts of interest?

Dr. Johnson and some of the other task force members reported multiple relationships with drug companies. Dr. Caselli has no financial disclosures.

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IDEAS Objectives/Aims

Open-label longitudinal cohort to assess the impact of amyloid PET scans on:

Aim 1 - **patient management** pre- and post- PET scan

N= 11,050 PET scanned
(40% dementia, 60% mild cognitive impairment (MCI))

Aim 2 – **economic outcomes** as assessed by hospital admission & ER visits as per CMS claims database (as compared with an unscanned cohort over 12 months)

N= 18,488 PET scanned
IDEAS    Outcome Measures

**Aim #1** Impact of amyloid PET on patient management

Case report forms w/ intended management before PET compared with Case report forms w/ actual management 90 days post PET

Hypothesis: Amyloid PET info will lead to a ≥ 30% change between intended & actual management, as measured by a cumulative (composite) endpoint of:
   - AD drug therapy
   - Other drug therapy
   - Counseling (about safety, future planning)
- A one-sided analysis planned for dementia & MCI groups separately
Potential impact of amyloid imaging on diagnosis and intended management in patients with progressive cognitive decline.


Collaborators (39)

Author information

Abstract
Changes in clinician behavior

• After receiving the results of the florbetapir scan, diagnosis changed in 125/229, or 54.6% [95% confidence intervals (CI), 48.1%-60.9%], of cases, and diagnostic confidence increased by an average of 21.6% (95% CI, 18.3%-24.8%). A total of 199/229 or 86.9% (95% CI, 81.9%-90.7%) of cases had at least 1 change in their management plan. Intended cholinesterase inhibitor or memantine treatment increased by 17.7% (95% CI, 11.8%-25.8%) of all cases with positive scans and decreased by 23.3% (95% CI, 16.5%-31.8%) of all those with negative scans. Among subjects who had not yet undergone a completed work up, planned brain structural imaging (computed tomographic/magnetic resonance imaging) decreased by 24.4% (95% CI, 17.5%-32.8%) and planned neuropsychological testing decreased by 32.8% (95% CI, 25.0%-41.6%). In summary, amyloid imaging results altered physician's diagnostic thinking, intended testing, and management of patients undergoing evaluation for cognitive decline.
Aim #2  Hypothesis: Amyloid PET is associated with ≥ 10% reduction in hospitalizations & ER visits

These outcomes will be compared over 12 months between those who were scanned and a cohort that were never scanned, with data coming from Medicare claims data.

An algorithm will be used to match those with PET scans to those who will not be scanned, by diagnosis, pre-scan dementia-related resource utilization, age, race, gender, ethnicity, geographic location, and comorbid chronic conditions.
REVEAL Phase 4
Combining risk factors ApO 4 and amyloid imaging

• Background problems
  • Pleotropic gene (cardiovascular plus)
  • Ethnicity – self identified African-americans

• Current problems
  • Risk curves with or without standard errors
  • Amyloid scans – either positive or negative but a continuum also with error

• Is knowledge power? – whose power and is it wisdom?
Five Things Physicians and Patients Should Question

1. Don’t use PET/CT for cancer screening in healthy individuals.
   - The likelihood of finding cancer in healthy adults is extremely low (around 1%), based on studies using PET/CT for screening.
   - Imaging without clear clinical indication is likely to identify harmless findings that lead to more tests, biopsy or unnecessary surgery.

2. Don’t perform routine annual stress testing after coronary artery revascularization.
   - Routine annual stress testing in patients without symptoms does not usually change management.
   - This practice may lead to unnecessary testing without any proven impact on patient management.

3. Don’t use nuclear medicine thyroid scans to evaluate thyroid nodules in patients with normal thyroid gland function.
   - Nuclear medicine thyroid scanning does not conclusively determine whether thyroid nodules are benign or malignant.
   - Cold nodules on thyroid scans will still require biopsy.
   - Nuclear medicine thyroid scans are useful to evaluate the functional status of thyroid nodules in patients who are hyperthyroid.

4. Don’t use PET imaging in the evaluation of patients with dementia unless the patient has been assessed by a specialist in this field.
   - Without objective evidence of dementia, the potential benefit of PET is unlikely to justify the cost or radiation risk.
   - Dementia subtypes have overlapping patterns in PET imaging. Clinical evaluation and imaging often provide additive information and should be assessed together to make a reliable diagnosis and to plan care.
My conclusion – if you have memory loss do not see an “expert”. See a primary care physician and if he/she gives you general health advice like diet and exercise then that is the best for your brain health too.
Opportunity costs

• Brain health with purpose and in community

• Arts and music

• Community development and public health
The Intergenerational School
Freeway Fighter
1960’s environmental activist
“Occupy Nature”: Passing Activism Across Generations

In the early 1960s, a group of community activists in Cleveland calling themselves the “Freeway Fighters” began mobilizing. The target of their protest was a proposed superhighway that would tear through 300 acres of undisturbed marsh, demolish a nature center, and saddle a stream called Deam Brook that meandered through several eastside neighborhoods and into the city’s cultural gardens in Rockefeller Park before emptying into Lake Erie. Championing the superhighway was a powerful and politically connected county engineer who considered the nature center and its waterways “a dinky little park” with a “two-bit duck pond” and argued the parkland was better viewed from a car than on foot. It was the height of the post-Eisenhower freeway boom, and the building frenzy seemed an unstoppable cultural force.

But it was also the era of civil rights and antiwar movements, and protest was in the air. Galvanized by the threat to their neighborhoods, the Freeway Fighters held public forums to educate the community, organized letter-writing groups, and arranged walks through the parklands with local politicians. “Better ducks than tanks” was their unifying cry. In 1970, after the group had waged a 7-year struggle, Ohio Governor James Rhodes officially scrapped the superhighway plan. Since then, more than 280,000 children have taken classes at the nature center on Deam Brook, whose oxygen-rich waters now flow into Lake Erie.

Many of the Freeway Fighters have since died, and those still living are experiencing the challenges of old age. Even so, the legacy of their activism is still embodied in the trees, waterways, and wildlife surrounding the nature center. One major beneficiary of the Freeway Fighters’ efforts has been The Intergenerational School (TIS), a Cleveland charter school located on a bluff above Deam Brook that uses the nature school as an educational resource and venue for intergenerational programming.

In March 2011, TIS students aged 12 to 14 visited a local retirement community called Judson Park—also located near Deam Brook—where nine Freeway Fighters resided. Students were charged not only with recording the stories of these activists, but also with expressing gratitude for the legacy they had left the region.

When students arrived at Judson Park, they shook hands with their elder partners and split into small groups for interviews. One Freeway Fighter, Kay Fuller, a 94-year-old woman whose memory is now challenged by mild to moderate dementia (Figure 1), energetically described to her young partners how she fought against the superhighway.

Figure 1. With a picture of the nature reserve in front of her, Kay Fuller describes her role as an activist to students from The Intergenerational School.

threat her into the unexpected position of a movement leader: “I just couldn’t believe that they would put a freeway through there . . . but I never fought anything in my life. I had always been shy and afraid of my own voice, so I really had to work on it.” Then a housewife and mother of three young children, Mrs. Fuller eventually found her voice in testifying at the local city council as well as before the U.S. Congress. When students asked what practical advice Mrs. Fuller would give their generation, she paused to reflect before saying, “I think you should take the lesson that, if there is something that is worthwhile, you should be aware of it and fight for it.”

In their reflective writing after the interviews, students expressed admiration at how the Freeway Fighters had preserved the local neighborhood, often assembling the formal language of their elder partners. As one student wrote: “There are some things that you really need to stand up and fight for when you think they’re wrong. You can’t just sit there and let people run over you, because that highway would’ve destroyed a beautiful part of this city that now is very integrated.” Another student concluded: “The freeway would’ve destroyed [our neighborhood]. It would have become neglected and empty.” Student narratives were combined with their interview
ALIVE INSIDE wins Sundance Audience Award!

ALIVE INSIDE

DR. PETER WHITEHOUSE
NEUROLOGIST

SPECIAL SCREENING + Q&A WITH DAN COHEN
led by Ohio Department of Aging Director, Bonnie K. Burman
Thursday, Sept. 4, 7pm
Regular Engagement Begins Fri. Sept. 5

2254 EAST MAIN STREET, COLUMBUS, OHIO
DREXEL.NET
Dementia Friendly Communities
SAVE THE DATE! JUNE 7-8, 2012

Healthy Environments Across Generations

Conference at:
The New York Academy of Medicine
1216 5th Avenue (at 103rd Street)
New York City

Thursday, June 7th
8:30-5:00 PM

Friday, June 8th
8:30-1:00 PM

Please join us for a participatory conference with leaders and innovators committed to creating healthier environments for all ages and across all sectors.

CURRENT LIST OF CO-SPIRORS:

AARP
Alliance for Aging Research
American Geriatric Society
American Society on Aging
American Society of Landscape Architects
Healthcare & Therapeutic Garden Network
Beth Johnson Foundation
Center for Health, Environment & Justice (CHEJ)
Children & Nature Network
Children's Environmental Health Center at Mount Sinai Medical Center

The Intergenerational School
Intergenerational Urban Institute
Worcester State University
International Society of Doctors for the Environment (ISDE)
Kate Dunn Theater
The John Merrill Fund
National Center for Creative Aging
National Council on Aging
National Environmental Education Foundation (NEEF)
The Orchard Foundation
STOPPING ALZHEIMER’S DISEASE AND RELATED DEMENTIAS: Advancing Our Nation’s Research Agenda

NIH BYPASS BUDGET PROPOSAL FOR FISCAL YEAR 2018
Emerging Imaging and Therapeutics in Alzheimer's Disease: Early Detection and Intervention

Rajani Duma, MD, Course Chair, Adam S. Fleisher, MD, MAS, Paul B. Rosenberg, MD
CME Released: 09/23/2013. Valid for credit through 09/23/2014

This activity was developed for neurologists, radiologists, nuclear medicine specialists, and other healthcare professionals involved in the treatment of patients with Alzheimer's disease. Alzheimer's disease (AD) is an irreversible, age-related neurodegenerative disorder characterized by gradual decline in understanding, memory, and ability to perform activities of daily living. AD accounts for 60% to 80% of all cases. Presentation to a physician is typically delayed well beyond symptom onset, when disabling symptoms and neuropathologic changes have become well-established. Early recognition and diagnosis continues to be a challenge for physicians, on behalf of individuals who satisfy the criteria for AD never receive a diagnosis. There is increasing evidence that early diagnosis is important for maximizing the benefits of treatment. The underlying process of amyloid beta (Aβ) plaques and tau protein (neurofibrillary tangles) are hallmarks of AD pathology. Amyloid pathology occurs during the sometimes decades-long preclinical phase, and neurofibrillary pathology serves as a precursor to the symptomatic phase of AD. Advances in imaging agents and techniques are allowing for early detection and identification of such pathologies, thus offering the potential for patients to be identified much earlier and appropriately monitored for disease progression and potential therapeutic interventions. Whereas current therapies focus on symptoms, disease-modifying therapies are being explored that may offer neuroprotection while maintaining cognitive function. New clinical practice guidelines reflect emerging advances in both AD imaging and potential disease-modifying therapeutics. In order to improve...
Diagnostic Tests for Alzheimer’s Disease: Generating and Evaluating Evidence to Inform Insurance Coverage Policy

Steven D. Pearson, MD, MSc, FRCP
Daniel A. Ollendorf, MPH, ARM
Jennifer A. Colby, PharmD

in conjunction with the
ICER Alzheimer’s Disease Diagnostics Policy Development Group
Biomarkers – CSF and Blood Tests

**ApoE**  The major cholesterol transporter in the brain
- ApoE4 – 1 copy: increase risk 2-3X; 2 copies 10X; reduces onset age, increases risk for vascular disease, Lewy body dementia
- ApoE3 No impact on risk
- ApoE2  Decreased risk

40% of AD patients carry at least one Apo4 . . . So over 50% do not

**CSF** – low levels of Ab 1-42
- CSF high levels of phospho tau, total tau
- Sensitivity & specificity of 85-95% for incipient AD in MCI populations (Mattson N & Zetterberg H Euro Neurol 2009)

“While this is of interest to researchers, public health policy makers and the diagnostics industry, they are of little use to clinicians.”
The Model for IDEAS: National Oncologic PET Registry

“A collaboration of the American College of Radiology Imaging Network, the American College of Radiology, and the Academy of Molecular Imaging, to ensure access to Medicare reimbursement for certain types of PET scans”

Start up funding: Academy of Molecular Imaging, sustained from fees from participating PET facilities

Chair: Dr. Bruce Hillner
Co-Chair: Dr. Barry Siegel

Data management and statistical analyses by the American College of Radiology and Brown University (Dr. C. Gatsonis)

CMS Decision Memo for Positron Emission Tomography (FDG) for Solid Tumors
June 11, 2013
- Reimbursement for many solid tumors despite no outcome advantage. Documented change in management
Aim 2: **A Twisted Rationale**

To compare hospitalizations, ER visits to an unscanned, cohort matched for age, cognitive impairment comorbidities

Protocol (p.15-16) twists the rationale: Cites (unpublished) data showing dementia patients seen in a multidisciplinary dementia program w/ their caregivers had fewer hospitalizations, ER visits

No specific diagnoses such as AD noted

Yet the investigators state: “Per these data, we propose that these elements of care, resulting from a more accurate diagnosis, are some of the mechanisms that will improve outcomes and reduce risk of emergency room visits and hospitalizations.”

A different conclusion:
All dementia patients and caregivers should be referred to a multidisciplinary dementia program
IDEAS: Eligibility/Inclusion Criteria

Medicare beneficiaries referred by “qualified dementia specialists” who:

Cognitive complaint verified by objectively confirmed cognitive impairment

Etiologic cause of cognitive impairment is uncertain after a comprehensive evaluation by a dementia expert

Alzheimer’s disease (AD) is a diagnostic consideration

Knowledge of amyloid PET status is expected to alter diagnosis and management

Recruitment into 1 of 2 cohorts:

Cohort 1  Progressive Mild cognitive impairment (MCI)

Cohort 2  Dementia of uncertain etiology
IDEAS - Coalition

Alzheimer’s Association (many pharma sponsors including Lilly, GE Healthcare)

American College of Radiology
- Dr. Barry Siegel Wash U (consultant GE Healthcare, Siemens; stock: Radiology Corp of America) (J Clin Onc 2016)
- Dr. Bruce Hillner VCU

Center for Statistical Sciences, Brown U School of Public Health
- Dr. Constantine Gatsonis

Medical Imaging and Technology Alliance (MITA)
- $^{18}$F- florbetabir (Amyvid) (Lilly)
- $^{18}$F-flutemetamol (Vizamyl) (GE Healthcare)
- $^{18}$F-florbetaben (Neuraceq) (Piramal Life Sciences)

Study chair: Dr. Gil Rabinovici (UCSF) (speaking fees GE Healthcare) (Ann Neur 2015)
Study Co-chair: Dr. Rachel Whitmer (Kaiser Permanente)

Operations Center: American College of Radiology Clinical Research Center, Philadelphia
The IDEAS Study is sponsored by the American College of Radiology and the American College of Radiology Imaging Network (NCI, industry also fund this), with funding that is being provided by the Alzheimer’s Association, the American College of Radiology, and the manufacturers of the FDA-approved radiopharmaceuticals for amyloid imaging.

Of the $100 million cost of the study, $80 million will be paid by Medicare to reimburse for PET scans
  - For 18,488 enrolled = $4,327/scan
From the protocol . . . “Accurate Diagnosis of Dementia”

(True or False?)

“. . . The majority of eligible patients do not receive cholinesterase inhibitors or memantine, drugs that have been shown to slow cognitive and functional decline . . . “

“. . . AD drugs are often used off-label in patients with nonAD causes of dementia such as frontotemporal dementia (FTD) . . . Use of these medications is associated with adverse outcomes . . . “

“. . . The lack of diagnostic accuracy also represents a barrier to developing and testing biologically specific therapies.”
1) Watchful waiting

2) Intended changes in AD therapy (cholinesterase inhibitors and/or memantine)

3) Intended changes in other medications

4) Guidance about safety and planning

5) Referral to family support systems (Alzheimer’s Association for care plans, legal and safety education)

6) Additional diagnostic procedures

7) Referral to non-pharmacologic interventions

8) Plans to refer individuals to clinical trials (for AD or non-AD dementia)
New Insights into the Dementia Epidemic
Larson EB et al NEJM 2013
“the vast majority of dementia cases, especially those occurring late in life, tend to
involve a mixture of Alzheimer’s disease, vascular disease, and other degenerative
factors.”

Dementia (Including Alzheimer’s Disease) Can be Prevented: Statement Supported by
International Experts Smith AD and Yaffe K, J of Alz Dis 2014

“We are confident that the same approach will work for dementia.”

Incidence of Dementia over Three Decades in the Framingham Heart Study

5000 people over 60

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44% fewer . . . Mostly vascular; AD just missed stat significance
Average age of diagnosis: 80 to 85
Categories of therapy

• Biological
  • Symptomatic
    • Cognitive e.g. nicotinic receptors
    • Behavioral e.g. prazosin
  • Prevention e.g. amyloid vaccines
    • Primary – asymptomatic, preclinical Alzheimer's
    • Secondary – MCI

• Psychosocial
  • Physical activity
  • Diet
  • Educational interventions
  • Brain games
  • Arts and music, especially dance
  • Community-based – intergenerational school and dementia friendly communities
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<td><strong>MonoClonal Antibodies</strong></td>
<td></td>
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</tr>
<tr>
<td>Bapineuzumab (AAB-001)</td>
<td>Janssen/Elan/Pfizer</td>
<td>1-5 (free N-terminus)</td>
<td>III</td>
</tr>
<tr>
<td>Solanezumab (LY2062430)</td>
<td>Eli Lilly</td>
<td>13-28</td>
<td>III</td>
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<tr>
<td>PF-04360365</td>
<td>Pfizer</td>
<td>33-40 (free C-terminus)</td>
<td>II</td>
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<tr>
<td>MABT5102A</td>
<td>Genentech</td>
<td>NP</td>
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<tr>
<td>GSK933776A</td>
<td>GlaxoSmithKline</td>
<td>NP</td>
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</tr>
<tr>
<td>Gantenerumab (R1450/RO4909832)</td>
<td>Hoffmann-La Roche</td>
<td>NP</td>
<td>I</td>
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<tr>
<td><strong>Intravenous Immunoglobulin</strong></td>
<td></td>
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<tr>
<td>Gammagard</td>
<td>Baxter; NIH Alzheimer's Disease Cooperative Study</td>
<td></td>
<td>III</td>
</tr>
<tr>
<td>Octagam</td>
<td>Octapharma</td>
<td></td>
<td>II</td>
</tr>
<tr>
<td><strong>Active Vaccines</strong></td>
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<tr>
<td>CAD106</td>
<td>Novartis</td>
<td>1-6</td>
<td>II</td>
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<tr>
<td>ACC001</td>
<td>Pfizer</td>
<td>1-7</td>
<td>II</td>
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<tr>
<td>UB311</td>
<td>United Biochemical</td>
<td>1-14</td>
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<tr>
<td>V950</td>
<td>Merck</td>
<td>NP</td>
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<tr>
<td>AD01/AD02</td>
<td>Affiris</td>
<td>**</td>
<td>I</td>
</tr>
</tbody>
</table>
A4 Trial Aims

- To determine whether decreasing Aβ burden will slow the rate of cognitive decline in clinically normal older Aβ+ individuals at risk for progression to MCI and AD dementia

- To investigate the impact of anti-Aβ treatment on “downstream” markers of neurodegeneration, and explore whether there is a “critical window” for anti-Aβ therapy within the preclinical stages of AD

- To develop more sensitive outcome measures to improve the efficiency of future secondary prevention trials
A4 Trial Design

- Clinically normal older individuals (> age 70) Aβ+ on PET imaging
- Treat with biologically active compound for 3 years in a randomized, double-blind, placebo-controlled trial
- Total N=1000 (N=500 per treatment arm)
- 2 year additional clinical follow-up
- Test the hypothesis that altering “upstream” amyloid accumulation will impact ”downstream” neurodegeneration and cognitive decline
- Include Aβ- arm (N = 500) for natural history study (no treatment) for clinical and novel outcomes
### Results

<table>
<thead>
<tr>
<th>Variable</th>
<th>Intervention (n=8)</th>
<th>Control (n=7)</th>
<th>Effect Size</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stress change, mean ± SD Decline</td>
<td>-2.50 ± 1.41</td>
<td>+3.14 ± 6.46</td>
<td>1.18</td>
<td>0.349*</td>
</tr>
<tr>
<td>Cognitive functioning change, mean ± SD Decline</td>
<td>-0.75 ± 2.86</td>
<td>-2.14 ± 1.34</td>
<td>0.57</td>
<td>0.197*</td>
</tr>
<tr>
<td>Sense of purpose change, mean ± SD Decline</td>
<td>0.00 ± 0.535</td>
<td>-0.43 ± 0.535</td>
<td>0.76</td>
<td>0.208*</td>
</tr>
<tr>
<td>Depression change, mean ± SD Decline</td>
<td>+0.50 ± 1.41</td>
<td>-2.57 ± 10.5</td>
<td>0.40</td>
<td>0.442*</td>
</tr>
<tr>
<td>Sense of usefulness Change, mean ± SD Decline</td>
<td>0.00 ± 0.926</td>
<td>-0.29 ± 0.756</td>
<td>0.32</td>
<td>0.543*</td>
</tr>
</tbody>
</table>

SD = standard deviation

* Mann-Whitney U-test

** Fisher’s exact test
## Qualitative results

<table>
<thead>
<tr>
<th>Quality of life:</th>
<th>Sub themes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Main themes</strong></td>
<td><strong>Sub themes</strong></td>
</tr>
<tr>
<td><strong>Perceived health benefits</strong></td>
<td>Reduced stress and depression</td>
</tr>
<tr>
<td></td>
<td>Youthful energy</td>
</tr>
<tr>
<td></td>
<td>Cognitive stimulation</td>
</tr>
<tr>
<td><strong>Sense of purpose and sense of usefulness</strong></td>
<td>Role continuation</td>
</tr>
<tr>
<td></td>
<td>Reminiscence</td>
</tr>
<tr>
<td></td>
<td>Joy of teaching children</td>
</tr>
<tr>
<td><strong>Relationships</strong></td>
<td>Physical touch</td>
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<tr>
<td></td>
<td>Proxy grandchildren</td>
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<tr>
<td></td>
<td>Racial reconciliation</td>
</tr>
<tr>
<td></td>
<td>Acceptance</td>
</tr>
<tr>
<td></td>
<td>Reciprocity</td>
</tr>
</tbody>
</table>
The Legacy of Clark Freeway Fighters
Web-Based Resource
Brain Imaging

**MRI:** Atrophy of hippocampus & entorhinal cortex – best established. Overlap with Lewy body, hippocampal sclerosis, Frontotemporal dementia

**PET – FDG** – Hypometabolism temporal, parietal

**Amyloid PET** – 1/3 of people without dementia can have positive scans, although these are more likely to go on to develop MCI or AD compared to those with negative scans
- Also positive in many with Lewy body dementia
- Can be useful to rule out Alzheimer’s disease, especially in a younger person; or perhaps to differentiate from FTD
ALIVE INSIDE wins Sundance Audience Award!