First Reversals of Cognitive Decline in Alzheimer’s Disease and its Precursors, 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.”
30,000,000

patients in 2012


160,000,000

patients in 2050
Women at the epicenter of the epidemic

- 65% of patients
- 60% of caregivers
- More common than breast cancer

0 Cures
Alzheimer’s Disease (AD) Therapeutic Landscape

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

- Bapineuzam
- Solanezumab
- Valproate
- Alzemed •
- Semagacestat•
- Flurizan•
- Rosiglitazone•
- Phenserine•
- EGCg

PHASE 3
- Solanezumab
- Bapineuzam
- Valproate
- Alzemed •
- Semagacestat•
- Flurizan•
- Rosiglitazone•
- Phenserine•
- EGCg

PHASE 2
- PBT2+
- AL-105+
- N15-15
- Bryostatin-1
- Nicotinamide
- EHT-0202+
- NP12
- ACC001
- SB742457
- PRX03140
- PUFA
- PF-04447943
- PUFA

PHASE 1
- GSK933776
- MA50102A
- UB311
- R1450
- V950
- E2012
- MK0752
- CHF5074
- CTS211

- Clinical Trial in AD terminated

“Game of Throwns” (243/244)

R.I.P. Dimebon x2
R.I.P. Semagacestat
R.I.P. Rosiglitazone
R.I.P. Alzhemed
R.I.P. Flurizan
R.I.P. Rember
R.I.P. Sapineuzumab

AN-1792
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.

20th 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.
Classical medicine: breaking through to AD cure?

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 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**

<table>
<thead>
<tr>
<th>Age/E4/E3</th>
<th>2013</th>
<th>2015 (MEND 2 yr)</th>
</tr>
</thead>
<tbody>
<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>
</tr>
</tbody>
</table>

**Metabolism and Cognition Go Hand in Hand**

<table>
<thead>
<tr>
<th>Age/E4/E3</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>17%ile</td>
<td>75%ile</td>
</tr>
</tbody>
</table>
## Improvement on ReCODE

<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>16%ile</td>
<td>73%ile</td>
</tr>
<tr>
<td>Composite memory</td>
<td>1%ile</td>
<td>61%ile</td>
</tr>
<tr>
<td>Verbal memory</td>
<td>3%ile</td>
<td>93%ile</td>
</tr>
<tr>
<td>Processing speed</td>
<td>37%ile</td>
<td>81%ile</td>
</tr>
<tr>
<td>Executive function</td>
<td>14%ile</td>
<td>58%ile</td>
</tr>
<tr>
<td>Cognitive flexibility</td>
<td>16%ile</td>
<td>61%ile</td>
</tr>
</tbody>
</table>

## Programmatic, not “pill-osophy” Algorithm and ReCODE

<table>
<thead>
<tr>
<th>Annotation</th>
<th>Key/No</th>
</tr>
</thead>
<tbody>
<tr>
<td>ApoE4 status?</td>
<td>Yes (4/3)</td>
</tr>
<tr>
<td>Neurocognitive test results</td>
<td>Yes (2/2)</td>
</tr>
<tr>
<td>Resting state fMRI</td>
<td>Yes (4/3)</td>
</tr>
<tr>
<td>PBB &gt; 700</td>
<td>Yes (4/3)</td>
</tr>
<tr>
<td>MRS &lt; 3.5</td>
<td>Yes (2/2)</td>
</tr>
<tr>
<td>Rest</td>
<td>No</td>
</tr>
<tr>
<td>Dopamine transporter scan</td>
<td>Yes (2/2)</td>
</tr>
<tr>
<td>Cerebral glucose metabolism</td>
<td>Yes (2/2)</td>
</tr>
<tr>
<td>Cerebral flow</td>
<td>Yes (2/2)</td>
</tr>
<tr>
<td>History of alcohol use/UD?</td>
<td>No</td>
</tr>
<tr>
<td>Diabetes?</td>
<td>No, not treated</td>
</tr>
<tr>
<td>Nonprescription medication use?</td>
<td>Yes (2/2)</td>
</tr>
<tr>
<td>Neurocognitive decline</td>
<td>Yes (2/2)</td>
</tr>
<tr>
<td>Metabolic syndrome?</td>
<td>Yes (2/2)</td>
</tr>
<tr>
<td>HDL cholesterol &gt; 150 mg/dL</td>
<td>Yes (2/2)</td>
</tr>
<tr>
<td>Albumin &gt; 3.5 g/dL</td>
<td>Yes (2/2)</td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>Yes (2/2)</td>
</tr>
</tbody>
</table>

1/12/2017
So how does one go about developing an effective treatment for an incurable disease?  
*2 fundamental approaches...*  

Canonical Alzheimer’s disease  

ApoE4 → ? → AD  
(p-τ, Aβ, etc.)
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

80,000 years ago

220,000 years ago

4 million years ago

5 million years ago

3 million years ago

2 million years ago

1 million years ago

The Chimp That Killed the Rhino
Evolution, Shortevity, Alzheimer’s, and the God Gene
ApoE4—new mechanism


ApoE4-promoter interactions by ChIP-Seq

Organisms produce amyloid in response to 3 major metabolic and toxic perturbations

- Inflammation (e.g., NFkB 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, trauma, and vascular insufficiency trigger amyloid via these same 3 major causes.


Chronic illnesses as signaling imbalances

Osteoporosis:
- Osteoblastic
- Cytoblastic

Cancer:

Alzheimer’s:
- Synaptoblastic
- Synaptoclastic


Synaptic element interdependence

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 resolvins, 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 21st-century physician

- We have mapped the many molecular mechanisms of cognitive decline and AD onto a treatment protocol.
- These include dozens of interventions, beginning with DESS, hormonal optimization, nutrients, targeted herbs, brain stimulation, drugs, etc.
- No one intervention closes all 36 holes.
- Approach: pull out all of the stops.

The ReCODE Protocol
ReCODE program

- Inflammation: resolution (resolvins), inhibition, removal of source(s).
- Infections (chronic): Borrelia, other tick-borne, chronic viruses, Stachybotrys, etc..
- Atrophic: optimization of hormones, homocysteine, methylation, trophic support, antioxidants, GSH, et al.
- Toxins: metals including Cu:Zn ratio, Hg; mycotoxins.
- Metabolism including glycotoxicity (type 1.5).
- Regeneration, protection.

Central concepts

- “Alzheimer’s disease” is a pathologist’s diagnosis. This term should not be followed by a period any more than fever should be—Alzheimer’s disease due to what?
- What is referred to as “Alzheimer’s disease” is actually a protective response to 3 major metabolic and toxic insults: inflammation/infection, trophic withdrawal, and toxin exposure.
- Evaluation of patients with cognitive decline reveals 5 major types (and combinations of these types): type 1 (inflammatory (“hot”)), 1.5 (glycotoxic (“sweet”)), 2 (atrophic (“cold”)), 3 (toxic (“vile”)), 4 (vascular (“pale”)), and 5 (traumatic (“dazed”)).
- There are approximately 100 biochemical, genetic, functional, and historical parameters that characterize each patient or person at risk.
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.

Evaluation Step 1: Determine Subtype(s)

- 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")
### Characteristics of type 3 AD

- Age at symptom onset < 65.
- ApoE4-negative (usually).
- Negative family history (or only older).
- Low triglycerides and/or zinc.
- HPA dysfunction.
- Depression.
- Problems with math or organization or word finding.
- Exposure to toxins (mercury, mycotoxins, CIRS-related such as Lyme, MARCoNS, surgical implants, others).
- Precipitation or exacerbation by stress.
- “Atypical Alzheimer’s,” often with frontal effects and imaging.

### Characteristics of type 3 AD (cont’d)

- High C4a (>2800), TGF-beta-1 (>2380); low MSH (<35).
- HLA-DR/DQ with “dreaded” multiple biotoxin sensitive or pathogen-specific (4-3-53, 11-3-52B, 12-3-52B, 14-5-52B).
- MARCoNS (multiple-antibiotic resistant coagulase-negative Staphylococcus, deep nasopharyngeal culture)—biofilm assessment.
- Visual contrast sensitivity abnormalities.
- Surprisingly, most do NOT have allergic symptoms.
- Most do not fulfill criteria for CIRS, yet have laboratory values compatible with CIRS.
- Potential relationship to Lewy body disease.
- Most difficult type of AD to treat successfully.
50 yo woman with depression post-hysterectomy

• Over the ensuing 4 years, developed word-finding difficulty, disorientation, difficulty following recipes, difficulty driving.

• Declined markedly with stress, sleep deprivation, and viral illness.

• Neuropsych: poor semantic fluency, paucity of speech, confabulation; frontal, temporal, and parietal deficits.

• FDG-PET: temporal and parietal > frontal reduced glucose utilization, compatible with Alzheimer’s disease.

• Seen at university dementia center, started on antidepressant and donepezil.

• ApoE3/3, negative family history, hs-CRP 0.2, C4a 5547, TGF-β1 7037, VCS failed, anti-Lyme negative, anti-thyroglobulin antibodies 1:2000.

• Treated with MEND, intranasal VIP. Improvements in memory, interaction, following directions, MoCA.

• Most difficult type of AD to treat successfully.

HLA-DR/DQ haplotypes in type 3 AD

<table>
<thead>
<tr>
<th>Age at symptom onset (years)</th>
<th>Major symptoms</th>
<th>HLA-DR/DQ Human Leucocyte Antigen type</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>Dyscalculia, executive</td>
<td>10-3-52B 10-5 (low MSH)</td>
<td>ApoE3/3</td>
</tr>
<tr>
<td>54</td>
<td>Executive, visual</td>
<td>12-3-52B 7-2-53</td>
<td>ApoE3/3</td>
</tr>
<tr>
<td>72</td>
<td>Executive, dyscalculia</td>
<td>15-6-51 * (Lyme)</td>
<td>ApoE3/3</td>
</tr>
<tr>
<td>65</td>
<td>Spatial &gt; verbal memory, attention, irritability, depression</td>
<td>11-3-52B * 13-6-52B *</td>
<td>ApoE3/3</td>
</tr>
<tr>
<td>54</td>
<td>Executive, vissuospatial, memory, depression</td>
<td>17-2-52A * 1-5 (low MSH)</td>
<td>ApoE4/4</td>
</tr>
<tr>
<td>59</td>
<td>Aphasia, executive, dyscalculia, depression</td>
<td>12-3-52B ** 15-6-51 * (Lyme)</td>
<td>ApoE2/3</td>
</tr>
<tr>
<td>59</td>
<td>Headache, executive</td>
<td>13-6-52C *</td>
<td>ApoE ND</td>
</tr>
<tr>
<td>66</td>
<td>Headache, executive, memory</td>
<td>13-6-52C *</td>
<td>ApoE ND</td>
</tr>
</tbody>
</table>

*Pathogen-specific HLA-DR/DQ-related sensitivity (mold or Lyme).
**Multiple-biotoxin-sensitive HLA-DR/DQ association.
### Characteristics of type 1 AD

- Inflammatory/infectious.
- Increase in hs-CRP and/or other inflammatory markers (e.g., increases in IL-6, IL-8, TNFα, etc.)
- Reduction in A/G ratio.
- Increase in M1/M2 ratio; reduction in MFI.
- ApoE4 is important risk factor.
- Presentation is typically amnestic.
- Hippocampal atrophy is common.
- Seek cause(s) of inflammation (e.g., gut leak, AGEs, diet, poor oral hygiene, etc.)

### Characteristics of type 2 AD

- Atrophic (“cold”).
- Patients tend to be older than type 1.
- Typically amnestic presentation; patients often protest that nothing is wrong.
- Reductions in trophic support (e.g., estradiol, progesterone, testosterone, vitamin D, pregnenolone, thyroid, NGF, BDNF).
- ApoE4 is risk factor.
- Rapid reductions in support are most concerning (cf. oophorectomy at <41 without HRT), c/w depR mismatch.
- Hippocampal atrophy is common.
- Optimizing support may be complicated by receptor response, HRT controversy, trophic factor delivery (intranasal vs. peptides vs. indirect, etc.).
Characteristics of type 1.5 AD

- Glycotoxic (“sweet”).
- Inflammatory part from AGEs (via RAGE, glyoxals, etc.) and related.
- Atrophic part from insulin resistance (e.g., IRS1 S/T phos.).
- Goetzl noted insulin resistance in 100% of the neural exosomes from AD patients (measured via IRS1).
- ApoE4 is an important risk factor.
- Amnestic presentation is common.
- Hippocampal atrophy is common.
- Paradox of insulin sensitization and trophic requirement.

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 MEND. Neurologist said he is now “normal.”
Why Memory Loss? Files and ReCODE

**EVALUATION: preliminary considerations**

- Exclude non-AD pathophysiology? Or consider the lack of successful Rx for FTD, LBD, PSP, and other neurodegenerative conditions?
- Vascular dementia? Mixed?
- CTE? Note combination of depression, aggression, and dementia.
- Frontotemporal lobar degeneration? Behavioral symptoms? Primary progressive aphasia?
- Less common: progressive supranuclear paralysis (PSP), multi-system atrophy (MSA), corticobasal degeneration (CBD), etc.
- Primarily amnestic or cortical? Aphasia, dyscalculia, visual agnosia, prosopagnosia?
- Executive dysfunction?
- Depression?
# EVALUATION: documentation

- MRI with volumetrics
- FDG-PET scan
- Amyloid PET and/or Tau PET
- Quantitative neuropsychological tests (standard vs. online)
- CSF? (reduced Aβ42, increased tau and p-tau)
- Genetics—genome vs. exome vs. SNPs—especially ApoE, PS1, PS2, APP, NALP1 (innate), CR1 (innate), CD33 (clearance), TREM2 (inflammation), VDR (NHR), klotho (anti-AD), MTHFR (methylation) (SNPs AD)
- Serum tests

# EVALUATION: inflammation

- hs-CRP
- IL-6
- TNF-α
- A/G ratio
- Infectious? HSV-1, P. gingivalis, other oral bacteria, Borrelia, other spirochetes and tick-borne pathogens, fungi (C. glabrata et al.)
- Many others optional
- Genetics—especially ApoE4, NALP1 (innate), CR1 (innate), TREM2 (inflammation)
**EVALUATION: glucose, insulin resistance**

- Fasting insulin
- Fasting glucose
- Hemoglobin A1c
- Neural exosome IRS1 phosphorylation ratio
- History of pre-diabetes or diabetes?
- Simple carbohydrates in diet? Carb craving?
- Stress? Nighttime eating? Cushingoid?

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**EVALUATION: one-carbon metabolism**

- Homocysteine and PP2A PTM (multiple mechanisms, e.g., ER stress, tau phosphorylation, excitotoxicity)
  - Protein phosphatase 2A is the major enzyme that dephosphorylates phospho-tau. It consists of 3 subunits, A, B, and C.
  - Homocysteine causes a modification in the catalytic subunit (C) to reduce binding to the regulatory subunit (B).
  - For comparison, ApoE4 also reduces PP2A activity but does so at the transcriptional level (R. Rao et al.).
- Vitamin B12 (200-900??)
- Methylmalonic acid (variability)
- Folate
- Pyridoxine
- Genetics—especially MTHFR (677, 1298, etc.), MTRR, BHMT (betaine homocysteine methyl transferase), CBS (cystathionine beta synthase)
EVALUATION: hormones

- Thyroid: basal body temperature, Thyroflex, fT3, fT4, rT3, fT3:rT3 ratio, TSH.
- Estradiol, progesterone, E2:P ratio, testosterone (total and free). Serum vs. salivary vs. urine. Blood spot? ZRT Labs or Precision?
- DHEA, pregnenolone, cortisol.
- Metabolite ratios (optional).
- Vitamin D (25-hydroxycholecalciferol vs. calcitriol) and the IOM.
- History of oophorectomy? Age?
- History of HRT? Bio-identical?
- History of anti-testosterone Rx?

EVALUATION: metal homeostasis

- Cu:Zn ratio (Brewer, Van Tiggelen)
- Serum copper, zinc, selenium.
- Ceruloplasmin; Cu – 3x ceruloplasmin <30.
- RBC magnesium.
- Calcium
- Potassium (risk factor)
- Heavy metals: Hg, Pb, Cd, As (metalloid)
- To provoke or not to provoke?

## EVALUATION: toxins (type 3 vs. all)

- Heavy metals, especially mercury.
- CIRS symptoms? Allergic—asthma, sinusitis, epistaxis, rashes, chemical sensitivities, MCAD (mast cell activation disorder), etc.
- HLA-DR/DQ.
- C4a (NJC-C4a).
- TGF-β1, MSH, MMP9; optional: leptin, ADH, VEGF, VIP, osmolality.
- MARCoNS culture.
- VCS (visual contrast sensitivity testing).
- RealTime Labs urinary mycotoxins.

## EVALUATION: cytoprotection

- Glutathione
- Vitamin E < 13?
- Selenium
- Ascorbate
- Breath MS for ROS.
EVALUATION: barrier leaks and the Smurf assay

- Cyrex Array 2: GI leak (trans-cellular or intercellular)
- Cyrex Array 20: blood-brain barrier leak
- Cyrex Array 3: gluten sensitivity
- Cyrex Array 4: other grain sensitivities
- Oral hygiene
- Nasopharyngeal MARCoNS, AD, and the rhinencephalon

EVALUATION: alerts

- Visual hallucinations, delusions, REM behavioral disturbance, constipation, anosmia, passing out, autonomic disturbance (e.g., arrhythmia, postural hypotension), newly sleeping late, resting tremor: alert re synucleinopathy, LBD or PD or MSA.
- Kleptomania, loss of empathy, saying inappropriate things, apathy, executive dysfunction, primary progressive aphasia: alert re FTLD.
- Atrial fibrillation, hypertension, dyslipidemia, sudden neurological changes, peripheral vascular disease: alert re vascular dementia.
- Conjugate upgaze or downgaze paresis: alert re PSP.
- Rapid course over weeks or a few months: alert re CJD, prion illnesses.
### The protocol works best for:

- Presymptomatics (cf. 7 million E4/4, 75 million E4).
- SCI (subjective cognitive impairment).
- MCI, especially if aMCI and identifiable contributors.
- Early AD, especially if not already on donepezil or memantine.
- People with cognitive changes who are otherwise healthy.
- Non-type 3 SCI, MCI, or early AD.
- Atrophy limited to hippocampus.
- Age < 75.

### The protocol works least well for:

- Advanced Alzheimer’s disease (except for behavior).
- Long-term, progressive symptoms (but note EC).
- Age > 75.
- Type 3 when beyond early MCI.
- On multiple medications, especially donepezil and memantine.
- Poorly compliant person/team (including family, MD).
- Those who are slow, with diffuse synaptic loss.
- **Beware candidates for congophilic angiopathy (esp. E4/4 males).**
Basic concepts of the protocol

- A key component of the program is that it is iterative.
- Drugs are the dessert, not the entrée.
- The earlier you treat, the greater your chance for complete reversal.
- As the metabolic parameters go, so goes the cognition.
- The prionic loop effect creates a threshold, so you do not usually need to do every step.

Closing the complexity gap (/chasm)
Closing the complexity gap

- Neural exosomes.
- Dense dynamic personalized data clouds (Institute for Systems Biology).
- Microbiomes (gut, rhinosinal, oral).
- Combining plasticity training with biochemical optimization (Posit Science).

Summary

- What is referred to as “Alzheimer’s disease” is the result of a protective response to 3 major metabolic and toxic perturbations: inflammation (be it infectious or sterile), trophic withdrawal (trophic factors, hormones, vitamins, etc.), and specific toxins (divalent metals, mycotoxins, et al.).

- There are 3 major subtypes of Alzheimer’s disease (and combinations of these 3 subtypes), and these are readily disclosed by metabolic and genetic profiling.

- Cognitive decline in early Alzheimer’s disease and its forerunners, MCI (mild cognitive impairment) and SCI (subjective cognitive impairment), is reversible, and improvement sustainable, using a programmatic approach rather than a monotherapy (Bredesen, *Aging* 2014; Bredesen et al., *Aging* 2016).

- Not surprisingly, the earlier that treatment is initiated, the greater chance for improvement: in the first 125 patients, over 50% saw improvement using our protocol, including nearly all who were in the early stages.

- We can reduce the global burden of dementia markedly, and increase the global cognitive ability, through metabolic profiling, prevention and early reversal, and personalized, programmatic approaches to cognitive (and overall) health. This could be a highly efficient use of practitioner time and healthcare finances.
A new dawn

SirT1-NFkB mutual inhibition
ApoE4: RelA dominant

ApoE3: SirT1 dominant

ApoE4 and plasticity ratio
EVALUATION: other risk factors

- Sleep apnea
- History of head trauma
- History of loss of consciousness
- Presence of dental amalgams
- History of hypertension
- Consumption of seed oils
- Neuroactive medications (especially with anticholinergic activity), direct or indirect: e.g., benzodiazepines, statins, proton pump inhibitors, antipsychotics, antihistamines, anesthetics, EtOH, illicit drugs, etc.
### EVALUATION: other risk factors (2)

- Poor oral hygiene? Root canal history?
- Sinusitis
- Metabolic syndrome
- History of alcohol withdrawal symptoms
- History of vascular disease
- Exposure to mitochondrial toxins (e.g., antibiotics, statins, ApoE4, griseofulvin, AZT, acetaminophen, NSAIDS, cocaine, methamphetamine, L-DOPA, EtOH)
- Renal, hepatic, or pulmonary disease?
- BMI > 25?

### EVALUATION: other risk factors (3)

- Sleep < 7 hours/night?
- Seropositive for HSV-1?
- Headaches?
- Mold exposure?
- History of meningitis?
- History of cancer?
- Gluten sensitivity or other food sensitivity?
The readout: plasticity ratio (cf. HDL:LDL)

AD has programmatic components: EMT (epithelial-mesenchymal transition)

<table>
<thead>
<tr>
<th>Developmental: Type 1 EMT</th>
<th>Chronic (fibrosoing) injury: Type 2 EMT</th>
<th>Malignancy: Type 3 EMT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Successive waves of EMT-MET generate embryonic tissues and organs</td>
<td>Various mesenchymal cells may be derived in the adult via EMT in the setting of chronic/fibrosoing injuries</td>
<td>Epithelial tumors (Carcinoma) acquire malignant features and metastasize via EMT</td>
</tr>
</tbody>
</table>
### Alzheimer’s and the EMT

<table>
<thead>
<tr>
<th>AD: Type IV EMT?</th>
<th>Organized (E)</th>
<th>Unicellular (M)</th>
<th>AD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolism</td>
<td>Oxphos</td>
<td>Glycolysis</td>
<td>Glycolysis</td>
</tr>
<tr>
<td>Inflammation</td>
<td>Low</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>SirT1/NFkB</td>
<td>SirT1 dominant</td>
<td>NFkB dominant</td>
<td>NFkB dominant</td>
</tr>
<tr>
<td>ROS</td>
<td>Low</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Cytoskeleton</td>
<td>Intact</td>
<td>Breakdown</td>
<td>Breakdown</td>
</tr>
<tr>
<td>Insulin signaling</td>
<td>Sensitive</td>
<td>Resistant</td>
<td>Resistant</td>
</tr>
<tr>
<td>Secretory</td>
<td>Low</td>
<td>High</td>
<td>??</td>
</tr>
<tr>
<td>Intercellular junctions</td>
<td>Present</td>
<td>Lost</td>
<td>Lost (synapses)</td>
</tr>
</tbody>
</table>

#### ApoE4-mediated RelA nuclear translocation

- **SHSY5Y-extract, IP: RelA**
  - Western Blot (WB): RelA, ApoE
  - Subcellular fraction: Cytoplasm (Cy) and Nucleus (Nuc)
  - ApoE genotypes: E3, E4

- **WB: RelA**
  - ApoE genotypes: E3, E4

- **WB: ApoE**
  - ApoE genotypes: E3, E4

- **GAPDH**
  - Normalization marker

- **PARP**
  - DNA fragmentation marker

- **Ladder input (Ab): ApoE Ab**
Is amyloid a “memory” component of the innate immune response?

- Increasing implication of amyloid-β as part of the inflammatory response (e.g., relationship to NFκB).
- In particular, as part of the innate immune system response (DAMP (damage/danger-associated molecular pattern)?).
- Amyloid noted for very long half-life.
- Hippocampus plastic, yet amyloid remains.
- Amyloid often present for years prior to symptoms.
- Dynamic nature suggests polymerization and depolymerization.
- Suggests model as on-site maintenance—essentially a “memory” component of the innate immune response, analogous to the more elegant memory mechanisms of the adaptive immune response.

SUMMARY

- The problem and the need.
- The success to date.
- Scientific background, resulting model, and implications.
- Details of evaluation.
- Details of treatment.
- Troubleshooting.
- Issues and concerns.
- Questions and discussion.
- Future directions.
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

The fifth P: Progressive
Any accurate theory of AD should explain:

- The AD11 mouse.
- The $\alpha_7$ paradox.
- Lack of successful therapeutic development to date.
- The remarkable diversity of risk factors for AD; relation to ASCVD.
- The high prevalence of AD in the elderly.
- The mechanism(s) by which ApoE4 increases risk for AD.
- The physiological role(s) of A$\beta$ peptides.
- The anatomic pattern of spread of AD pathology.
- The association of plastic brain regions with AD pathology.
- Why some people (and transgenic mice) collect large amounts of A$\beta$ peptide without displaying symptoms of AD.
- The relationship between A$\beta$ and tau pathology.
Frame of reference and points of view

Taking a seemingly insoluble problem and making it soluble by changing the coordinate system or frame of reference.

Back to basics: cellular dependence

Rita Levi-Montalcini, the 1986 Nobel Prize, and the trophic factor hypothesis.

It has been generally assumed that trophic factor withdrawal is associated with the loss of a positive survival signal, such as that associated with the phosphorylation of Akt.

However, data accumulated over the past 20 years argue that there is a complementary cell death signal mediated by specific receptors, dubbed dependence receptors, activated by trophic ligand withdrawal but blocked by ligand binding (Rabizadeh et al., Science 1993; Mehlen et al., Nature 1998).
Levi-Montalcini and the classic view

The old view: passive death
The Dependence Receptor Concept

Diversity of Dependence Receptors
An engineer’s view of the neuron

Integration
Analog → digital
Electrical (chemical) input
Via membrane conductance
Σ = Electrical input → electrical output
Integration over anatomical vs. biochemical space

- **Cholesterol Metabolism** (ApoE, ABCA1, etc.)
- **Neurotransmitters** (Ach, glutamate, GABA, etc.)
- **Vitamin D**
- **Hormones** (Thyroid, Estrogen, Progesterone)
- **Reelin**
- **ECM** (collagen, laminin, netrin, heparin, etc.)
- **Trophic Factors** (NGF, BDNF, N1, etc.)

Integration

Analog → digital (slow) output
Receptor signaling input
Via nuclei and cytoplasm
Σ = Chemical milieu input → morphogenetic output
The big problem with neurodegenerative disease

Healthy Brain  Advanced Alzheimer’s

PET Scans:

Normal  Alzheimer’s

Crump Institute for Biological Imaging

The Status Quo:
Alzheimer’s is a disease of toxicity

• Focus is on the chemical & physical effects of Aβ peptide:
  – Lysosomotropic detergent
  – Metal-binding peptide
  – Reactive oxygen species
  – Many other theories

• Approach reinforced by 50,000+ papers…all of which fail to answer key questions

• Why do healthy brains produce Aβ peptide?

• Recent results from transgenic mice
Why do neurons degenerate?
A New View of Alzheimer’s Disease

Proliferation Migration Integration

Cancer: imbalance in proliferation/survival vs. turnover

Proliferation Migration Integration

Oncogenes Tumor Suppressor Genes Cancer
Alzheimer’s disease: imbalance in plasticity

Proliferation  Migration  Integration

Synaptic Reorganization  Synaptic Maintenance

APP—candidate mediator of plasticity balance
Amyloid Precursor Protein (APP)

The Mouse That Remembered to Roar: Alzheimer's Electrophysiology Normalized by Blocking C31

Galvan et al., PNAS 2006
Control mice in Morris water maze
“Mouzheimer’s”

Mouzheimer’s no more
Is APP involved in physiological plasticity?

Normal mouse (trial #8)
Modeling human disorders in *Drosophila*
Alzflymer’s

Left: Off   Right: On
Activity Assay

Total Activity: 24 hours

APP,BACE/GS

Response to treatment with d-amphetamine

Before D-amphetamine treatment  On D-amphetamine  24hr off D-amphetamine

Total Activity: 24 hours

APP,BACE/GS
A Drosophila Hyperactivity Disorder (ADHD)

- Males >> Females.
- Exacerbated markedly by high CHO:protein diet.
- Reduced with aging.
- Associated with sleep/nocturnal dysrhythmic pattern.
- Reversibly responsive to d-amphetamine.
- “Paradoxical response” to d-amphetamine.

Research to Clinical Development: Bench to Bedside

Alzheimer's Drug Development Network
Varghese John, Ph.D., and Dale E. Bredesen, M.D.
F03: Multiple Mechanisms Against Alzheimer’s

- Reduces Aβ
- Increases sAPPα
- Blocks ApoE4 effect
- Improves LTP
- Blocks neuronal programmed cell death
- Excellent blood-brain barrier penetration
- High therapeutic index
- Markedly outperforms memantine and donepezil in Tg Mo

F03 restores novel object recognition completely
Conclusions from the research bench

- APP is an integrating dependence receptor.
- APP is a mediator of both neurite outgrowth and neurite retraction, depending on its incoming signals.
- APP functions as a molecular switch, with prionic loop feedback (i.e., anti-homeostatic).
- Connectomic studies reveal many different inputs to the plasticity balance mediated by APP, linking epidemiological studies with molecular studies.
- APP downstream signaling links to phospho-tau and other characteristics of AD, such as WAVE-1.
- ApoE4 functions by a novel mechanism (and by multiple mechanisms) to alter cellular programming.

Combining the research and clinical findings offers a novel look at what AD actually represents

- What is referred to as “Alzheimer’s disease” is actually a protective response to 3 major metabolic and toxic insults and combinations thereof.
- 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).
- The role of toxic exposures in AD has been under-recognized.
- For optimal responses, monotherapeutics should be replaced by programmatics.
20th-century evaluation of cognitive decline

- Neurological exam—often negative.
- Behavioral assessment—doesn’t reveal etiology or suggest therapy.
- Quantitative neuropsychological examination—causes stress and takes several hours.
- MRI without volumetrics—usually negative or showing mild atrophy.
- Labs—basic chemistries, usually unrevealing.
- The vast majority of critical parameters is left unevaluated.

Playing chess with the devil
Goals and arrows in the quiver
Nutrition: Ketoflex 12/3

- Nutrition—arguably the single most powerful of all of the protocol elements.
- Almost no one with cognitive decline presents with an optimal diet.
- Nutrition as outlined by a neuroscientist...(with thanks to Dr. L and JG).
- Avoid the “Berfuda Triangle” (simple carbohydrates, saturated fats, and low fiber).
- Convert from CHO-based to good-fats-based; sensitize insulin receptor (cf. neural exosomes for IRS1 phos.), optimize nutrients, plant-based, induce autophagy (12/3), mild ketosis.
- Majority of calories from non-starchy vegetables (best local, organic) and good fats. Include cooked and raw vegetables, dark green, rainbow, and crucifers.
- Include detoxifying vegetables such as cilantro, cruciferous vegetables, Jerusalem artichoke.
- Low glycemic fruits (no fruit juice!) such as berries; no pineapple or high glycemic fruits.
- Fats such as avocado, coconut oil, MCT oil (8 vs. 12 C)

MEND: Goals and arrows in the quiver

- Nutrition (cont’d).
- “Meat is a condiment.” If used at all, it should be as grass-fed beef or pastured poultry.
- If fish: wild caught, SMASH fish (salmon, mackerel, anchovies, sardines, herring). Avoid fish with high Hg (long-lived, large mouth).
- Mild ketosis (0.5-2mM β-OH-butyrate target per JG).
- Pastured eggs.
- Avoid gluten, dairy, and other sensitive items.
- Dirty dozen vs. clean 15.
- Heal gut (bone broth or colostrum, not L-glutamine), then pro-biotics and pre-biotics.
- Compare Gundry (esp. re lectins), Fuhrman, Hyman, Perlmutter.
Sleep is critical

- “When does MCI improve?”—conversation with expert.
- Exclude sleep apnea!
- Good sleep hygiene (dark, no EMF, wind down, quiet, etc.).
- Timing as close to 8 hours/night as possible; preferably begin before midnight (best with natural light).
- May precede with “meditation on steroids.”
- Melatonin physiological dose.
- Tryptophan if ruminations.
- No food for at least 3 hours prior to bedtime.

MEND: Goals and arrows in the quiver

- Exercise: both aerobic and strength, total 5x/wk for 45-60’.
- Stress: (1) Issue for all, but especially type 3; (2) Meditation, Neural Agility; (3) Breathing; (4) Cortisol, rT3; (5) Adrenal fatigue; (6) Joy, music, and lifestyle.
- Remove contributors! PPI, statins, neuroactive medications, simple CHO, etc.
- When to use HBOT?
MEND: Arrows in the quiver (2)

- Hormone optimization with bio-identical where indicated: (1) Pregnenolone; (2) fT3, fT4, rT3, TSH; (3) E2, P, E2:P, bio-identical HRT; (4) Test.; (5) Insulin; (6) Cortisol; DHEA; (7) Vitamin D + K2.
- Herbs (e.g., Ashwagandha to increase receptor-mediated clearance of amyloid-β; Bacopa monnieri (multiple mechanisms), Hericium, Rhodiola, Gotu kola, Shankpushpi, etc.).
- Optimize metal metabolism: (1) Cu:Zn ratio; (2) RBC Mg; (3) K; (4) Hg, Pb, Cd, As; (5) Se; (6) Li.
  - (Mg, Zn, Cu:Zn ratio, Se, Mn, Fe, Hg, etc.).
- Provide synaptic components: citicoline and omega-3.
- Goal: homocysteine < 7. Mg-B12 (and adenosyl), Me-folate, P5P, TMG.
- Goal: 25-OH-D3 50-80ng/ml, with vit K2 (100mcg).
- Barriers: oral, gut, nasal, cutaneous, ocular, blood-brain, respiratory, etc.
- Goal: (1) FINS < 5, HgbA1c < 5.6, FBS < 90. Insulin and CHO; (2) Combination to optimize; (3) May need insulin-inducing drug ultimately.

MEND: Arrows in the quiver (3)

- Brain training controversy; over-training.
- Anti-inflammation vs. resolution of inflammation vs. hypo-inflammation. ISIS (WAR) vs. (mal-)adaptive
- DHA and other omega-3 vs. CAA vs. protected omega-3.
- Detox protocols. Sauna, Castille soap, l-GSH, etc.
- Intranasal trophic support. Pros/cons SNIFF.
- When are stem cells appropriate?
- Anti-microbials? Anti-biofilms? MARCoNS?
- When are drugs helpful? Include monoclonals? F03?
Protocol Linchpins

Hormonal optimization: (1) Pregnenolone; (2) fT3, fT4, rT3, TSH; (3) E2, P, E2:P, bio-identical HRT; (4) Test.; (5) Insulin; (6) Cortisol; DHEA; (7) Vitamin D + K2.

Critical herbs: (1) Bacopa monnieri; (2) Withania somnifera; (3) Turmeric (curcumin source); (4) Hericium erinaceus; (5) Rhodiola; (6) Others (mint, sage, cilantro, etc.).

Barriers: (1) GI; (2) BBB; (3) Oral; (4) Nasal/sinus; (5) Integument (skin, nails, hair).

Antioxidants: Se, C, E (mixed), GSH, lipoic acid, SOD, MT, etc.

Trophic factors: (1) NGF—ALCAR, Hericium; (2) BDNF—exercise; (3) VIP—intranasal; (4) Insulin, IGF.

Protocol Linchpins

Key modulators: (1) Coconut oil or MCT; (2) Curcumin; (3) Resveratrol; (4) Citicoline; (5) Omega-3; (6) Nicotinamide riboside; (7) D-ribose; (8) Ubiquinol.

Resolvins (SPM Active).

GI health: (1) Evaluate (Cyrex 2); (2) Heal (bone broth, or colostrum, or L-glutamine); (3) Repopulate (pro-biotics); (4) Support (pre-biotics); (5) Cherish (avoid sugar, gluten); (6) Assist (digestive enzymes, S. boulardi, betaine-HCl).

Toxins: (1) Type 3; (2) Heavy metals; (3) CIRS, mycotoxins, and Lyme (Borrelia); (4) Cu:Zn ratio.

Brain exercise (Brain HQ, Lumosity, Dakim, etc.)
Practical matters

- Toxins: (1) Metals; (2) Mycotoxins; (3) Others
- GI health: (1) Evaluate (Cyrex 2); (2) Heal (bone broth, or colostrum, or L-glutamine); (3) Repopulate (pro-biotics); (4) Support (pre-biotics); (5) Cherish (avoid sugar, gluten); (6) Assist (digestive enzymes, S. boulardi, betaine-HCl).
- Stress: Neural Agility?
- A few words on sleep: (1) Cleansing; (2) Rule out sleep apnea; (3) Melatonin, tryptophan, 5HT, others; (4) Timing; (5) Noise, EMF, light.
- Infections and Alzheimer’s: HSV-1, P. gingivalis, Candida, others.
- Brain training options (Posit, Lumosity, Dakim, et al.) and issues (efficacy, exhaustion, timing, environment)

Characteristics of success

- Diligence with program.
- Attention to detail.
- Improvement in lab values.
- Supportive spouse or significant other.
- Follow-up.
- Repeated optimization.
- Helpful physician.
Characteristics of reduced success

- Lack of diligence with program.
- Lack of attention to detail.
- Lack of improvement in lab values.
- Delay in starting program until late in the illness.
- Lack of follow-up.
- Assuming the first phase is the final plan.
- Unhelpful physician.

Objections and concerns

- But I don’t want to give up ice cream.
- But I don’t want to give up chocolate.
- But I love pizza.
- But I can’t eat dinner until late at night.
- I have sugar cravings.
- My husband isn’t that much better than I am.
- Coconut oil is saturated fat—isn’t that bad?
- I can’t get more than 5 hours of sleep per night.
- I don’t have time to exercise.
- The program is too complicated.
Objections and concerns (2)

- I can’t reduce stress in my life.
- But I love meat.
- But I have a sweet tooth.
- I’d rather wait to do the program until I’m more affected—I’m not that bad now.
- Isn’t celiac disease rare?
- None of the program components sounds like a cure.
- Can’t you just give me a pill?
- But there is nothing better than junk food!
- But my doctor told me that everyone knows Alzheimer’s is untreatable.

Window on the mind: neural exosomes
Enhancements on the way

- Neural exosomes (e.g., Nanosomix).
- Neurovision retinal imaging.
- NeuroTrack and mesial temporal lobe.
- Intranasal trophic peptides (beyond VIP, insulin, ADNP).
- Non-intranasal trophic peptides (e.g., IV Cerebrolysin).
- Novel PET tracers (beyond tau-binding).
- Stem cell improvements.
- Improved understanding of CIRS-type 3 AD connection, and CIRS-LBD connection.
- Enhanced detoxification protocols.
- Continued optimization of critical nutritional components.
- Role of nitric oxide.

Key takeaways:

- Cognitive decline from early Alzheimer’s disease and its precursors, MCI and SCI, can be reversed, and improvement sustained.
- This requires science, diligence, and attention to detail; of course there is no guarantee, but results are unequaled.
- Metabolic status and cognitive status go hand in hand.
- The first thing for people/patients to do is to take a deep breath, relax, and abandon all feelings of hopelessness and despair.
- The next thing to do is to get serious about following the program. A health coach may be very helpful.
- The third thing to do is to recognize that it will take time (3-12 months) and optimization to make a real difference.
Therapeutic Convergence

Rx (20th century) \(\rightarrow\) t-\(\rightarrow\) Dx (20th century)
Therapeutic Convergence

Rx (20th century) \( \rightarrow \) t-\( \rightarrow \) Dx (20th century)

Rx (21st century) \( \leftarrow \) Dx (21st century)

Memory...

Inflammation
Diet
Stress
Reduced Mitochondrial Function

Trophic Factors
Vitamin D3
Sleep
Mitochondrial Function
Hormones

And many other things…
And many other things…
Forgettory...

Trophic Factors
Vitamin D3
Sleep
Mitochondrial Function
Hormones
And many other things...

What is wrong with clinical trials for Alzheimer’s disease? (Everything…)

<table>
<thead>
<tr>
<th>CLINICAL TRIALS</th>
<th>Current</th>
<th>Future</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goal</td>
<td>Less decline</td>
<td>Improve (optimally back to normal) and sustain</td>
</tr>
<tr>
<td>Therapeutic space sampled</td>
<td>Small</td>
<td>Large</td>
</tr>
<tr>
<td>Focus</td>
<td>FDA-centric; Pharma-centric; NIH-centric</td>
<td>Patient-centric</td>
</tr>
<tr>
<td>Trials</td>
<td>Many patients, high cost, long trials, to identify small effect</td>
<td>Short, few patients, rapidly iterative, seek large effect</td>
</tr>
<tr>
<td>Rx</td>
<td>Mono Rx</td>
<td>Systems of Rx</td>
</tr>
<tr>
<td>Analysis</td>
<td>1 variable</td>
<td>Multi-variable</td>
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<tr>
<td>When Rx</td>
<td>AD</td>
<td>Early MCI and A3ix</td>
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<tr>
<td>Goal of Rx</td>
<td>Incremental, financial</td>
<td>Disruptive; minimize pt. cost</td>
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<tr>
<td>Trial length</td>
<td>Long (e.g., 18 mos.)</td>
<td>Short (e.g., 2-3 mos.), iterative</td>
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<tr>
<td>Trial cost</td>
<td>High</td>
<td>Low</td>
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<tr>
<td>Data gathering on patients</td>
<td>Extensive, lengthy</td>
<td>Focus on key points</td>
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<tr>
<td>Rx paradigm</td>
<td>One size fits all</td>
<td>Personalized</td>
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<td>Evaluation</td>
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<td>Rx space sampled</td>
<td>Small</td>
<td>Large</td>
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<tr>
<td>Target</td>
<td>Pharma, FDA</td>
<td>Patients</td>
</tr>
<tr>
<td>Strategy</td>
<td>Inside the box (and a tiny box, at that)</td>
<td>Outside the box</td>
</tr>
</tbody>
</table>
The ReCODE Protocol

- We have mapped the many molecular mechanisms of cognitive decline and AD onto a treatment protocol.
- These include dozens of interventions, beginning with DESS, hormonal optimization, nutrients, targeted herbs, brain stimulation, drugs, etc.
- No one intervention closes all 36 holes.
- Approach: pull out all of the stops.
- Practical issues:
  - Nutrition: Ketoflex 12/3: anti-inflammatory, no simple carbohydrates, heal GI leak and BBB leak, change metabolism to fat from CHO, nutrient dense, 12hr/3hr fast, low glycemic index, good fats, color, veg. first (cf. Fuhrman, Hyman, Katz).
**MEND 3.0 Protocol Linchpins**

- Exercise: need both CV and weights, >30’, 5x/wk.
- A few words on sleep: (1) Cleansing; (2) Rule out sleep apnea; (3) Melatonin, tryptophan, 5HT, others; (4) Timing; (5) Noise, EMF, light.
- Stress: (1) Issue for all, but especially type 3; (2) Meditation, Neural Agility; (3) Breathing; (4) Cortisol, rT3; (5) Adrenal fatigue; (6) Joy and lifestyle.
- Homocysteine: (1) Target <7; (2) Me-B12, Me-THF, P5P, TMG.
- Insulin and CHO: (1) FINS, FBS, HgbA1c; (2) Combination to optimize; (3) May need insulin-inducing drug ultimately.
- Metal optimization: (1) Cu:Zn ratio; (2) RBC Mg; (3) K; (4) Hg, Pb, Cd, As.

**MEND 3.0 Protocol Linchpins (3)**

- Key modulators: (1) Coconut oil; (2) Curcumin; (3) Resveratrol; (4) Citicoline; (5) Omega-3; (6) Nicotinamide riboside; (7) D-ribose; (8) Ubiquinol.
- Resolvins (SPM Active).
- GI health: (1) Evaluate (Cyrex 2); (2) Heal (bone broth, or colostrum, or L-glutamine); (3) Repopulate (pro-biotics); (4) Support (pre-biotics); (5) Cherish (avoid sugar, gluten); (6) Assist (digestive enzymes, S. boulardi, betaine-HCl).
- Toxins: (1) Type 3; (2) Heavy metals; (3) CIRS, mycotoxins, and Lyme (Borrelia); (4) Cu:Zn ratio.
- Brain exercise (Posit, Lumosity, Dakim, etc.)
MEND: Practical matters

• Toxins: (1) Metals; (2) Mycotoxins; (3) Others

• GI health: (1) Evaluate (Cyrex 2); (2) Heal (bone broth, or colostrum, or L-glutamine); (3) Repopulate (pro-biotics); (4) Support (pre-biotics); (5) Cherish (avoid sugar, gluten); (6) Assist (digestive enzymes, S. boulardi, betaine-HCl).

• Stress: Neural Agility?

• A few words on sleep: (1) Cleansing; (2) Rule out sleep apnea; (3) Melatonin, tryptophan, 5HT, others; (4) Timing; (5) Noise, EMF, light.

• Infections and Alzheimer’s: HSV-1, P. gingivalis, Candida, others.

• Brain training options (Posit, Lumosity, Dakim, et al.) and issues (efficacy, exhaustion, timing, environment)
APP-selective BACE Inhibitors (ASBI)

- Novel inhibitors that interact with the catalytic site of BACE & bind to the ectodomain of APP.
- Inhibitors are effective in ↓sAPPβ & ↓Aβ42 in cells transfected with APPwt but not APPsw.
- Exhibit selectivity for APP over NRG1 and PSGL1.

Strategy for AD and MCI Rx

All molecular mechanisms (36) → Evaluation → Why memory loss?

System 1.0: comprehensive, personalized
The first systems therapeutics clinical trial

- Systems Therapeutics (and U.S. case)
- F03
- Synaptik (multiple network-specific components)
- Computer-based assessment and memory training
- Sleep enhancement
- Exercise-induced BDNF increase
- AD-specific diet

First clinical trial proposed for 2011.

“Game of Throwns” (243/244)

R.I.P. Dimebon x2
R.I.P. Semagacestat
R.I.P. Rosiglitazone
R.I.P. AN-1792
R.I.P. Alzhemed
R.I.P. Flurizan
R.I.P. Rember
R.I.P. Bapineuzumab
## Metabolism, cognition, and the phagocytosis index

<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>17%ile</td>
<td>75%ile</td>
</tr>
</tbody>
</table>

## Proof of Improvement on MEND

<table>
<thead>
<tr>
<th>71 yo E4/3</th>
<th>2013</th>
<th>2015 (MEND 2 yr)</th>
</tr>
</thead>
<tbody>
<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>
</tr>
</tbody>
</table>
**Improvement on MEND**

<table>
<thead>
<tr>
<th></th>
<th>2015</th>
<th>2016 (MEND 5 mos.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurocognitive index</td>
<td>16%ile</td>
<td>73%ile</td>
</tr>
<tr>
<td>Composite memory</td>
<td>1%ile</td>
<td>61%ile</td>
</tr>
<tr>
<td>Verbal memory</td>
<td>3%ile</td>
<td>93%ile</td>
</tr>
<tr>
<td>Processing speed</td>
<td>37%ile</td>
<td>81%ile</td>
</tr>
<tr>
<td>Executive function</td>
<td>14%ile</td>
<td>58%ile</td>
</tr>
<tr>
<td>Cognitive flexibility</td>
<td>16%ile</td>
<td>61%ile</td>
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**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
Synaptoblastic:synaptoclastic imbalance

Trophic, Anti-AD

Anti-trophic, Pro-AD

Everyone here is helping to effect change:

“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
Effecting change:

“Never doubt the ability of a small group of committed individuals to change the world. Indeed, it is the only thing that ever has.”

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BUCK INSTITUTE
ADVANCING AGE RESEARCH
### System 1.0 Pilot

#### Patient History and Evaluation

<table>
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<tr>
<th>Patient</th>
<th>History and Evaluation</th>
<th>Diagnosis</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>JB; 67F 3/3</td>
<td>2yr memory ↓; FH+</td>
<td>MCI</td>
<td>Normal x 2 yrs; working</td>
</tr>
<tr>
<td>DB; 70M 4/3</td>
<td>12yr memory ↓; PET+, NPs+</td>
<td>MCI</td>
<td>“Clearly improved;” working</td>
</tr>
<tr>
<td>DT; 70M 4/3</td>
<td>4yr memory ↓; M,NPs+</td>
<td>Early AD</td>
<td>Improved; MemTrax +</td>
</tr>
<tr>
<td>RM; 75M 3/3</td>
<td>1yr memory ↓</td>
<td>SCI</td>
<td>Improved; working</td>
</tr>
<tr>
<td>KH; 75F C677T</td>
<td>1yr memory ↓</td>
<td>SCI</td>
<td>Improved</td>
</tr>
<tr>
<td>CF; 55F 3/3</td>
<td>4yr memory ↓</td>
<td>MCI</td>
<td>Normal x occ. Working</td>
</tr>
<tr>
<td>RM2; 72M 3/3</td>
<td>7yr memory ↓</td>
<td>MCI</td>
<td>Improved; working</td>
</tr>
<tr>
<td>DL; 55M 4/3</td>
<td>2yr memory ↓</td>
<td>SCI</td>
<td>Normal; working</td>
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<tr>
<td>SB; 63F 4/3</td>
<td>FH dementia</td>
<td>SCI</td>
<td>ASx, normal PET</td>
</tr>
<tr>
<td>MR; 60F 4/3</td>
<td>4yr rapid decline; MoCA 6, PiB+</td>
<td>Late AD</td>
<td>Decline</td>
</tr>
</tbody>
</table>
Effecting change:

The opaque, impenetrable Alzheimer’s pane is shattering, and we are peering into the engine driving cognitive decline.

Hippocrates comes to Silicon Valley

- The need for large datasets.
- Extensive networks, not single targets.
- Programmatic, not pills.
- Personalized programs, not one-size-fits-all.
- Previously impossible disease subtyping.
- Predictive power, thus preventive power.
- Complex algorithms.
- New trends toward “patient” knowledge and empowerment.
- Result: dramatic reduction in chronic illness, cost of healthcare.
### Characteristics of success

- Diligence with program.
- Attention to detail.
- Improvement in lab values.
- Supportive spouse or significant other.
- Follow-up.
- Repeated optimization.
- Helpful physician.

### Characteristics of reduced success

- Lack of diligence with program.
- Lack of attention to detail.
- Lack of improvement in lab values.
- Delay in starting program until late in the illness.
- Lack of follow-up.
- Assuming the first phase is the final plan.
- Unhelpful physician.
What this program is not:

- A program of supplements.
- A simple lifestyle program.
- A substitute for your physician.
- The standard, ineffective approach of Aricept and Namenda (which is not to say that these should be discontinued—there are concerns about discontinuation).

What this program is:

- A medical information program based on 25 years of basic science research.
- A foundation on which to build.
- A novel approach called MEND, the first one showing success in reversing cognitive decline (as published in 2014).
From the Alzheimer’s Association:

• “Myth 8: There are treatments available to stop the progression of Alzheimer’s disease

• Reality: At this time, there is no treatment to cure, delay or stop the progression of Alzheimer’s disease. FDA-approved drugs temporarily slow worsening of symptoms for about 6 to 12 months, on average, for about half of the individuals who take them.”

Key takeaways from these 4 days:

• Cognitive decline from early Alzheimer’s disease and its precursors, MCI and SCI, can be reversed, and improvement sustained.

• This requires science, diligence, and attention to detail; of course there is no guarantee, but results are unequaled.

• Metabolic status and cognitive status go hand in hand.

• The first thing to do is to take a deep breath, relax, and abandon all feelings of hopelessness and despair.

• The next thing to do is to get serious about following the program.

• The third thing to do is to recognize that it will take time (3-12 months) and optimization to make a real difference.
Is Alzheimer’s disease incurable?

- Show success of MEND—Julie G and slides
- Small amount of scientific background--OK
- Key point is that AD is, up to a point, a metabolic disease with many different contributors.
- Key contributors: insulin resistance, inflammation, homocysteine, hypovitaminosis D, hormonal imbalance, etc.
- These combine to cause problems, and therefore, need to address as many as possible.
- What it is, and what it is not.

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).
67 y.o. woman with 2-yr history of progressive cognitive decline

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Just stop for a moment, and think:

What would a world with dementia rates slashed look like?

Goal: reduce dementia costs in California by 50% ($10B/yr)

- Program on prevention and early reversal (C-PPD).
- **2S-4A** = “Too Smart For Alzheimer’s” = State program to reduce dementia.
- Elements of the program:
  - Public service announcements.
  - Support for testing everyone over 45.
  - High ROI given current dementia costs.
  - Many interested individuals may be helpful.
Thanks for your support of Alzheimer’s disease research and therapy

Veronica Galvan (UTSA)           Karen Poksay
Shahrooz Rabizadeh (Nantworks)  Ram Rao
Darci Kane                       Alexei Kurakin
Brittany Philpot                 Clare Peters-Libeu
Patricia Spilman                 Matthew Hart (UTSA) Varghese John
David Madden                     Olivia Gorostiza Qiang Zhang
Alex Matalis                     Olivier Descamps Veena Theendakara
Michael Mitsumori                Jesus Campagna
Collaborators: Krys Bankiewicz, Pankaj Kapahi, Patrick Mehlen, Ed Koo, Allan Butterfield

---

Therapeutic Convergence

Rx (20th century) ➔ t-> t-> Dx (20th century)
Therapeutic Convergence

Rx (20th century) \(\xrightarrow{t\rightarrow}\) Dx (20th century)

Rx (21st century) \(\xleftarrow{}\) Dx (21st century)

70 y.o. man with accelerating memory loss due to Alzheimer’s disease
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The fifth P: Progressive

The current dogma

“There is nothing that will prevent, reverse, or slow the progress of Alzheimer’s disease.”
A critical goal of research is to challenge the dogma

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

Is Alzheimer’s disease incurable?

“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
Many questions to answer

• How late in the course is this therapeutic approach effective?

• How long can the therapeutic benefit be sustained?

• Are there AD subtypes for which this approach is more (or less) effective?

• Is this program effective in familial AD?

• Would an analogous approach be effective for Parkinson’s, Lewy body disease (LBD), frontotemporal lobar degeneration (FTLD), progressive supranuclear palsy (PSP), ALS, and other neurodegenerative diseases?

• Might this program serve as a platform on which to test new drugs for AD that would fail as monotherapeutics?
• Patients who were struggling at work, or having to terminate their employment, were able to return to work or continue their work.

• Improvement has been sustained, with the longest ongoing treatment being two and one-half years.

• None of the patients was able to follow the entire protocol, but a threshold effect suggests that following at least a significant part of it may be sufficient.

• The therapeutic program, dubbed MEND, is personalized, and designed to address the many contributors to the plasticity network that are imbalanced in AD, as well as serving as a platform for novel drug candidate testing.

• Continued iteration, both for each patient and for the system as a whole, is optimal.
### What is wrong with clinical trials for Alzheimer’s disease? (Everything…)

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<td>Dx</td>
<td>Causes of problem</td>
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<td>Small</td>
<td>Large</td>
</tr>
<tr>
<td><strong>Target</strong></td>
<td>Pharma, FDA</td>
<td>Patients</td>
</tr>
<tr>
<td><strong>Strategy</strong></td>
<td>Inside the box (and a tiny box, at that)</td>
<td>Outside the box</td>
</tr>
</tbody>
</table>

### A roof with 36 holes…

![A roof with 36 holes](image-url)
Frame of reference

- Taking a seemingly insoluble problem and making it soluble by changing the coordinate system or frame of reference.

Any accurate theory of AD should explain:

- The AD11 mouse.
- The α7 paradox.
- Lack of successful therapeutic development to date.
- The remarkable diversity of risk factors for AD; relation to ASCVD.
- The high prevalence of AD in the elderly.
- The mechanism(s) by which ApoE4 increases risk for AD.
- The physiological role(s) of Aβ peptides.
- The anatomic pattern of spread of AD pathology.
- The association of plastic brain regions with AD pathology.
- Why some people (and transgenic mice) collect large amounts of Aβ peptide without displaying symptoms of AD.
- The relationship between Aβ and tau pathology.
- Mono-explanations: AβO, p-τ, inflam, ROS, metal binding, lysosomatrophic detergent, channels, Ab-PrP, pro-NGF, p75NTR, TNF, NO, glutamate, PirB,
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

Back to basics: cellular dependence

• Rita Levi-Montalcini, the 1986 Nobel Prize, and the trophic factor hypothesis.

• It has been generally assumed that trophic factor withdrawal is associated with the loss of a positive survival signal, such as that associated with the phosphorylation of Akt.

• However, data accumulated over the past 20 years argue that there is a complementary cell death signal mediated by specific receptors, dubbed dependence receptors, activated by trophic ligand withdrawal but blocked by ligand binding (Rabizadeh et al., Science 1993; Mehlen et al., Nature 1998).
Levi-Montalcini and the classic view

The old view: passive death
The Dependence Receptor Concept

Trophic ligand

No ligand (or anti-trophic ligand)

Dependence Receptor

Programmed Cell death

Diversity of Dependence Receptors

Integrins β, α, MIDAS motif

p75NTR

DCC

UNC5Hs

Chopper

(D1185, D1290)

(ZU-5, D112, D129)

RET

Cadherin domain

D707

D1017

Hirschsprung's Disease (megacolon)

Medullary Carcinoma

Immunoglobulin-like domain

Thrombospondin type I-like domain

Fibronectin-like domain

Death domain

Cysteine-rich domain

Tyrosine kinase domain
An engineer’s view of the neuron

Integration
Analog $\rightarrow$ digital
Electrical (chemical) input
Via membrane conductance
$\Sigma =$ Electrical input $\rightarrow$ electrical output
Integration over anatomical vs. biochemical space

- **Reelin**
- **Vitamin D**
- **Hormones** (Thyroid, Estrogen, Progesterone)
- **Trophic Factors** (NGF, BDNF, N1, etc.)
- **Cholesterol Metabolism** (ApoE, ABCA1, etc.)
- **Neurotransmitters** (Ach, glutamate, GABA, etc.)
- **ECM** (collagen, laminin, netrin, heparin, etc.)

Integration
- Analog → digital (slow) output
- Receptor signaling input
- Via nuclei and cytoplasm
- $\Sigma = \text{Chemical milieu input} \rightarrow \text{morphogenetic output}$
Normal mouse (trial #8)
“Sheldon Cooper mouse”

F03: Multiple Mechanisms Against Alzheimer’s

- Reduces Aβ
- Increases sAPPα
- Blocks ApoE4 effect
- Improves LTP
- Blocks neuronal programmed cell death
- Excellent blood-brain barrier penetration
- High therapeutic index
- Markedly outperforms memantine and donepezil in Tg Mo
F03 restores novel object recognition completely

APP-selective BACE Inhibitors (ASBI)

- Novel inhibitors that interact with the catalytic site of BACE & bind to the ectodomain of APP.
- Inhibitors are effective in ΔsAPPβ & ΔAβ42 in cells transfected with APPwt but not APPsw.
- Exhibit selectivity for APP over NRG1 and PSGL1.
ApoE4: RelA dominant

ApoE3: SirT1 dominant

The EMT (epithelial-mesenchymal transition)

Developmental: Type 1 EMT

Chronic (fibrosing) injury: Type 2 EMT

Malignancy: Type 3 EMT

Successive waves of EMT-MET generate embryonic tissues and organs

Various mesenchymal cells may be derived in the adult via EMT in the setting of chronic/fibrosing injuries

Epithelial tumors (Carcinoma) acquire malignant features and metastasize via EMT
### Alzheimer's and the EMT

<table>
<thead>
<tr>
<th>AD: Type IV EMT?</th>
<th>Organized (E)</th>
<th>Unicellular (M)</th>
<th>AD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolism</td>
<td>Oxphos</td>
<td>Glycolysis</td>
<td>Glycolysis</td>
</tr>
<tr>
<td>Inflammation</td>
<td>Low</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>SirT1/NFkB</td>
<td>SirT1 dominant</td>
<td>NFkB dominant</td>
<td>NFkB dominant</td>
</tr>
<tr>
<td>ROS</td>
<td>Low</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Cytoskeleton</td>
<td>Intact</td>
<td>Breakdown</td>
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</tr>
<tr>
<td>Insulin signaling</td>
<td>Sensitive</td>
<td>Resistant</td>
<td>Resistant</td>
</tr>
<tr>
<td>Secretory</td>
<td>Low</td>
<td>High</td>
<td>??</td>
</tr>
<tr>
<td>Intercellular junctions</td>
<td>Present</td>
<td>Lost</td>
<td>Lost (synapses)</td>
</tr>
</tbody>
</table>

### What is wrong with clinical trials for Alzheimer’s disease? (Everything…)

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Window on the mind: *neural exosomes*

Strategy for AD and MCI Rx

All molecular mechanisms (36) → Evaluation → Why memory loss?

System 1.0: comprehensive, personalized
Summary--Conceptual

Our findings suggest that AD is fundamentally related to a plasticity balance, analogous to oncogene:tumor suppressor gene balance.

In this model, AD results from a synaptoblastic:synaptoclastic imbalance that is metabolically induced, mediated by dependence receptors (including APP), and amplified by prionic loops.

Therefore, one translational approach involves correcting this imbalance by targeting APP signaling directly.

However, an optimal approach would include impacting multiple network components, as physiologically and as far upstream as possible.

We have had initial success both pre-clinically and clinically with this approach, but much more proof is needed, as well as optimization of each network component therapeutic.
• Our findings suggest that AD is fundamentally related to a plasticity balance, analogous to oncogene:tumor suppressor gene balance.

• In this model, AD results from a synaptoblastic:synaptoclastic imbalance that is metabolically induced, mediated by dependence receptors (including APP), and amplified by prionic loops.

• Therefore, one translational approach involves correcting this imbalance by targeting APP signaling directly.

• However, an optimal approach would include impacting multiple network components, as physiologically and as far upstream as possible.

• We have had initial success both pre-clinically and clinically with this approach, but much more proof is needed, as well as optimization of each network component therapeutic.

---

The fifth P: Progressive
The ApoE4-interacting promoters identify genes mediating the very processes associated with AD.

These results thus offer new insight into the mechanism by which ApoE4 confers risk for the development of Alzheimer’s disease, as well as novel targets for AD therapeutics.
The ApoE4-interacting promoters identify genes mediating the very processes associated with AD.

These results thus offer new insight into the mechanism by which ApoE4 confers risk for the development of Alzheimer's disease, as well as novel targets for AD therapeutics.
Memory...

Inflammation
Diet
Stress
Reduced Mitochondrial Function

And many other things…

Trophic Factors
Vitamin D3
Sleep
Mitochondrial Function
Hormones

Forgettory...

Inflammation
Diet
Stress
Reduced Mitochondrial Function

And many other things…

Trophic Factors
Vitamin D3
Sleep
Mitochondrial Function
Hormones

And many other things…
The readout: plasticity ratio (cf. HDL:LDL)

The first systems therapeutics clinical trial

- Systems Therapeutics (and U.S. case)
- F03
- Synaptik (multiple network-specific components)
- Computer-based assessment and memory training
- Sleep enhancement
- Exercise-induced BDNF increase
- AD-specific diet

Medicine Synaptik Nutrition Guidance Cognitive Exercise Physical Exercise Sleep Aid

First clinical trial is set for 2014.
A small set of genes is associated with the appearance of hominids 5-7 million years ago. Prominent among these are pro-inflammatory genes. ApoE has 3 alleles: ApoE2, 3, and 4. ApoE4 is primordial. ApoE4 pro-inflammatory effect allowed us to come down from the trees, roam the savannah, eat raw meat, fight. Antagonistic pleiotropy, longevity, ApoE4.

The Mouse That Remembered to Roar: Alzheimer’s Electrophysiology Normalized by Blocking C31

Galvan et al., PNAS 2006
Control mice in Morris water maze
“Mouzheimer’s”

Mouzheimer’s no more
Is APP involved in physiological plasticity?

Theendakara et al., PNAS 2013
The Status Quo: 
Alzheimer’s is a disease of toxicity

- Focus is on the chemical & physical effects of Aβ peptide:
  - Lysosomotropic detergent
  - Metal-binding peptide
  - Reactive oxygen species
  - Many other theories
- Approach reinforced by 50,000+ papers...all of which fail to answer key questions
- Why do healthy brains produce Aβ peptide?
- Recent results from transgenic mice

---

<table>
<thead>
<tr>
<th>Patient</th>
<th>History and Evaluation</th>
<th>Diagnosis</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>JB; 67F 3/3</td>
<td>2yr memory ↓; FH+</td>
<td>MCI</td>
<td>Normal x 2 yrs; working</td>
</tr>
<tr>
<td>DB; 70M 4/3</td>
<td>12yr memory ↓; PET+, NPs+</td>
<td>MCI</td>
<td>“Clearly improved;” working</td>
</tr>
<tr>
<td>DT; 70M 4/3</td>
<td>4yr memory ↓; M, NPs+</td>
<td>Early AD</td>
<td>Improved; MemTrax +</td>
</tr>
<tr>
<td>RM; 75M 3/3</td>
<td>1yr memory ↓</td>
<td>SCI</td>
<td>Improved; working</td>
</tr>
<tr>
<td>KH; 75F C677T</td>
<td>1yr memory ↓</td>
<td>MCI</td>
<td>Improved</td>
</tr>
<tr>
<td>CF; 55F 3/3</td>
<td>4yr memory ↓</td>
<td>MCI</td>
<td>Normal x occ. Working</td>
</tr>
<tr>
<td>RM2; 72M 3/3</td>
<td>7yr memory ↓</td>
<td>MCI</td>
<td>Improved; working</td>
</tr>
<tr>
<td>DL; 55M 4/3</td>
<td>2yr memory ↓</td>
<td>SCI</td>
<td>Normal; working</td>
</tr>
<tr>
<td>SB; 63F 4/3</td>
<td>FH dementia</td>
<td>SCI</td>
<td>ASx, normal PET</td>
</tr>
<tr>
<td>MR; 60F 4/3</td>
<td>4yr rapid decline; MoCA 6, PiB+</td>
<td>Late AD</td>
<td>Decline</td>
</tr>
</tbody>
</table>
A Roof with 36 holes…

70 y.o. man with accelerating memory loss due to Alzheimer’s disease
Better patches for the holes...

Optimal solution for each hole...
Any accurate theory of AD should explain:

• The AD11 mouse.
• The $\alpha_7$ paradox.
• Lack of successful therapeutic development to date.
• The remarkable diversity of risk factors for AD; relation to ASCVD.
• The high prevalence of AD in the elderly.
• The mechanism(s) by which ApoE4 increases risk for AD.
• The physiological role(s) of A$\beta$ peptides.
• The anatomic pattern of spread of AD pathology.
• The association of plastic brain regions with AD pathology.
• Why some people (and transgenic mice) collect large amounts of A$\beta$ peptide without displaying symptoms of AD.
• The relationship between A$\beta$ and tau pathology.

Is Alzheimer’s disease incurable?

• “I've gone over…to the bright side.”

• After it was clear that cardiovascular disease and AD have similar epidemiology, I had a duh-huh moment…
Lineage-specific mutations mapped onto a schematic of the APOE protein (A) and primate phylogeny (B).

http://www.plosone.org/article/info:doi/10.1371/journal.pone.0047760

<table>
<thead>
<tr>
<th>CLINICAL TRIALS</th>
<th>Current</th>
<th>Future</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goal</td>
<td>Less decline</td>
<td>Improve (optimally back to normal) and sustain</td>
</tr>
<tr>
<td>Therapeutic space sampled</td>
<td>Small</td>
<td>Large</td>
</tr>
<tr>
<td>Focus</td>
<td>FDA-centric; Pharma-centric; NIH-centric</td>
<td>Patient-centric</td>
</tr>
<tr>
<td>Trials</td>
<td>Many patients, high cost, long trials, to identify small effect</td>
<td>Short, few patients, rapidly iterative, seek large effect</td>
</tr>
<tr>
<td>Rx</td>
<td>Mono Rx</td>
<td>Systems of Rx</td>
</tr>
<tr>
<td>Analysis</td>
<td>1 variable</td>
<td>Multi-variable</td>
</tr>
<tr>
<td>When Rx</td>
<td>AD</td>
<td>Early MCI and A3x</td>
</tr>
<tr>
<td>Goal of Rx</td>
<td>Incremental, financial</td>
<td>Disruptive; minimize pt. cost</td>
</tr>
<tr>
<td>Trial length</td>
<td>Long (e.g., 18 mos.)</td>
<td>Short (e.g., 2-3 mos.), iterative</td>
</tr>
<tr>
<td>Trial cost</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Data gathering on patients</td>
<td>Extensive, lengthy</td>
<td>Focus on key points</td>
</tr>
<tr>
<td>Rx paradigm</td>
<td>One size fits all</td>
<td>Personalized</td>
</tr>
<tr>
<td>Evaluation</td>
<td>Dx</td>
<td>Causes of problem</td>
</tr>
<tr>
<td>Rx space sampled</td>
<td>Small</td>
<td>Large</td>
</tr>
<tr>
<td>Target</td>
<td>Pharma, FDA</td>
<td>Patients</td>
</tr>
<tr>
<td>Strategy</td>
<td>Inside the box (and a tiny box, at that)</td>
<td>Outside the box</td>
</tr>
</tbody>
</table>
The Chimp That Killed the Rhino
Evolution, Shortevity, Alzheimer’s, and the God Gene

6 million years ago

7 million years ago

2 million years ago

3 million years ago

4 million years ago

5 million years ago

1 million years ago

220,000 years ago

80,000 years ago

ApoE3

ApoE2

ApoE4
ApoE4: RelA dominant

ApoE3: SirT1 dominant

East Meets West
Modeling human disorders in *Drosophila*

Alzflymer’s
Alzflymer’s
Left: Off   Right: On

Activity Assay

![Graph showing total activity over 24 hours for different conditions: DR-, DR+, AL-, AL+, with APP, BACE/GS highlighted.](image)
Response to treatment with d-amphetamine

Before D-amphetamine treatment  On D-amphetamine (1.0 mg/ml)  24hr off D-amphetamine

Total Activity, 24 hours

APP, BACE/GS

A Drosophila Hyperactivity Disorder (ADHD)

• Males >> Females.
• Exacerbated markedly by high CHO:protein diet.
• Reduced with aging.
• Associated with sleep/nocturnal dysrhythmic pattern.
• Reversibly responsive to d-amphetamine.
• “Paradoxical response” to d-amphetamine.
Trophic Factors

Inflammation
Diet
Stress
Reduced Mitochondrial Function

Vitamin D3
Sleep
Mitochondrial Function
Hormones

And many other things...

Memory...

Forgettory...
Leaky gut and calories (Dr. P. Kapahi)
1/12/2017

The Chimp That Ate 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
Research to Clinical Development: Bench to Bedside

Alzheimer’s Drug Development Network
Varghese John, Ph.D., and Dale E. Bredesen, M.D.

Research & Target ID
Team
Johnson
Clare
Ram
Alexander
Sonia
Darci
Mike

Screening
Team
Olivier: Alpha
Lisa: Assays
& Compound Libraries
(FDA & CNS focused)

PK/PD Chronic Efficacy
Team
Patricia
Karen
Olivia
Alex
Sylvia
IAS

Analoging
Team
Barbara
Davos

ADME-TOX Regulatory “Candidate”
Team
Mahta
Remy
Stelios
Clinical Consult.
CEREB

Clinical Development

IND
Phase 1, etc.

Screening for Novel Therapeutics
Drugs: maybe the dessert; not the entrée

Crack Cookies

Made with love and crack
(but mostly crack)

[signature]

(crack = oatmeal, chocolate and cherry)

Placeholder for taking down 3-4 holes and showing what they are.
New insights: “Field of Seem”

- It seems that, although neurodegenerative pathologically, Alzheimer’s disease is largely driven metabolically, which may bode well for successful intervention.

- It seems that the origin of prions may reside in biological signal amplification, and that such amplification loops may underlie the neurodegenerative process.

- It seems that “aggregation” may arise from amplification of signal, and “misfolding” may result from alternative structures.

- It seems that many chronic illnesses, such as AD, ASCVD, osteoporosis, and cancer, may result from chronic imbalances in physiological signaling, amplified by anti-homeostatic signaling (i.e., molecular switches such as APP).
New insights: “Field of Seems” (2)

• It seems that Alzheimer’s disease features a network imbalance that impacts plasticity, arguing for multiple targets that should be engaged simultaneously.

• It seems that our current clinical trials—monotherapeutic, one-size-fits-all, expensive, and lengthy—may be appropriately complemented by trials that are polytherapeutic, multi-modal, personalized, and rapid.

• It seems that it may be advantageous to combine western, mechanistic approaches with eastern, combinatorial approaches to therapy.

OK, how about those 36 holes?

• Homocysteine
• Vitamin B12
• Vitamin D
• Sleep! (Timing, melatonin, autophagy, opening clearance, sleep apnea)
• Copper/Zinc ratio
• Diet!
• CRP, A/G ratio
• Estradiol, testosterone, pregnenolone, progesterone, cortisol (and kittens)
• Free T3, free T4, TSH, RT3
• Hemoglobin A1c, fasting insulin, GTT insulin (ketones)
• 23&Me; ApoE4; PiB scan, Neurotrack, MemTrax, MoCA
• Exercise and BDNF
Women at the epicenter of the epidemic

- 65% of patients
- 60% of caregivers
- More common than breast cancer
OK, let’s talk about those 36 holes...

- Systems Therapeutics (and U.S. case)
- F03
- Synaptik (multiple network-specific components)
- Computer-based assessment and memory training
- Sleep enhancement
- Exercise-induced BDNF increase
- AD-specific diet

First clinical trial is set for 2013

Developing treatment and prevention for AD: like playing chess with the devil.
ApoE4 and plasticity ratio

State of Confusion
CFN case (have testimonials??)

Phenoprinting
The Chimp That Killed the Rhino
Evolution, Shortevity, Alzheimer’s, and the God Gene
Alzheimer’s Disease: The facts and figures

There are **5.4 million people** with Alzheimer’s in the U.S.; this number will exceed 13 million by 2050.

Every 68 seconds someone is diagnosed with AD.

AD costs the U.S. **over $180 billion** annually.

No truly effective Rx has been developed for AD.

While many diseases are on the decline, **AD is on the rise**.

---

Diversity of Dependence Receptors

- **p75NTR**
- **DCC**
- **UNC5Hs**
- **Integrins**
- **RET**
- **Chopper**
- **D412**
- **D1290**
- **ZU-5**
- **(D1185)**
- **D707**
- **D1212**
- **D1392**

- Immunoglobulin-like domain
- Thrombospondin type I-like domain
- Fibronectin-like domain
- Death domain
- Cysteine-rich domain
- Tyrosine kinase domain
- PolyQ repeat
- DNA-binding site
- Hormone-binding site
A small set of genes is associated with the appearance of hominids 5-7 million years ago.

Prominent among these are pro-inflammatory genes.

ApoE has 3 alleles: ApoE2, 3, and 4. ApoE4 is primordial.

ApoE3 did not appear until 220,000 years ago, and ApoE2 not until 80,000 years ago.

ApoE4 pro-inflammatory effect allowed us to come down from the trees, roam the savannah, eat raw meat, fight.

Antagonistic pleiotropy, longevity, ApoE4.
The Key: Memory Maintenance and AD Prevention

- Network of abnormalities (36 mechanisms)
- Systems Therapeutics
- Supplement combination
- Specific herb combination
- Sleep optimization
- Additional systems components

The first systems therapeutics clinical trial

- Systems Therapeutics
- F03
- 20 additional components
- Computer-based assessment and memory training
- Sleep enhancement
- Exercise-induced BDNF increase
- AD-specific diet
Alzheimer’s Drug Discovery Network (ADDN) Includes:

- **Disease models**: B254, B21, J20, J9, I5, M631L
- **Assays**: AlphaLisa, APPneo, sAPPα, sAPPβ, p-tau, Aβ42, etc.
- **Network of scientists and consultants** with expertise in medicinal chemistry, neuroscience, neurology, screening, animal models, behavioral science, pre-clinical development, clinical trials
- **Intellectual property** regarding novel therapeutics for AD
- **25 years of experience** with programmed cell death and neurodegeneration; 20 years of experience with drug development for AD
- **Pipeline** for additional drug development and optimization
Disease models B254, B21, J20, J9, I5, M631L

Assays: AlphaLISA, APPneo, sAPPα, sAPPβ, p-tau, Aβ42, etc.

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Pipeline for additional therapeutic development and optimization

25 years of experience with programmed cell death and neurodegeneration; 20 years of experience with drug development for AD

**ASBI (APP-specific BACE inhibitors)**

Mechanism of ASBI inhibitors of BACE-APP cleavage
Alzheimer’s Disease (AD) Therapeutic Landscape

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

**PHASE 3**
- Solanezumab
- ELND005
- Bapineuzumab
- Valproate
- Alzemed
- Antioxidant
- Semagacestat
- Statins
- Flurizan
- Dimebon
- Rosiglitazone
- EGCG
- Phenserine

**PHASE 2**
- PBT2
- AL-108
- N1C5.15
- PF04360365
- Bryostatin-1
- Nicotinamide
- EHT-0202
- NP12
- ACC001
- SM3708163
- Lithium
- AN1792
- ABT089
- NFG
- CAD106
- AZD3480
- SB742457
- PRX03140
- PUFA
- PF-04447943

**PHASE 1**
- GSK933776
- MABT5102A
- UB311
- R1450
- V950
- E2012
- MK0752
- CHF5074
- CTS21166

*Clinical Trial in AD terminated*

---

**Cognitive protection and optimization**

- **Need for prevention of dementia.**
- **Increased recognition and assessment of early changes.**
- **Major concern of aging individuals.**
- **Increased understanding of underlying mechanisms.**
Cognitive protection and optimization: competition

- Brainstrong, Neuro Optimizer, Memoractiv, Ginkgo Smart, Procera AVH, etc.

- Most have one or a few components.

- All fail to address critical mechanisms of cognitive decline.

- Assumption that antioxidants are always helpful, ignoring recent data.

Origination of Synaptik

- Goal: to address all 36 mechanisms underlying age-associated cognitive decline.

- Two indications:
  - Prevention.
  - With AD and MCI drugs, for optimization of drug effects.

- GRAS components.

- Cost effective.

- IP filed.

- Freedom to operate evaluated.

- Trial for 2012.
Galangin

A

![Graph A]

B

![Graph B]
ASBI and BACE inhibitors

- Using FDA library find a target gene product
- Validate activity in primary neuronal
- Obtain analog and subtype information
- In vivo validation of analogs & target
- In vivo validation of analogs & target - could lead to IND
- Biochemical validation of target - can lead to larger screening & analoging

Plate with phenotype cells

Add one clinical compound per well

Select compound that inhibits phenotype & further evaluate protein target for compound

Using a panel of analogs of target class identify subtype that inhibits phenotype
Rationale for comprehensive therapeutic trial

- New pathogenetic insights: depR-based, prionic, molec. switch
- Compare HIV results
- Modest results from many mono-therapeutics
- No precedent for comprehensive therapy for AD
- Analogy to cancer, osteoporosis, atherosclerosis
- Failure of therapeutic trials to date
- Prevention, early Rx, later Rx
**Prionic loops and anti-prions**

APP + Aβ → 2Aβ + sAPPβ + Jcasp + C31

![Graph showing Total Abeta 1-42](image)

**Novel prions and anti-prions**

APP + Aβ → 2Aβ + sAPPβ + Jcasp + C31

(“4 Horsemen”)

APP + Netrin-1 → sAPPα + αCTF

(“Alpha Couple”)


Dependence Receptors as Molecular Switches

Rationale for comprehensive therapeutic trial
Rationale for comprehensive therapeutic trial

“Switching drug:” F03 in vivo

APP species (% Control)

<table>
<thead>
<tr>
<th></th>
<th>sAPPalpha raw</th>
<th>Abeta 42 MG</th>
<th>APPneo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>140 ± 10</td>
<td>40 ± 2</td>
<td>100 ± 5</td>
</tr>
</tbody>
</table>

Appropriate bar chart with error bars representing data for each condition.
Optimizing Your Brain
Dale Bredesen, MD