Reversal of cognitive decline in Alzheimer’s disease, MCI, and SCI

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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.”
70 y.o. man with 12-yr history of accelerating memory loss

• ApoE4 positive (heterozygote)
• FDG-PET scan typical of AD (temporoparietal reduced Glu)
• Neuropsych testing 2003, 2007, 2013
• Progressive loss: CVLT from 84%ile to 3%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
### Proof of Improvement on ReCODE Protocol

<table>
<thead>
<tr>
<th></th>
<th>2013</th>
<th>2015 (ReCODE 2 yr)</th>
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<tbody>
<tr>
<td><strong>71 yo E4/3</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVLT-II B</td>
<td>3%ile</td>
<td>84%ile (3SD)</td>
</tr>
<tr>
<td>Total Recog Hits</td>
<td>&lt;1%ile</td>
<td>50%ile</td>
</tr>
<tr>
<td>CVLT-II</td>
<td>54%ile</td>
<td>96%ile</td>
</tr>
<tr>
<td>Auditory delayed memory</td>
<td>13%ile</td>
<td>79%ile</td>
</tr>
<tr>
<td>Reverse digit span</td>
<td>24%ile</td>
<td>74%ile</td>
</tr>
<tr>
<td>Processing speed*</td>
<td>93%ile</td>
<td>98%ile</td>
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Alzheimer’s: A Sad State of Affairs

• **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.
20\textsuperscript{th} century evaluation of cognitive decline

- “MRI of the brain and blood for CBC, metabolic panel, thyroids, B12.”

- “I asked the patient and his wife to keep an eye on his disabilities to manage money, medications and transportation.”

- “I prescribed donepezil 5mg once per day.”

- No genetics (no ApoE status, TREM2, CD33, NALP1, PS1, etc.), no hs-CRP or IL-6 or anything re inflammation, no homocysteine, no fasting insulin, no hormonal status, nothing re toxin status, nothing re innate immune system status, nothing on gut health, no microbiome, no blood-brain barrier analysis, no MRI volumetrics, etc., etc., etc…

- Prescribing donepezil without diagnosis.

- BMI was 33—nothing even noted, no plan to address this.

- Pre-diabetes, a key risk factor—nothing to address this.
So how does one go about developing an effective treatment for an incurable disease?
Shrink: 30 years of research in 20 minutes
The big problem with neurodegenerative disease

Healthy Brain  Advanced Alzheimer’s

PET Scans:

Normal  Alzheimer's

Alzheimer’s Disease Histopathology

Crump Institute for Biological Imaging
Chronic illnesses as signaling imbalances

Osteoporosis:
- Osteoblastic
- Cytoblastic

Cancer:
- Synaptoblastic
- Cytoclastic

Alzheimer’s:
- Synaptoclastic
Synaptic element interdependence

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

- **APP + $A_{\beta}$**
  - $\uparrow C_{31}$
  - $\downarrow \text{APP-Fe65}$
  - $\downarrow \text{APP-Dab}$
  - $\uparrow \text{sAPP}_{\beta}$
  - $\downarrow \text{sAPP}_{\alpha}$
  - $\uparrow \text{Thr668 phos}$

**Trophic Factors**

**Anti-trophic Factors**
Trophic, Anti-AD

Anti-trophic, Pro-AD

sAPP$_{\alpha}$

CTF$_{\alpha}$

sAPP$_{\beta}$

A$\beta$

J$_{\text{casp}}$

C$_{31}$

Neurite Retraction

A$\beta$ plaques

TAU Neurofibrillary Tangle

Mitochondria
A roof with 36 holes...
The perfect Alzheimer’s drug would:

Reduce APP β-cleavage, reduce γ-cleavage, increase α-cleavage, reduce caspase-6 cleavage, reduce caspase-3 cleavage, prevent oligomerization, increase neprilysin, increase IDE, increase microglial clearance of Aβ, increase autophagy, increase BDNF, increase NGF, increase netrin-1, increase ADNP, reduce homocysteine, increase PP2A activity, reduce phospho-tau, increase phagocytosis index, increase insulin sensitivity, improve axoplasmic transport, enhance mitochondrial function and biogenesis, reduce oxidative damage and optimize ROS production, enhance cholinergic neurotransmission, increase synaptoblastic signaling, reduce synaptoclastic signaling, improve LTP, optimize estradiol, progesterone, E2:P ratio, free T3, free T4, TSH, pregnenolone, testosterone, cortisol, DHEA, and insulin, reduce inflammation, increase resolvinbs, enhance detoxification, improve vascularization, increase cAMP, increase glutathione, provide synaptic components, optimize all metals, increase GABA, increase vitamin D signaling, increase SirT1, reduce NFkB, increase telomere length, reduce glial scarring, enhance repair, etc.
The 21\textsuperscript{st}-century physician
Research findings → Clinical implications
Research: “Alzheimer’s” is a protective response to 3 major metabolic and toxic perturbations

- Inflammation (e.g., NFκB activation), be it infectious (e.g., from biofilms) or sterile (e.g., AGE-modified proteins).
- The withdrawal of trophic support (e.g., nerve growth factor, estradiol, testosterone, vitamin D, etc.).
- Exposure to toxins, such as divalent metals (e.g., mercury).
- These form the basis for types 1, 2, and 3 AD/MCI/SCI, respectively.
- Combinations of these types are common, for example glycotoxic (type 1.5), in which the advanced glycation endproducts (AGEs) cause inflammation and the insulin resistance leads to trophic withdrawal signaling.
- Other inputs such as sleep apnea, vascular insufficiency (type 4), and trauma (type 5) trigger amyloid via these same 3 major mechanisms.
Clinical: Identify subtypes, all contributors

- Do not reduce the amyloid until you remove the cause(s) of the amyloid response. This requires a fundamental change of thinking about AD.

- Most symptomatic individuals manifest 10-25 contributors.

- From what is the brain protecting itself?


- Toxins, such as divalent metals (e.g., mercury) or biotoxins?
Research: APP is a mediator of plasticity balance
Clinical: AD is associated with APP imbalanced signaling

- Synaptoblastic: sAPP$_\alpha$, $\alpha$CTF.
- Synaptoclastic: sAPP$_\beta$, A$\beta$, Jcasp, C31.
- Probability of AD $\alpha \Sigma$(synaptoclastic signals) / $\Sigma$(synaptoblastic signals).
- Therefore, reduce all synaptoclastic signals, and increase all synaptoblastic signals.
- Major synaptoclastic signals: NF$\kappa$B and other inflammatory mediators, homocysteine, PAMPs/DAMPs, trophic withdrawal, toxin exposure, leaky blood-brain barrier, lack of nutrients or structural components.
- Major synaptoblastic signals: resolvins, anti-inflammatory mediators (e.g., omega-3), neurotrophins (BDNF, NGF, NT-3, GDNF, etc.), hormones, vitamin D, toxin reduction, nutrients.
Research: APP is a molecular switch, with prionic loop amplification

- The amyloid actually begets more of itself, through interaction with APP—thus it is prionic.
- Therefore, as you start to go down the “wrong” side of APP, it’s like a snowball rolling downhill—it amplifies.
- The same goes for the good (synaptoblastic) side.
Clinical: Threshold effect

- Keep treating the identified abnormalities until improvement begins. Remember that you are addressing years of pathophysiology, so do not expect improvement for 3-6 months.

- The first positive sign is that progression stops.

- Even the most modest improvement is an excellent sign of continued improvement to come.

- Continued progression means that something has been missed—cognitive decline does not occur without reason.

- The most common reasons for failure are lack of compliance and ignoring key contributors.

- As the biochemistry goes, so goes the cognition—keep optimizing!
Research: Apolipoprotein E ε4 allele (ApoE4) is the major risk factor for AD
The Chimp That Killed the Rhino
Evolution, Shortgevity, Alzheimer’s, and the God Gene
The Chimp That Killed the Rhino
Evolution, Shortevity, 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

ApoE4
ApoE3
ApoE2

- 220,000 years ago
- 80,000 years ago
ApoE4—new mechanism as transcriptional repressor
ApoE4-promoter interactions by ChIP-Seq

- Glucose homeostasis & diabetes
- Microtubule disassembly
- Synapse dysfunction
- Inflammation
- Ageing & SirT
- Neurotrophins and cell death
Clinical: Evaluate ApoE4 status

- 0 copies (e.g., ApoE3/3 or 2/3) → 9% lifetime risk.
- 1 copy ApoE4 (heterozygous) → 30% lifetime risk (75 million Americans).
- 2 copies (homozygous) → 50-90% lifetime risk (7 million Americans).
- Increases inflammation, thus increases risk for AD but reduces risk for parasite-associated dementia, and also may reduce risk for type 3 AD.
- Affects Rx regarding diet, fasting time, fat absorption, lipid profile effects, treatment of inflammation, etc.
- Critical to identify early and prevent or reverse cognitive decline of AD.
Research: There are *many* contributors to the APP signaling balance

- Initially identified 36; likely >50, <100.
- Example: estradiol binds ER, increases $\alpha$-secretase, thus increasing sAPP$\alpha$, thus increasing synaptoblastic signaling.
- NF$\kappa$B increases $\beta$-secretase and $\gamma$-secretase, thus increasing sAPP$\beta$ and A$\beta$, thus increasing synaptoclastic signaling.
- A$\beta$ is produced as an endogenous antimicrobial.
- Metals such as iron increase translation of APP (iron response element in APP mRNA).
- IL-1 increases translation of APP via mRNA element.
- Diet, stress, sleep, exercise all affect the APP signaling balance.
- The many monoetiological theories of AD fail to explain the pathophysiology and therapeutic responses.
Clinical: Programmatics, not monotherapeutics

- Drugs are the dessert, not the entrée.
- Multi-variable trials, with programs and drug candidates, should be considered.
- After determining the contribution from each subtype, address all contributors: inflammatory, infectious, insulin resistance, trophic loss, hormone reduction, nutrient support, toxin exposure, etc.
- Personalized programs, not one size fits all.
Treatment: playing chess with the devil
The ReCODE Protocol

• We have mapped the many molecular mechanisms of cognitive decline and AD onto a network evaluation, subtype determination, and personalized treatment protocol.

• First determine all potential contributors and subtype(s); this allows you to prioritize the therapeutic program.

• No one intervention is curative. Not a silver bullet—silver buckshot.

• Continue to optimize.

• Improvement typically requires 3-6 months.

• Compliance is important; health coaching helpful.
Why Memory Loss? Files and ReCODE
Basic concepts of the protocol

• Identify all contributors to the imbalanced plasticity network (from 100, e.g., copper:zinc ratio > 1.3, RBC Mg < 5.2, hs-CRP > 1.0, homocysteine > 7, fasting insulin > 4.5, C4a > 2800, free T3 < 3.2, TSH > 2.0, Cyrex Array 2 +, etc., etc., etc.). From these, we use a software algorithm to construct a “why memory loss” table weighted for each type.

• Determine the degree of contribution to types 1 (inflammatory (“hot”)), 1.5 (glycotoxic (“sweet”)), 2 (atrophic (“cold”)), 3 (toxic (“vile”)), 4 (vascular (“pale”)), or 5 (traumatic (“dazed”)).

• For each abnormality identified, we want to go beyond simply normalizing the test, we want to optimize the value.

• We want to address as many of the abnormalities as possible, not just one, and the earlier in the process, the greater chance for success.

• For each treatment we include, the goal is to design the treatment so that it will be as physiological and upstream as possible.

• The program is personalized and targeted at mechanisms and subtype, and includes diet (Ketoflex 12/3 with ketone meter), exercise (aerobic and strength), sleep (and R/O hypopnea), stress reduction, BHRT as needed, synaptic support (neuroceuticals), targeted herbs, “meditation on steroids,” hygiene, detox, CIRS Rx if indicated, pharma as appropriate, health coaching.

• The bottom line: Alzheimer’s disease, and other forms of cognitive decline, do not occur for no reason—identify the contributors and address each one.
66 yo man with “senior moments”

- Family history+ in both parents.
- ApoE3/4, amyloid PET markedly positive, FDG-PET typical for AD, hippocampal volume reduced, neuropsych testing MCI.
- Fasting insulin 32, HgbA1c 5.5, FBS 96.
- Homocysteine 15.1.
- Vitamin D 21.
- Testosterone 264, free T3 2.4, TSH 2.21.
- Responded metabolically, cognitively, and volumetrically to ReCODE. Neurologist said he is now “normal.”
### Metabolism and Cognition Go Hand in Hand

<table>
<thead>
<tr>
<th>66M ApoE4/3</th>
<th>2014</th>
<th>2015 (Rx 10 mos.)</th>
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<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>17%ile</td>
<td>75%ile</td>
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Cognitive decline associated with Alzheimer’s disease can now be reversed, and improvement sustained, using a personalized programmatic approach that is targeted to the underlying pathophysiology.
Clearing the fog of Alzheimer’s disease