BRAIN AGING:
What we fear, what it is, and what we can do about it

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Disclosures: Dr. Bennett is the inventor on multiple US & international patents involving the use of the neuroprotective drug R(+) pramipexole in degenerative diseases of brain, eye, heart and skeletal muscle.
What We Fear
We bring you forth as babies, then that you may attain your maturity; and of you is he who is caused to die, and of you is he who is brought back to the worst part of life, so that after having knowledge he does not know anything.

Qu’ran 22.5
What Is Brain Aging?
Aging

Mitotic tissues
Skin, blood, GI

Non-mitotic tissues
brain, muscle, retina

Mitotic tissues
Skin, blood, GI
Why is Brain Aging a Looming Disaster for Our Society?
World Alzheimer Report 2010

THE GLOBAL ECONOMIC IMPACT OF DEMENTIA

September, 2010
1% of current GDP; 18th largest economy
Current and projected numbers for people with Alzheimer’s or another dementia worldwide (in millions)

Today: 35.6
2030: 65.7
2050: 115.4

Figure 1: Proportion of People Age 65 and Older with Alzheimer’s Disease and Other Dementias, by Race/Ethnicity, Washington Heights-Inwood Columbia Aging Project, 2006

<table>
<thead>
<tr>
<th>Age</th>
<th>White</th>
<th>African-American</th>
<th>Hispanic</th>
</tr>
</thead>
<tbody>
<tr>
<td>65 to 74</td>
<td>2.9</td>
<td>9.1</td>
<td>7.5</td>
</tr>
<tr>
<td>75 to 84</td>
<td>10.9</td>
<td>19.9</td>
<td>27.9</td>
</tr>
<tr>
<td>85+</td>
<td>30.2</td>
<td>58.6</td>
<td>62.9</td>
</tr>
</tbody>
</table>
U.S. POPULATION OF THOSE 65 AND OLDER  Source: U.S. Bureau of the Census
(d. Ltn) *Boomerus antiquus*: A subpecies of *homo sapiens* appearing in mid 20th century, noted for its refusal to accept normal aging events. *B. antiquus* regularly seeks pharmacological, behavioral, cosmetic and fashion help to avoid decline into the inevitable.
<table>
<thead>
<tr>
<th>Region</th>
<th>Informal care (all ADL)</th>
<th>Direct costs</th>
<th>Total costs</th>
<th>Total costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australasia</td>
<td>13812</td>
<td>2262, 16296</td>
<td>32370</td>
<td></td>
</tr>
<tr>
<td>Asia Pacific High Income</td>
<td>12243</td>
<td>1852, 14963</td>
<td>29057</td>
<td></td>
</tr>
<tr>
<td>Oceania</td>
<td>4526</td>
<td>1026, 508</td>
<td>6059</td>
<td></td>
</tr>
<tr>
<td>Asia Central</td>
<td>1295</td>
<td>845, 723</td>
<td>2862</td>
<td></td>
</tr>
<tr>
<td>Asia East</td>
<td>2774</td>
<td>788, 517</td>
<td>4078</td>
<td></td>
</tr>
<tr>
<td>Asia South</td>
<td>515</td>
<td>259, 128</td>
<td>903</td>
<td></td>
</tr>
<tr>
<td>Asia Southeast</td>
<td>711</td>
<td>595, 295</td>
<td>1601</td>
<td></td>
</tr>
<tr>
<td>Europe Western</td>
<td>12479</td>
<td>4328, 13315</td>
<td>30122</td>
<td></td>
</tr>
<tr>
<td>Europe Central</td>
<td>7801</td>
<td>2423, 2667</td>
<td>12891</td>
<td></td>
</tr>
<tr>
<td>Europe Eastern</td>
<td>4261</td>
<td>1832, 1573</td>
<td>7667</td>
<td></td>
</tr>
<tr>
<td>North America High Income</td>
<td>17968</td>
<td>8403, 22233</td>
<td>48605</td>
<td></td>
</tr>
<tr>
<td>Caribbean</td>
<td>4570</td>
<td>2371, 2151</td>
<td>9092</td>
<td></td>
</tr>
<tr>
<td>Latin America Andean</td>
<td>1375</td>
<td>1200, 1089</td>
<td>3663</td>
<td></td>
</tr>
<tr>
<td>Latin America Central</td>
<td>1335</td>
<td>2202, 1999</td>
<td>5536</td>
<td></td>
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<tr>
<td>Latin America Southern</td>
<td>3838</td>
<td>2309, 2095</td>
<td>8243</td>
<td></td>
</tr>
<tr>
<td>Latin America Tropical</td>
<td>2057</td>
<td>2529, 2295</td>
<td>6881</td>
<td></td>
</tr>
<tr>
<td>North Africa / Middle East</td>
<td>1660</td>
<td>1794, 472</td>
<td>3926</td>
<td></td>
</tr>
<tr>
<td>Sub-Saharan Africa Central</td>
<td>648</td>
<td>289, 143</td>
<td>1081</td>
<td></td>
</tr>
<tr>
<td>Sub-Saharan Africa East</td>
<td>787</td>
<td>224, 111</td>
<td>1122</td>
<td></td>
</tr>
<tr>
<td>Sub-Saharan Africa Southern</td>
<td>5149</td>
<td>1127, 558</td>
<td>6834</td>
<td></td>
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<tr>
<td>Sub-Saharan Africa West</td>
<td>609</td>
<td>241, 119</td>
<td>969</td>
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<tr>
<td><strong>All</strong></td>
<td>7084</td>
<td>2711, 7191</td>
<td>16986</td>
<td></td>
</tr>
</tbody>
</table>
# Monetary Costs of Dementia in the United States

Michael D. Hurd, Ph.D., Paco Martorell, Ph.D., Adeline Delavande, Ph.D., Kathleen J. Mullen, Ph.D., and Kenneth M. Langa, M.D., Ph.D.

## Yearly Cost per Person (95% CI)

<table>
<thead>
<tr>
<th></th>
<th>Adjusted for Demographic Characteristics and Coexisting Conditions</th>
<th>Unadjusted</th>
<th>dollars</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grand total</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Care purchased in marketplace plus caregiving time valued according to replacement cost</td>
<td>64,168 (48,406–79,928)</td>
<td>56,290 (42,746–69,834)</td>
<td></td>
</tr>
<tr>
<td>Care purchased in marketplace plus caregiving time valued according to cost of forgone wages</td>
<td>47,920 (35,433–60,406)</td>
<td>41,689 (31,017–52,362)</td>
<td></td>
</tr>
</tbody>
</table>
Future Dementia Costs May Equal Defense Department Budget

Current Annual Dementia Costs: $215-220 billion
FY 2017 DoD Base Budget $523.9 billion
Is US Dementia Rate Declining?

| Cognitive Function | 2000 (n = 10,546) | 2012 (n = 10,511) | Age- and Sex-Standardized Rate$^b,c$
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>6966 (67.2) [65.8-68.6]</td>
<td>7114 (72.4) [71.1-73.6]</td>
<td>7114 (72.6) [71.1-73.6]</td>
</tr>
<tr>
<td>CIND</td>
<td>2293 (21.2) [20.1-22.3]</td>
<td>2224 (18.8) [17.8-19.9]</td>
<td>2224 (18.8) [17.8-19.9]</td>
</tr>
<tr>
<td>Dementia</td>
<td>1287 (11.6) [10.7-12.7]</td>
<td>1173 (8.8) [8.2-9.4]</td>
<td>1173 (8.6) [8.1-9.3]</td>
</tr>
</tbody>
</table>

Abbreviation: CIND, cognitive impairment—no dementia.

$^a$ Values in parentheses are weighted percentages (95% CIs) derived using the HRS sampling weights to adjust for the complex design of the Health and Retirement Study.$^{16}$

$^b$ $p < .001$ for difference between 2000 and 2012.

$^c$ The age- and sex-standardized weighted percentages, after direct standardization of the 2012 cohort to the 2000 cohort.
The Neuropathology of Brain Aging
Degenerative Causes of Dementia

- Alzheimer’s disease (~60%)
- “Vascular” (~20%)
- Parkinson’s disease (10-20%)
- Lewy body disease (<10%)
- Others (5-10%)
- Fronto-temporal degenerations (rare)
Brain Pathology in Alzheimer’s

beta-amyloid plaques  fibrillary “tangles”
“Vascular Cognitive Impairment”

VCI: ...a syndrome of clinical stroke or subclinical vascular brain injury and cognitive impairment affecting at least one cognitive domain

“Vascular Dementia”

VD: ...the most severe form of VCI
Brain MRI in Vascular ("Multi-Infarct") Dementia

http://radiopaedia.org/images/540186

emedicine.medscape.com
“Pure” Vascular Dementia is Rare

extensive small blood vessel strokes with little or no Alzheimer’s pathology
“Pure” Vascular Dementia (rare)

Most dementia is a mixture of blood vessel (“vascular”) and AD pathology

“Pure” Alzheimer’s Dementia (rare)
Brain Aging as an Energy Failure
Your Brain is an Energy Factory

- Brains are ~2-3% of body weight yet use ~20-25% of blood flow and oxygen
- Nerve cells (neurons) are among the most energy requiring cells in the body
- If neurons can’t make this level of energy, they cannot function as neurons, but could remain morphologically present (ie, functionally “dead” but anatomically “present”) - *zombie neurons*
- Neurons use fuels to make energy (glucose is preferred, fatty acids will work during starvation)
Neuronal MtDNA Deletions Increase with Aging and Loss of COX

- individual substantia nigra neurons isolated by LCM
- analyzed for abundance of deleted mtDNA species
- correlated with loss of COX histochemical staining

5 kilobase "common deletion"
Human Brain Glucose Uptake Decreases with Aging

6.9% per decade
Pupi, et al, 2009

Yellow = older (60-85 yrs) less than younger (21-37 yrs)
Brain Glucose Uptake Decline in Aging Tracks with Depression

<table>
<thead>
<tr>
<th>NPS</th>
<th>Abnormal FDG-PET (N=204)</th>
<th>Normal FDG-PET (N=454)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td>Agitation</td>
<td>5 (2.5)</td>
<td>9 (2.0)</td>
<td>1.21 (0.38–3.79)</td>
</tr>
<tr>
<td>Depression</td>
<td>31 (15.2)</td>
<td>33 (7.3)</td>
<td><strong>2.12 (1.23–3.64)</strong>*</td>
</tr>
<tr>
<td>Anxiety</td>
<td>13 (6.4)</td>
<td>19 (4.2)</td>
<td>1.61 (0.76–3.42)</td>
</tr>
<tr>
<td>Apathy/Indifference</td>
<td>9 (4.4)</td>
<td>20 (4.4)</td>
<td>0.86 (0.37–1.97)</td>
</tr>
</tbody>
</table>

*Significant difference
Human Brain Glucose Metabolism Decreases with Aging

Why?

- Decrease in neurons and nerve endings (synapses)
- Loss of connectivity between brain regions
- Increased blood vessel pathology with decreased glucose entry into brain
- *Brain insulin resistance* ("Type 3 diabetes")
- *Molecular changes in energy producing systems* (mitochondria)
Brain Glucose but Not Ketone Uptake Declines with Aging
Brain Glucose Metabolism is Lost in Alzheimer’s Disease
Brain Glucose But Not Fatty Acid Uptake is Reduced in Early AD

HBA = hydroxy butyric acid (a fatty acid)
Would dietary ketones solve the energy deficit in Alzheimer’s?
If the brain is ‘starving” (low energy production), brain oxygen ($O_2$) consumption will decline.

In early AD, no loss of brain $O_2$ consumption

In later AD, brain $O_2$ consumption declines

Early AD brain has impaired glucose metabolism (“low carb diet”) and uses alternative fuels ($ketones, fatty acids$)

Later AD brain has impaired energy metabolism for all fuels
What about $\beta$-amyloid imaging?

$\beta$-amyloid

glucose

65 yo CTL
What about $\beta$-amyloid imaging?

$\beta$-amyloid

glucose

71 yo AD
What about $\beta$-amyloid imaging?

CTL

AD
Predicting MCI/AD

Amyloid in CSF
Amyloid PET scan
FDG PET scan
Clinical function
Cognitive function
Tau in CSF
Clinical Disease Stage

Journal of Cerebral Blood Flow & Metabolism (2012), 1-16
What if a parent has AD?
Cognitively normal FHm but not FHp have increased brain $\beta$-amyloid.
What is “Oxidative Stress”? 

- Life depends on oxygen, which allows most energy to be made from sugars and fats.
- This process is not 100% efficient (~98%).
- As a result, we constantly form and inactivate (“scavenge”) oxygen free radicals.
- If more free radicals are created than scavenged, then a state of “oxidative stress” exists.
- Oxygen radicals damage all cell components.
- “Oxygen free radical theory of aging”
Fuels

Energy

Oxygen

Water

damaging oxygen free radicals
(increased in AD brain)
Cognitively normal FH\textsubscript{m} but not FH\textsubscript{p} have increased CSF Isoprostanes (oxidative stress markers)
Predicting Cognitive Decline in Subjects at Risk for Alzheimer Disease by Using Combined Cerebrospinal Fluid, MR Imaging, and PET Biomarkers

- **Alzheimer Disease Neuroimaging Initiative**
- Examined 97 subjects with MCI who converted (n=43) or did not convert (n=54) to AD dementia over several years
- Searched for most sensitive and reliable biomarkers of AD conversion
- MRI, FDG-PET, spinal fluid AD proteins (β-amyloid, tau)
Brain FDG-PET is single most sensitive test to predict conversion of MCI to AD
Aging-related dementia will overwhelm our social, economic and medical resources in 20 years.

Most aging-related dementia is mixed Alzheimer’s-microvascular pathologies, and is what we now call “Alzheimer’s disease” (AD).

AD is preceded by increased brain and decreased spinal fluid amyloid (5-10 years), MCI (2-5 years), depressed brain glucose uptake (>5 years), with increased oxidative stress damage (>? years).

Maternal AD history increases brain and spinal fluid markers for MCI/AD development.

FDG-PET scans best single marker for progression into AD.
What to Do?
Mediterranean Diet
Mediterranean Diet and Mild Cognitive Impairment

Nikolaos Scarineas, MD; Yaakov Stern, PhD; Richard Mayeux, MD; Jennifer J. Manly, PhD; Nicole Schupf, PhD; Jose A. Luchsinger, MD

2364 Nondemented

1800 Cognitively normal
184 Missing dietary data
223 With CDR of 0.5
1393 With final finding of cognitively normal

564 With MCI
82 Missing dietary data
482 With final finding of MCI

mean F/U 4.5 +/- 2.7 years
MeDi on 9-point scale
Mediterranean Diet Reduces Risk of Developing MCI

Table 3. Cox Proportional Hazard Ratios for Incidence of Mild Cognitive Impairment for Subjects Who Were Cognitively Normal at the First Evaluation by Mediterranean Diet Score

<table>
<thead>
<tr>
<th>Predictor</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MeDi continuous</td>
<td>0.93 (0.87-1.00)</td>
<td>.06</td>
</tr>
<tr>
<td>MeDi tertile</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>1 [Reference]</td>
<td>NA</td>
</tr>
<tr>
<td>Middle</td>
<td>0.87 (0.66-1.14)</td>
<td>.33</td>
</tr>
<tr>
<td>High</td>
<td>0.73 (0.53-1.00)</td>
<td>.05</td>
</tr>
<tr>
<td>Trend</td>
<td>0.85 (0.73-1.00)</td>
<td>.05</td>
</tr>
<tr>
<td>Adjusted</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MeDi continuous</td>
<td>0.92 (0.85-0.99)</td>
<td>.04</td>
</tr>
<tr>
<td>MeDi tertile</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>1 [Reference]</td>
<td>NA</td>
</tr>
<tr>
<td>Middle</td>
<td>0.83 (0.62-1.12)</td>
<td>.24</td>
</tr>
<tr>
<td>High</td>
<td>0.72 (0.52-1.00)</td>
<td>.05</td>
</tr>
<tr>
<td>Trend</td>
<td>0.85 (0.72-1.00)</td>
<td>.05</td>
</tr>
</tbody>
</table>

Cumulative Probability of Remaining MCI-Free

Arch Neurol. 2009;66(2):216-225
Mediterranean Diet Reduces Risk of Progressing From MCI to Alzheimer’s

Table 4. Cox Proportional Hazard Ratios for Incidence of Alzheimer Disease for Subjects With Mild Cognitive Impairment at the First Evaluation by Mediterranean Diet Score

<table>
<thead>
<tr>
<th>Predictor</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted^a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MeDi continuous</td>
<td>0.95 (0.85-1.07)</td>
<td>.48</td>
</tr>
<tr>
<td>MeDi tertile</td>
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<tr>
<td>Low</td>
<td>1 [Reference]</td>
<td>NA</td>
</tr>
<tr>
<td>Middle</td>
<td>0.62 (0.39-0.98)</td>
<td>.04</td>
</tr>
<tr>
<td>High</td>
<td>0.69 (0.41-1.14)</td>
<td>.15</td>
</tr>
<tr>
<td>Trend</td>
<td>0.82 (0.63-1.07)</td>
<td>.15</td>
</tr>
<tr>
<td>Adjusted^b</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MeDi continuous</td>
<td>0.89 (0.78-1.02)</td>
<td>.09</td>
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<tr>
<td>MeDi tertile</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>1 [Reference]</td>
<td>NA</td>
</tr>
<tr>
<td>Middle</td>
<td>0.55 (0.34-0.90)</td>
<td>.01</td>
</tr>
<tr>
<td>High</td>
<td>0.52 (0.30-0.91)</td>
<td>.02</td>
</tr>
<tr>
<td>Trend</td>
<td>0.71 (0.53-0.95)</td>
<td>.02</td>
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<tr>
<td>Study no.</td>
<td>Study author</td>
<td>Study design (Country of origin)</td>
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<tr>
<td>-----------</td>
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</tr>
<tr>
<td>1</td>
<td>Scarmack et al. (USA)</td>
<td>Prospective cohort (USA)</td>
</tr>
<tr>
<td>2</td>
<td>Larner et al. (USA)</td>
<td>Prospective cohort (France)</td>
</tr>
<tr>
<td>3</td>
<td>Scarmack et al. (USA)</td>
<td>Multicentric longitudinal study (USA)</td>
</tr>
<tr>
<td>4</td>
<td>Gi et al (China)</td>
<td>Prospective cohort (USA)</td>
</tr>
<tr>
<td>5</td>
<td>Mead et al. (USA)</td>
<td>Retrospective single group (Australia)</td>
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<tr>
<td>6</td>
<td>Ying et al. (China)</td>
<td>Data analysis of the NHANES study longitudinal study (USA)</td>
</tr>
<tr>
<td>7</td>
<td>Chen et al. (China)</td>
<td>Longitudinal study (Australia)</td>
</tr>
<tr>
<td>8</td>
<td>Verhage et al. (USA)</td>
<td>Prospective cohort (USA)</td>
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<td>9</td>
<td>Keszyckik et al. (USA)</td>
<td>Prospective cohort (USA)</td>
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<tr>
<td>10</td>
<td>Martin et al. (USA)</td>
<td>Multicentric randomized (USA)</td>
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<tr>
<td>11</td>
<td>Sumit et al. (USA)</td>
<td>Prospective cohort (USA)</td>
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<td>12</td>
<td>Guerin et al. (USA)</td>
<td>Randomized double-blind (USA)</td>
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<tr>
<td>13</td>
<td>Rea et al. (USA)</td>
<td>Prospective cohort (USA)</td>
</tr>
<tr>
<td>14</td>
<td>Tuli et al. (USA)</td>
<td>Prospective cohort (USA)</td>
</tr>
<tr>
<td>15</td>
<td>Venkatesh et al. (USA)</td>
<td>Prospective cohort (USA)</td>
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<tr>
<td>16</td>
<td>Lee et al. (USA)</td>
<td>Randomized controlled trial (USA)</td>
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<tr>
<td>17</td>
<td>Vally et al. (USA)</td>
<td>Randomized controlled trial (USA)</td>
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<td>18</td>
<td>Vally et al. (USA)</td>
<td>Randomized controlled trial (USA)</td>
</tr>
<tr>
<td>19</td>
<td>Vally et al. (USA)</td>
<td>Randomized controlled trial (USA)</td>
</tr>
<tr>
<td>20</td>
<td>Vally et al. (USA)</td>
<td>Randomized controlled trial (USA)</td>
</tr>
</tbody>
</table>
Homocysteine-Lowering by B Vitamins Slows the Rate of Accelerated Brain Atrophy in Mild Cognitive Impairment: A Randomized Controlled Trial
Elevated Plasma Homocysteine Increases Dementia Risk
B-vitamin supplements reduce loss of brain grey matter over 2 years of treatment.
Low B-vitamin levels can directly cause dementia

Is Serum [Hcy] a Toxin or Marker for Decreased Folate (vit B9)

Cumulative incidence of dementia in 816 community-dwelling subjects (mean age 73.6 years) over 5 years, according to quartiles of plasma total homocysteine (tHcy) or serum folate at baseline. Data are for 816 subjects; the number of incident dementia cases was 112. For tHcy from the top to the bottom quartiles, n = 55, 21, 23, and 13 with dementia; for folate from the top to the bottom quartiles, n = 18, 18, 32, and 44 with dementia.

Effect of B vitamin treatment on patients with mild Alzheimer’s disease (AD) in the VITAL trial. In the patients who had a clinical dementia rating (CDR) score of 0.5 at baseline (mild AD), B vitamin treatment (folic acid, vitamins B6 and B12) significantly slowed cognitive decline over the 18-month period of the trial (general estimating equations, $P = 0.017$, unadjusted for multiple comparisons). No significant effect was found in the total trial participants, which included those with moderate as well as mild AD (see Reference 1 MMSE, Mini-Mental State Examination).
What About Exercise?

- Exercise prevents brain atrophy in hippocampus (brain region of memory storage)
- Physical activity reduces risk of developing AD
- These beneficial effects of exercise appear to be mediated by *Brain-Derived Neurotrophic Factor (BDNF)*, a protein that stimulates growth and connectivity of neurons
  - *BDNF* is decreased ~75% in AD hippocampus
  - AD risk is increased by lower serum [BDNF]
  - Vigorous exercise in mice increases *BDNF* gene expression
BDNF and AD

BDNF protein is reduced ~75% in AD hippocampus

Serum [BDNF] predicts AD risk

B. Connor et al. / Molecular Brain Research 49 (1997) 71–81

JAMA Neurol. doi:10.1001/jamaneurol.2013.4781
Published online November 25, 2013.
Daily Exercise Increases BDNF and “New Neurons” in Mouse Hippocampus

BDNF gene expression levels “new neurons” from stem cells

Sed = sedentary    Ex = exercised (treadmill 1hr/day X 7 days)
SH = standard housing    En = enriched environment

R.G. Bechara, Á.M. Kelly / Behavioural Brain Research 245 (2013) 96–100
BRAIN AGING:
Can America Survive the Looming Crisis of Dementia?

• From brain aging we are rapidly approaching unsustainable personal and societal costs
• We are outliving our neurons
• Aging brains fail to make energy
• AD/dementia is a complex syndrome:
  – Heterogenous across individuals + vascular risks
  – No single “cure”
  – Combination of oxidative stress, energy failure
  – Abnormal proteins likely secondary, not primary
Present and Future

**Present**
- Mediterranean diet
- B-vitamin supplements
- Physical activity (increase BDNF in hippocampus)
- *Eliminate obesity+diabetes*

**Future**
- Reverse brain oxidative stress damage
- Restore brain energy metabolism
- Amyloid protein removal strategies don’t work
- Characterize molecular phenotypes
Established June, 2015
501(c)3 non-profit, biomedical research
James P. Bennett, Jr. M.D., Ph.D. President (founder) and Chief Scientific Officer
Focused on neurodegenerative disease discovery and "personalized treatment"
Making Induced Pluripotential Stem Cells (iPSC’s) from WBC’s

Paula Keeney
Making iPSC’s from WBC’s

1. Anticoagulated whole blood sample (<50 ml)
2. Ficoll gradient separation of mononuclear cells
3. Storage (-80°C)/analysis of mononuclear cells
4. Culturing of mononuclear cells for 4-6 weeks to yield pure monocyte cells
5. Electroporation insertion of reprogramming plasmid containing 5 reprogramming genes
6. Culturing for 4-6 weeks to yield pluripotent iPSC’s
7. Harvesting of iPSC clusters for analysis and storage at -80°C
8. Differentiation in culture (2-3 months) of iPSC’s into neural precursor cells (NPC’s)
Induced Stem Cells from individual patients are turned into neurons

test new drugs

give to patient (“personalized medicine”)
activated microglia
amyloid plaques

Brain (2016) 139:1265-81
AD brain microglial “balance” is tipped towards destructive M1 type.
Agents That Reduce Inflammation

- curcumin (in turmeric)
- bupropion (Wellbutrin®)
- apigenin (from fruits)
- non-steroidal anti-inflammatory drugs (NSAID)
- man-made molecules (e.g. colony stimulating factor-1 receptor (CSF1R) antagonists)
My Colleagues

- Norah Algarzae
- David Brohawn
- Kristen Bergquist
- Paula Keeney
- Essie Komla
- Amy Ladd
- Laura O’Brien
- Ann Rice
- Ravi Thomas
- Patricia Trimmer

Our Support

- VCU Parkinson’s Center
- NS390788
- ALS WorldWide
- Alzheimer’s Drug Discovery Foundation
- Va. Biosciences Health Research Council
- Anonymous donors