Cognitive Health: Dawn of the era of treatable Alzheimer’s disease

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“There is nothing that will prevent, reverse, or slow the progress of Alzheimer’s disease.”

“Everyone knows someone who is a cancer survivor; no one knows an Alzheimer’s survivor.”
“Shocking truths” from the research bench

• What is referred to as “Alzheimer’s disease” is actually a protective response to 5 metabolic and toxic insults.

• For many people, “Alzheimer’s disease” is not a disease—it is a programmatic downsizing of the neural plasticity network.

• “AD” is not a mysterious, untreatable brain disease—it is a reversible, metabolic/toxic, usually systemic illness with a relatively large window for treatment.

• With respect to treatment of AD, drugs are the dessert, not the entrée (and salad is the salad).

• There may be 500,000 Americans with “inhalational Alzheimer’s disease” (IAD).

• For optimal responses, monotherapeutics should be replaced by programmatic.
East Meets West
30,000,000

patients in 2012

3rd leading cause (James, 2014)

Pres. Obama and NAPA, 2011
160,000,000 patients in 2050
Cures
Women at the epicenter of the epidemic

- 65% of patients
- 60% of caregivers
- More common than breast cancer
• **PATIENTS** often do not seek medical care because they have been told there is nothing that can be done, and they fear loss of driver’s license, the stigma of a diagnosis, inability to obtain long-term care, and ultimately nursing home placement. Thus they often present very late in the process.

• **PRIMARY CARE PROVIDERS** often do not refer, since they realize that there is no truly effective therapy. Therefore, they typically simply start donepezil (Aricept), often without a firm diagnosis.

• **SPECIALISTS** often put the patients through hours of neuropsychological testing, expensive imaging, lumbar punctures, and then have little or nothing to offer therapeutically.
Where is classical medicine headed?
Alzheimer’s Disease (AD) Therapeutic Landscape

**APPROVED**
- Donepezil (Aricept)
- Rivastigmine (Exelon)
- Galantamine (Razadyne)
- Tacrine (Cognex)
- Memantine (Namenda)

**PHASE 3**
- Solanezumab
- Bapineuzmab
- Alzemed *
- Semagacestat*
- Flurizan*
- Rosiglitazone*
- Phenserine*
- ELND005
- Valproate*
- Antioxidant
- Statins
- Dimebon
- EGCg

**PHASE 2**
- PBT2*
- NIC5-15
- Bryostatin-1
- EHT-0202*
- BMS708163
- ABT089*
- AZD3480*
- Huperzine-A*
- EVP6124
- MEM3454
- AL-108*
- PF04360365
- Nicotinamide
- NP12
- ACC001
- Lithium*
- AN1792*
- NGF
- SB742457
- PRX03140*
- PUFA*
- PF-04447943

**PHASE 1**
- GSK933776*
- MABT5102A
- UB311
- R1450
- V950
- E2012*
- MK0752
- AF102B*
- Talsaclidine
- Begacestat
- PF3084014
- CTS21166
- CHF5074

* Clinical Trial in AD terminated

- ↓ Aβ production
- ↓ Aβ aggregation
- ↑ Aβ clearance
- ↓ Tau aggregation/phosphorylation
- Cholinergic drugs
- Others
“Game of Thrown" (243/244)

- Dimebon x2
- Semagacestat
- Rosiglitazone
- Alzhemed
- Flurizan
- Rember
- Bapineuzumab
- AN-1792
- R.I.P.
Why do neurons degenerate?
A New View of Alzheimer’s Disease

Proliferation

Migration

Integration
Cancer: imbalance in proliferation/survival vs. turnover

**Proliferation**

- Oncogenes

**Migration**

- Tumor Suppressor Genes

**Integration**

- Cancer
Alzheimer’s disease: imbalance in plasticity

Proliferation

Migration

Integration

Synaptic Reorganization

Synaptic Maintenance

Alzheimer’s Disease
Chronic illnesses as signaling imbalances

Osteoporosis:
Osteoblastic < Osteoclastic

Cancer:
Cytoblastic > Cytoclastic

Alzheimer’s:
Synaptoblastic < Synaptoclastic
Synaptic element interdependence

\[ \text{APP + Trophic Factor} \]
\[ \{ \downarrow C_{31}, \beta \text{CTF, sAPP}_\beta, \alpha \text{APP} \]
\[ \uparrow \text{AICD, KA11} \]
\[ \uparrow \text{APP-Fe65} \]
\[ \uparrow \text{APP-Dab} \]
\[ \downarrow \text{Thr668 phos} \]

\[ \text{APP + } \alpha \text{APP} \]
\[ \{ \uparrow C_{31} \]
\[ \downarrow \text{APP-Fe65} \]
\[ \downarrow \text{APP-Dab} \]
\[ \uparrow \text{sAPP}_\beta \]
\[ \downarrow \text{sAPP}_\alpha \]
\[ \uparrow \text{Thr668 phos} \]

\[ \text{Trophic Factors} \]
\[ \text{Anti-trophic Factors} \]
Trophic, Anti-AD

Anti-trophic, Pro-AD

sAPPα

CTFα

Neurite Retraction

Aβ plaques

Mitochondria

TAU Neurofibrillary Tangle

sAPPβ

Aβ

J_{casp}

C_{31}
A roof with 36 holes...
67 y.o. woman with 2-yr history of progressive cognitive decline

- Mother died with dementia, onset age 62.
- Unable to navigate on freeway.
- Could not remember what she had read.
- Unable to prepare reports for work.
- Unable to recall even 4-digit numbers.
- Retinal scan positive for amyloid (greater than London pt.).
- Treated with MEND (metabolic enhancement for neurodegeneration).
70 y.o. man with 12-yr history of accelerating memory loss

- ApoE4 positive (heterozygote)
- FDG-PET scan typical of AD (temporoparietal reduced Glu)
- Progressive loss: CVLT from 84%ile to 1%ile
- Unable to remember lock combination, faces, schedule
- Difficulty at work, and with numbers; Dx—early AD
- Improvement at 6 months: co-workers, schedule, faces, nos.
- Wife notes accelerated decline completely stopped.
Patient two

FDG-PET scan indicated a pattern typical of Alzheimer’s disease
<table>
<thead>
<tr>
<th>Test</th>
<th>2013</th>
<th>2015 (MEND 2 yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVLT-II B</td>
<td>&lt;5%ile</td>
<td>&gt;70%ile (3SD)</td>
</tr>
<tr>
<td>Total Recog Hits</td>
<td>&lt;1%ile</td>
<td>&gt;45%ile</td>
</tr>
<tr>
<td>CVLT-II</td>
<td>&lt;60%ile</td>
<td>&gt;90%ile</td>
</tr>
<tr>
<td>Auditory delayed memory</td>
<td>&lt;20%ile</td>
<td>&gt;75%ile</td>
</tr>
<tr>
<td>Reverse digit span</td>
<td>&lt;25%ile</td>
<td>&gt;70%ile</td>
</tr>
<tr>
<td>Processing speed*</td>
<td>&lt;95%ile</td>
<td>&gt;95%ile</td>
</tr>
</tbody>
</table>
55 y.o. attorney with 4-yr history of severe memory loss

- Left stove on multiple times when leaving home.
- Recorded conversations since she could not remember.
- Carried iPad to note everything.
- Unable to practice or to learn new information.
- Lost mid-sentence; had a talk with her children.
- Iterative Rx returned her to normal over 10 mos.
- Back at work, learning new areas of law, and learned Spanish.
- iPad optional
Patient three
<table>
<thead>
<tr>
<th>Association</th>
<th>Yes/No</th>
</tr>
</thead>
<tbody>
<tr>
<td>ApoE4? Heterozygote? Homozygote?</td>
<td>Yes (4/3)</td>
</tr>
<tr>
<td>Homocysteine &gt;7?</td>
<td>Yes (15.1)</td>
</tr>
<tr>
<td>Vitamin B12 &lt; 500?</td>
<td>Yes (328)</td>
</tr>
<tr>
<td>CRP &gt; 1.0?</td>
<td>Yes (9.9)</td>
</tr>
<tr>
<td>A/G ratio &lt; 1.8?</td>
<td>Yes (1.6)</td>
</tr>
<tr>
<td>HgbA1c &gt; 5.6? Fasting insulin &gt; 6 ulU?</td>
<td>HgbA1c 5.5 Insulin 32</td>
</tr>
<tr>
<td>Simple CHO in diet?</td>
<td>Yes</td>
</tr>
<tr>
<td>FBS &gt; 90?</td>
<td>Yes (96)</td>
</tr>
<tr>
<td>Thyroid: TSH &gt; 2.0?</td>
<td>Yes (2.21)</td>
</tr>
<tr>
<td>Free T3 &lt; 3.2? RT3 &gt; 20?</td>
<td>Yes (2.4)</td>
</tr>
<tr>
<td>Free T4 &lt; 1.3?</td>
<td>Yes (0.8)</td>
</tr>
<tr>
<td>Sleep apnea/hypopnea?</td>
<td>No</td>
</tr>
<tr>
<td>Low androgen? Total T &lt; 500? Free T &lt; 6.5?</td>
<td>Yes (264) Yes (41, 4.1)</td>
</tr>
<tr>
<td>Low pregnenolone? &lt;20?</td>
<td>Pd.</td>
</tr>
<tr>
<td>Vitamin D &lt; 30?</td>
<td>Yes (21)</td>
</tr>
<tr>
<td>History of head trauma? LOC?</td>
<td>No</td>
</tr>
<tr>
<td>Diabetes?</td>
<td>No, but insulin resistant</td>
</tr>
<tr>
<td>Neuroactive medications? Which?</td>
<td>No</td>
</tr>
<tr>
<td>History of illicit drug use?</td>
<td>No</td>
</tr>
<tr>
<td>Metabolic syndrome?</td>
<td>Yes (TG, BP, glu, insulin)</td>
</tr>
<tr>
<td>Cholesterol &gt; 225? &lt; 150?</td>
<td>Yes</td>
</tr>
<tr>
<td>Abnormal HDL:LDL ratio?</td>
<td>Yes</td>
</tr>
<tr>
<td>Post-menopausal?</td>
<td>NA</td>
</tr>
</tbody>
</table>
Metabolism and Cognition Go Hand in Hand

<table>
<thead>
<tr>
<th>66M ApoE4/3</th>
<th>2014</th>
<th>2015 (MEND 10 mos.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting insulin</td>
<td>32</td>
<td>8</td>
</tr>
<tr>
<td>Hs-CRP</td>
<td>9.9</td>
<td>3</td>
</tr>
<tr>
<td>Homocysteine</td>
<td>15</td>
<td>8</td>
</tr>
<tr>
<td>Vitamin D3</td>
<td>21</td>
<td>40</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Struggling</td>
<td>Working full-time</td>
</tr>
<tr>
<td>MRI hippocampal volume</td>
<td>&lt;25%ile</td>
<td>&gt;70%ile</td>
</tr>
</tbody>
</table>
Alzheimer’s disease: not one illness

• Presymptomatic vs. SCI vs. MCI vs. AD.

• Several different metabolic syndromes are called “Alzheimer’s disease:”

• Type 1: Inflammatory (“Hot”)

• Type 2: Atrophic (“Cold”)

• (Type 1.5: Glycotoxic (“Sweet” combines 1 and 2))

• Type 3: Toxic (“Vile”)—a fundamentally different problem.

• Type 4: Vascular (“Pale”)

• Type 5: Traumatic (“Dazed”)

The Chimp That Killed the Rhino
Evolution, Shortgevity, Alzheimer’s, and the God Gene
The Chimp That Killed the Rhino
Evolution, Shortgevity, Alzheimer’s, and the God Gene

- 7 million years ago
- 6 million years ago
- 5 million years ago
- 4 million years ago
- 3 million years ago
- 2 million years ago
- 1 million years ago

ApoE3

ApoE4

ApoE2

220,000 years ago

80,000 years ago
ApoE4 Domain Interaction
Effect of Position 112 on Structure

ApoE4
- Arg-112
- NH₂-domain
- CO₂H-domain
- Arg-61
- Glu-255

ApoE3
- Cys-112
- NH₂-domain
- CO₂H-domain
- Glu-255
- Arg-61
ApoE4—new mechanism
ApoE4-promoter interactions by ChIP-Seq

Glucose homeostasis & diabetes

Microtubule disassembly

Synapse dysfunction

Inflammation

Aging & SirT

Neurotrophins and cell death
## Improvement on MEND

<table>
<thead>
<tr>
<th>55F ApoE4/4</th>
<th>2015</th>
<th>2016 (MEND 5 mos.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurocognitive index</td>
<td>&lt;20%ile</td>
<td>&gt;70%ile</td>
</tr>
<tr>
<td>Composite memory</td>
<td>&lt;5%ile</td>
<td>&gt;50%ile</td>
</tr>
<tr>
<td>Verbal memory</td>
<td>&lt;5%ile</td>
<td>&gt;&gt;50%ile</td>
</tr>
<tr>
<td>Processing speed</td>
<td>&lt;40%ile</td>
<td>&gt;&gt;50%ile</td>
</tr>
<tr>
<td>Executive function</td>
<td>&lt;20%ile</td>
<td>&gt;50%ile</td>
</tr>
<tr>
<td>Cognitive flexibility</td>
<td>&lt;20%ile</td>
<td>&gt;50%ile</td>
</tr>
</tbody>
</table>
“Never doubt the ability of a small group of committed individuals to change the world. Indeed, it is the only thing that ever has.”

--- Margaret Mead