# Cognitive Health: Dawn of the era of treatable Alzheimer's disease

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### "There is nothing that will prevent, reverse, or slow the progress of Alzheimer's disease."

# "Everyone knows someone who is a cancer survivor; no one knows an Alzheimer's survivor."

### "Shocking truths" from the research bench

- What is referred to as "Alzheimer's disease" is actually a protective response to 5 metabolic and toxic insults.
- For many people, "Alzheimer's disease" is not a disease—it is a programmatic downsizing of the neural plasticity network.
- "AD" is not a mysterious, untreatable brain disease—it is a reversible, metabolic/toxic, usually systemic illness with a relatively large window for treatment.
- With respect to treatment of AD, drugs are the dessert, not the entrée (and salad is the salad).
- There may be 500,000 Americans with "inhalational Alzheimer's disease" (IAD).
- For optimal responses, monotherapeutics should be replaced by programmatics.

# East Meets West





# patients in 2012 3<sup>rd</sup> leading cause (James, 2014) Pres. Obama and NAPA, 2011

# 160,000,000

# patients in 2050



# Cures

# Women at the epicenter of the epidemic

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

#### **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.

# Where is classical medicine headed?



#### **Alzheimer's Disease (AD) Therapeutic Landscape**



\* Clinical Trial in AD terminated

## "Game of Throwns" (243/244)



#### Why do neurons degenerate? A New View of Alzheimer's Disease



#### Cancer: imbalance in proliferation/survival vs. turnover



#### **Alzheimer's disease: imbalance in plasticity**



# Chronic illnesses as signaling imbalances

#### Osteoporosis:

Cancer:

#### Alzheimer's:







#### Synaptoblastic





#### Cytoclastic







# Synaptic element interdependence



# Trophic, Anti-AD

# Anti-trophic, Pro-AD



# A roof with 36 holes...







- 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 (<u>metabolic enhancement for</u> <u>neurodegeneration</u>).

- ApoE4 positive (heterozygote)
- FDG-PET scan typical of AD (temporoparietal reduced Glu)
- Neuropsych testing 2003, 2007, 2013
- Progressive loss: CVLT from 84%ile to 1%ile
- Unable to remember lock combination, faces, schedule
- Difficulty at work, and with numbers; Dx—early AD
- Improvement at 6 months: co-workers, schedule, faces, nos.
- Wife notes accelerated decline completely stopped.

#### Patient two

#### FDG-PET scan indicated a pattern typical of Alzheimer's disease

#### **Proof of Improvement on MEND**

71 yo E4/3	2013	2015 (MEND 2 yr)
CVLT-II B	<5%ile	>70%ile (3SD)
Total Recog Hits	<1%ile	>45%ile
CVLT-II	<60%ile	>90%ile
Auditory delayed memory	<20%ile	>75%ile
Reverse digit span	<25%ile	>70%ile
Processing speed*	<95%ile	>95%ile

#### 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

#### **Metabolism and Cognition Go Hand in Hand**

Association	Yes/No
ApoE4?	Yes (4/3)
Heterozygote?	
Homozygote?	
Homocysteine >7?	<mark>Yes</mark> (15.1)
Vitamin B12 < 500?	Yes (328)
CRP > 1.0?	<mark>Yes</mark> (9.9)
A/G ratio < 1.8?	Yes (1.6)
HgbA1c > 5.6?	HgbA1c 5.5
Fasting insulin > 6	Insulin 32
uIU?	
GTT insulin?	
Simple CHO in diet?	<mark>Yes</mark>
FBS > 90?	<mark>Yes</mark> (96)
Thyroid: TSH > 2.0?	<mark>Yes</mark> (2.21)
Free T3 < 3.2? RT3 >	<mark>Yes</mark> (2.4)
20?	
Free T4 < 1.3?	<mark>Yes</mark> (0.8)
Sleep	No
apnea/hypopnea?	
Low androgen? Total	<mark>Yes</mark> (264)
T < 500? Free T < 6.5?	<mark>Yes</mark> (41, 4.1)
Low estradiol? Post-	NA
menopausal?	
E2<100? E2:P >300?	
Hysterectomy at <41	
y.o.?	-
Low pregnenolone?	Pd.
<20?	
Vitamin D < 30?	Yes (21)
History of head	No
trauma? LOC?	
Diabetes?	No, but insulin
NY	resistant
Neuroactive	NO
medications? which?	N
History of illicit drug	NO
use?	
Metabolic syndrome?	res (TG, BP, glu,
Chalastenal 2252 (	Insulinj
1502	res
15U:	Vaa
ADHORMAI HDL:LDL	res
	NIA
Post-menopausal?	INA

66M ApoE4/3	2014	2015 (MEND 10 mos.)
Fasting insulin	32	8
Hs-CRP	9.9	3
Homocysteine	15	8
Vitamin D3	21	40
Symptoms	Struggling	Working full-time
MRI hippocampal volume	<25%ile	>70%ile

### Alzheimer's disease: not one illness

- Presymptomatic vs. SCI vs. MCI vs. AD.
- Several different metabolic syndromes are called "Alzheimer's disease:"
- Type 1: Inflammatory ("Hot")
- Type 2: Atrophic ("Cold")
- (Type 1.5: Glycotoxic ("Sweet" combines 1 and 2))
- Type 3: Toxic ("Vile")—a fundamentally different problem.
- Type 4: Vascular ("Pale")
- Type 5: Traumatic ("Dazed")

#### **The Chimp That Killed the Rhino** Evolution, Shortgevity, Alzheimer's, and the God Gene



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



### ApoE4 Domain Interaction Effect of Position 112 on Structure



# **ApoE4**—new mechanism



#### **ApoE4-promoter interactions by ChIP-Seq**



#### **Improvement on MEND**

55F ApoE4/4	2015	2016 (MEND 5 mos.)
Neurocognitive index	<20%ile	>70%ile
Composite memory	<5%ile	>50%ile
Verbal memory	<5%ile	>>50%ile
Processing speed	<40%ile	>>50%ile
Executive function	<20%ile	>50%ile
Cognitive flexibility	<20%ile	>50%ile

## **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." --- Margaret Mead