ReCODE Protocol: Reversal of Cognitive Decline

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Financial disclosures and off-label use

- **Consultant: Apollo Health, LifeSeasons.**

- **Off-label use: none.**

Learning objectives

- **Learn to evaluate, prevent, and treat cognitive decline associated with Alzheimer's disease and pre-Alzheimer's conditions (SCI, MCI).**

- **Learn subtypes of Alzheimer's disease.**

THE TIMES | Thursday April 4 2019

Concorde pilot 'took own life after killing his wife'

David Brown Chief News Correspondent
Harry Shukman

A pioneering Concorde pilot is believed to have murdered his wife of 61 years before killing himself, having struggled to cope with her worsening dementia.

Tony Meadows and his wife Paula, both 84, were found dead on Tuesday evening at their sprawling farmhouse near the Duchess of Cambridge's home village. Police said they were treating the deaths as a murder and suicide.

The couple, who had three children, had lived at their home near Bucklebury, Berkshire, for more than 30 years. Mr Meadows, an RAF veteran, had been a captain with British Airways and was co-pilot on the inaugural Concorde flight from Heathrow to New York in December 1977. He flew the Queen and the Duke of Edinburgh to Kuwait at the start of a tour of the Middle East in 1979.

Jock Lowe, a fellow pilot, said Mr Meadows had discussed his concerns about his wife's health last month when they sat next to each other at an annual meeting of Concorde pilots at the RAF Club in London.

"He told me that his wife was very ill and it was certainly playing on his mind a bit," Mr Lowe said. "He said it was hard work, her being ill. I assumed it was dementia. It was clearly troublesome for him. Paula was a wonderful woman with a very

the Duchess of Cambridge's parents, Carole and Michael Middleton, who have both worked for British Airways.

The Meadowses' next-door neighbours for the past 13 years have been Robin and Claudia Ranken. Mrs Ranken's daughter, Anneke von Trotha Taylor, was married in 2014 to Charlie Gilkes, a close friend of Prince Harry. The prince attended the wedding in Italy along with the Duchess of Cambridge's sister, Pippa Middleton.

Another neighbour, who did not want to be named, said: "Paula had dementia. Tony was looking after her extremely well and that was no doubt a strain for him. He was a lovely chap, very friendly and with a great sense of humour." Bob Smith, 38, a builder from Bucklebury who had worked on the Meadows property, said: "Tony was full of beans. I think she [Paula] wasn't all right, she would walk around in her nightie."

A villager, Erica Tipton, 77, said: "They lived a long time in the village. He was keen on rare sheep, which he kept, and very supportive of the community. They were active but I haven't seen them at anything recently."

Another villager said: "It is so sad. Dementia is a terrible thing. Tony was coping so well with Paula's disease but it obviously just became too much for him in the end."

A friend of the family said she saw the

This is a story about much more than Alzheimer's…

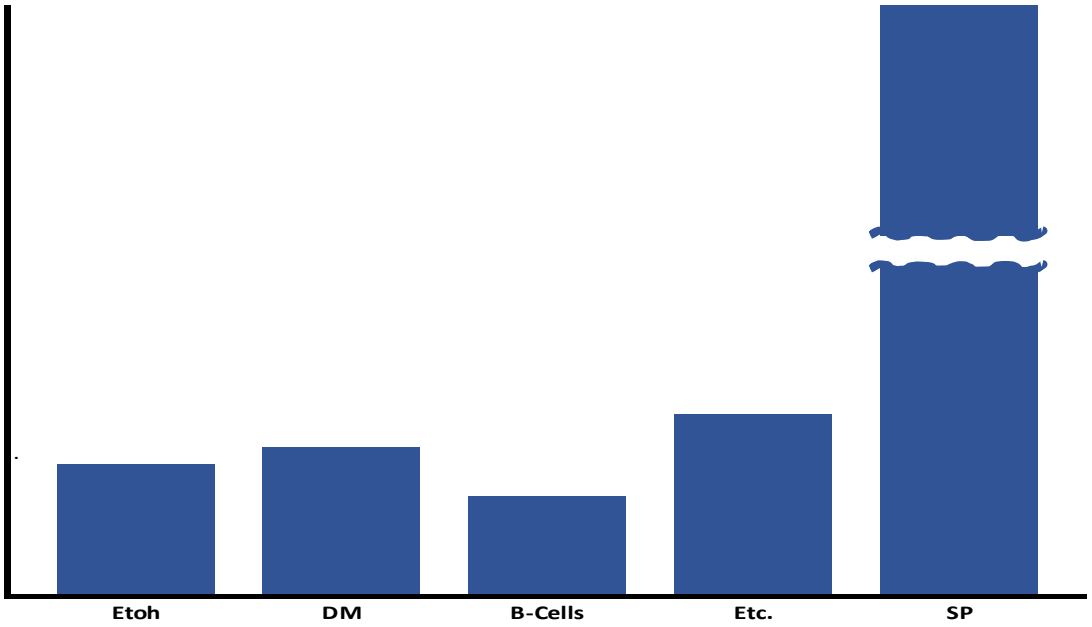
Alzheimer's: A Sad State of Affairs

•**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.

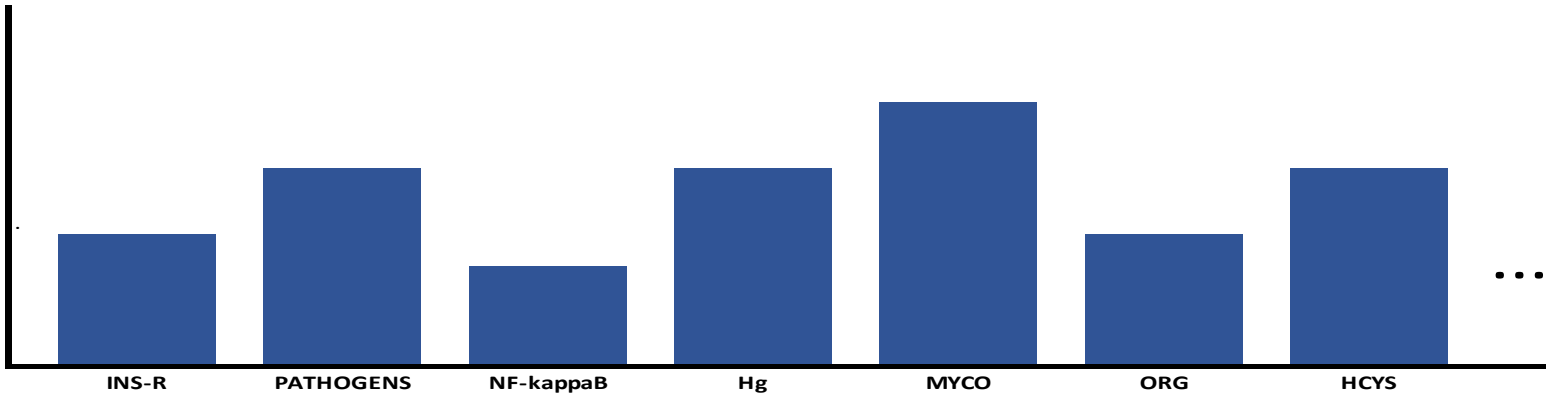
•**PRIMARY CARE PROVIDERS** often do not refer, since they realize that there is no truly effective therapy. Therefore, they typically simply start donepezil (Aricept), often without a firm diagnosis.

•**SPECIALISTS** often put the patients through hours of neuropsychological testing, expensive imaging, lumbar punctures, and then have little or nothing to offer therapeutically.

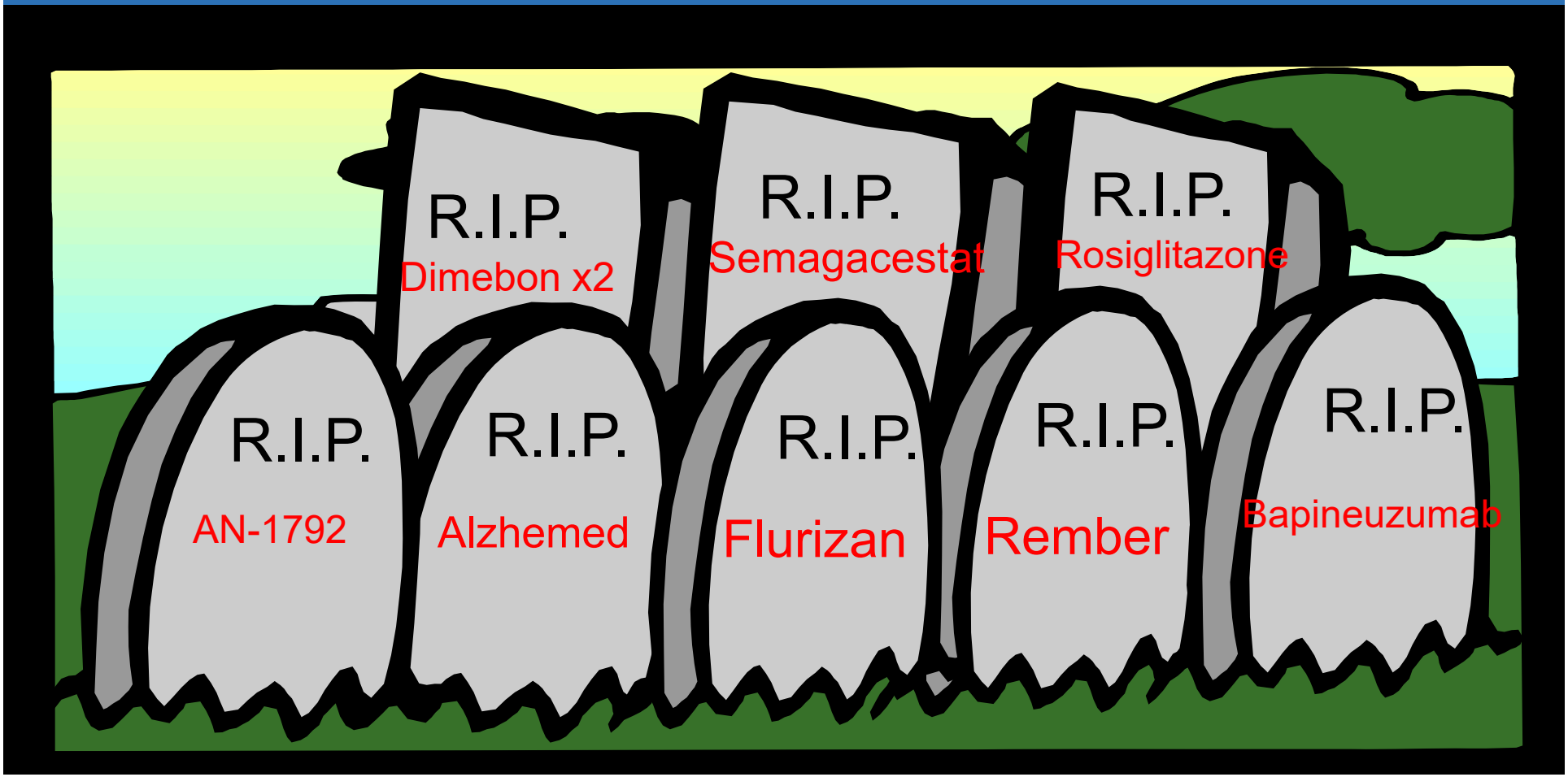
Simple illness: e.g., pneumococcal pneumonia



Complex illness: e.g., Alzheimer's disease



“Game of Throwns” (243/244)

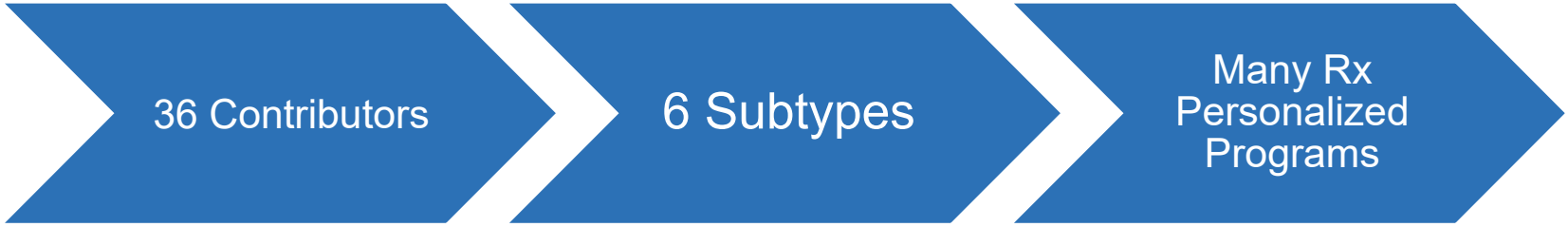


PARADIGM SHIFT

CURRENT STANDARD OF CARE

CURRENT STANDARD:

RESEARCH FINDINGS:



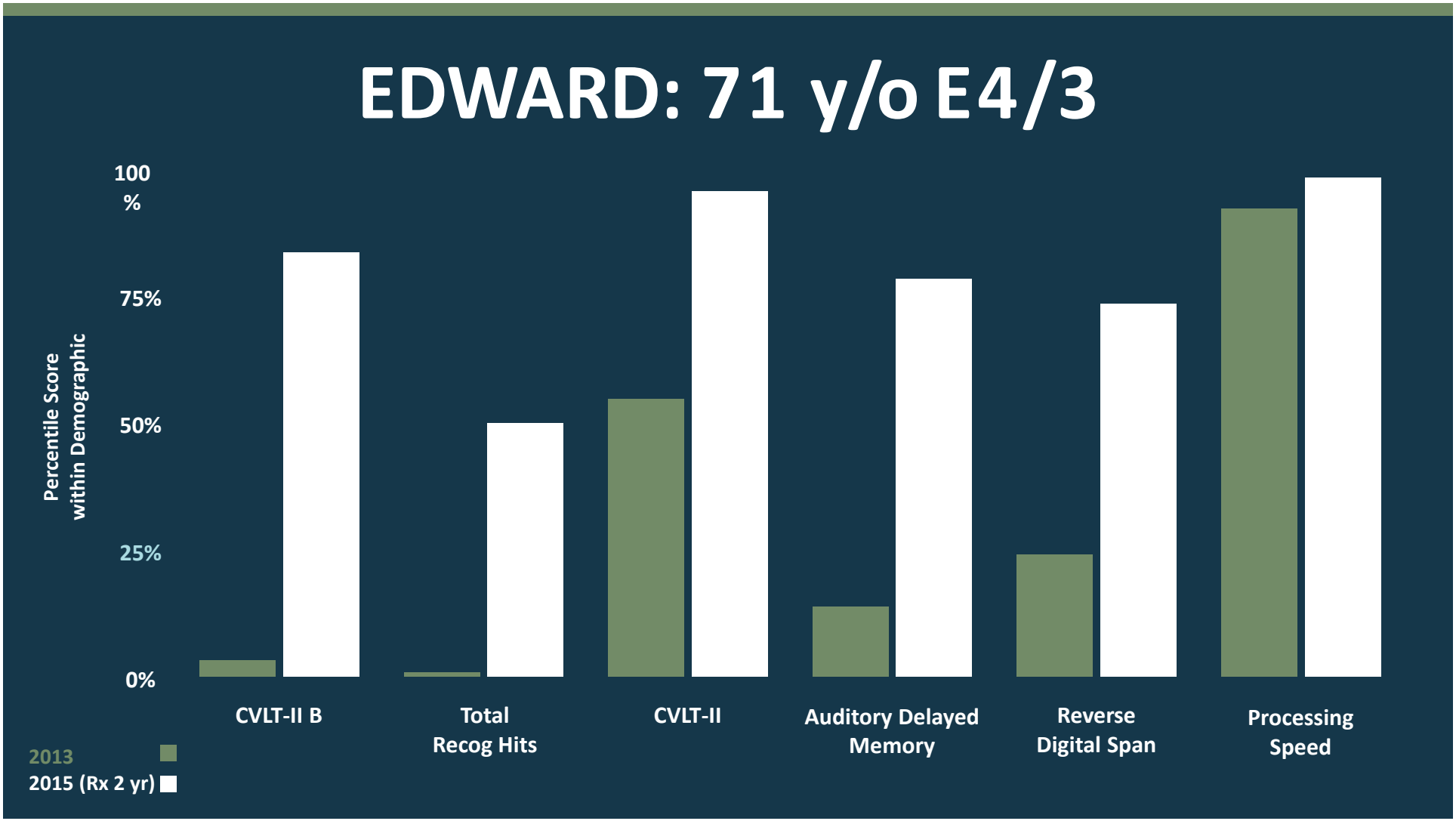
The perfect Alzheimer's drug would:

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.

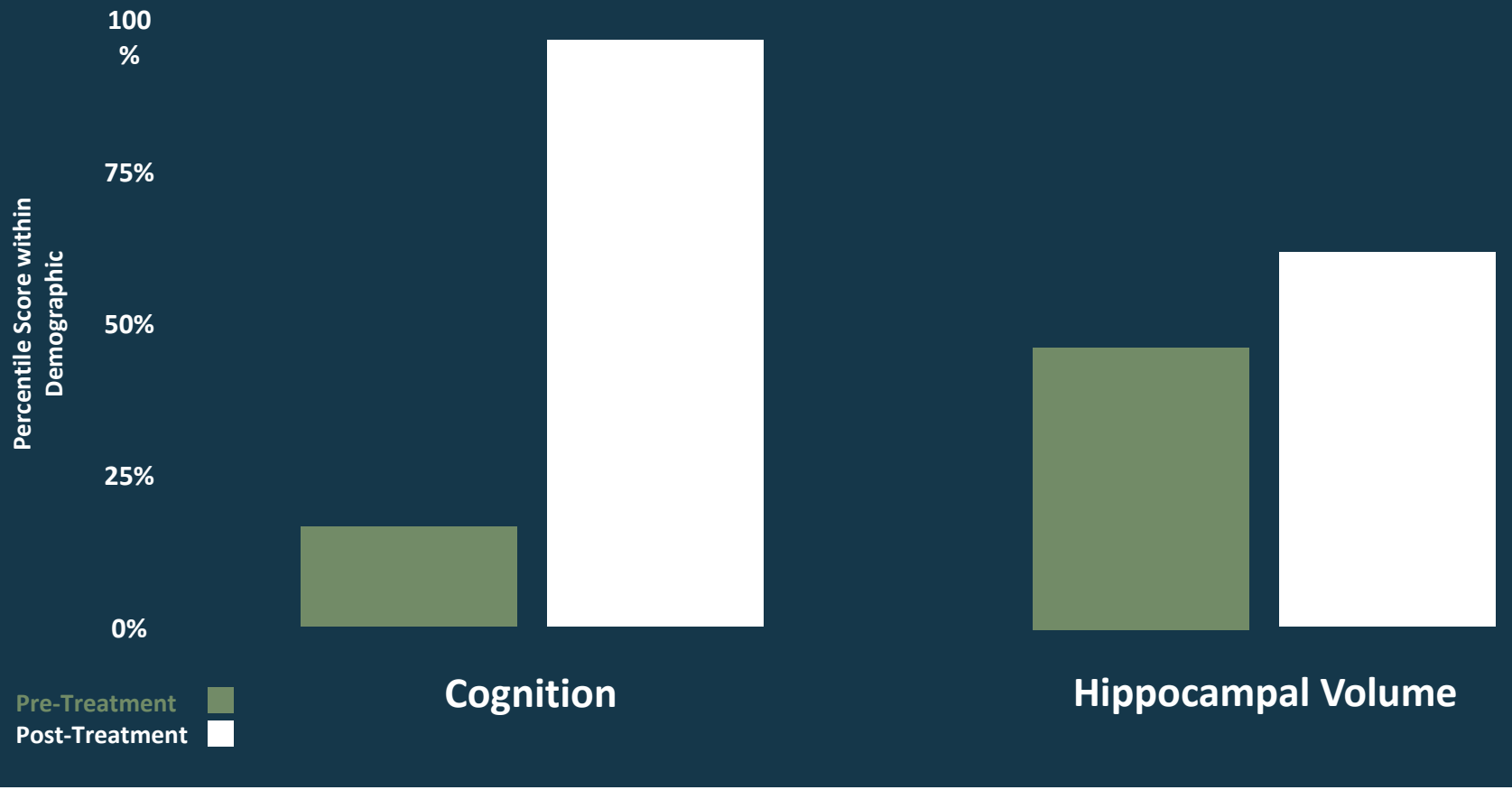
Patient Zero follow-up (2012-2020)

- 75 years old.
- Working without problems.
- Went off protocol 4x; each time, experienced decline within 7-10 days.

EDWARD: 71 y/o E4/3



MARCY: 74 y/o with AD



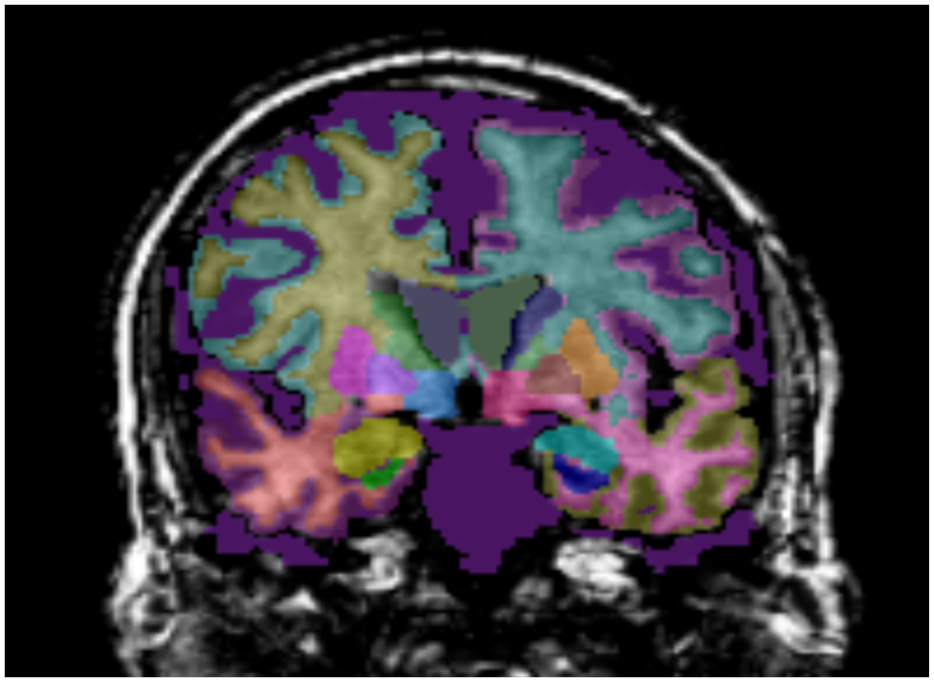
66 yo man with “senior moments”

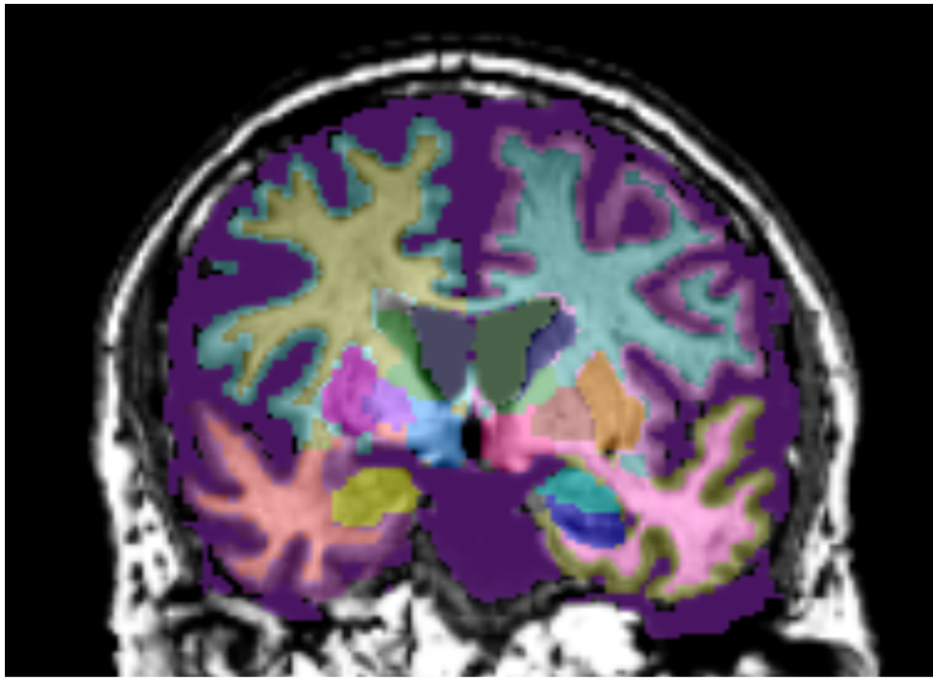
- **Family history+ in both parents.**
- **ApoE3/4, amyloid PET markedly positive, FDG-PET typical for AD, hippocampal volume reduced, neuropsych testing MCI.**
- **Hs-CRP 9.9.**
- **Homocysteine 15.1.**
- **Vitamin D 21.**
- **Testosterone 264, free T3 2.4, TSH 2.21.**
- **Responded metabolically, cognitively, and volumetrically to ReCODE. Neurologist said he is now “normal.”**

Metabolism and Cognition Go Hand in Hand

66M ApoE4/3	2014	2015 (Rx 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	17%ile	75%ile

Increase in gray matter volume with treatment





BEFORE: Gray Matter Volume = 419.5 cc

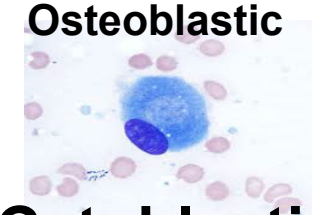
AFTER: Gray Matter Volume = 531.5 cc

23%

Chronic illnesses as signaling imbalances

Osteoporosis:

Osteoblastic



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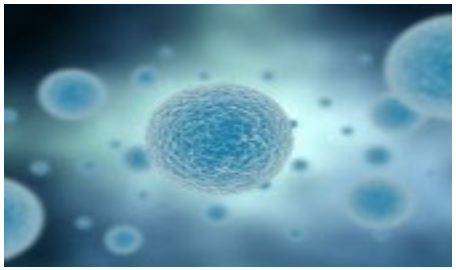
Osteoclastic

Cancer:

Cytoblastic



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Cytoclastic

Alzheimer's:

Synaptoblastic

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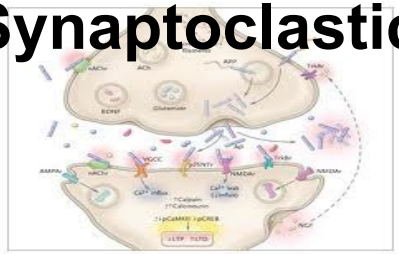
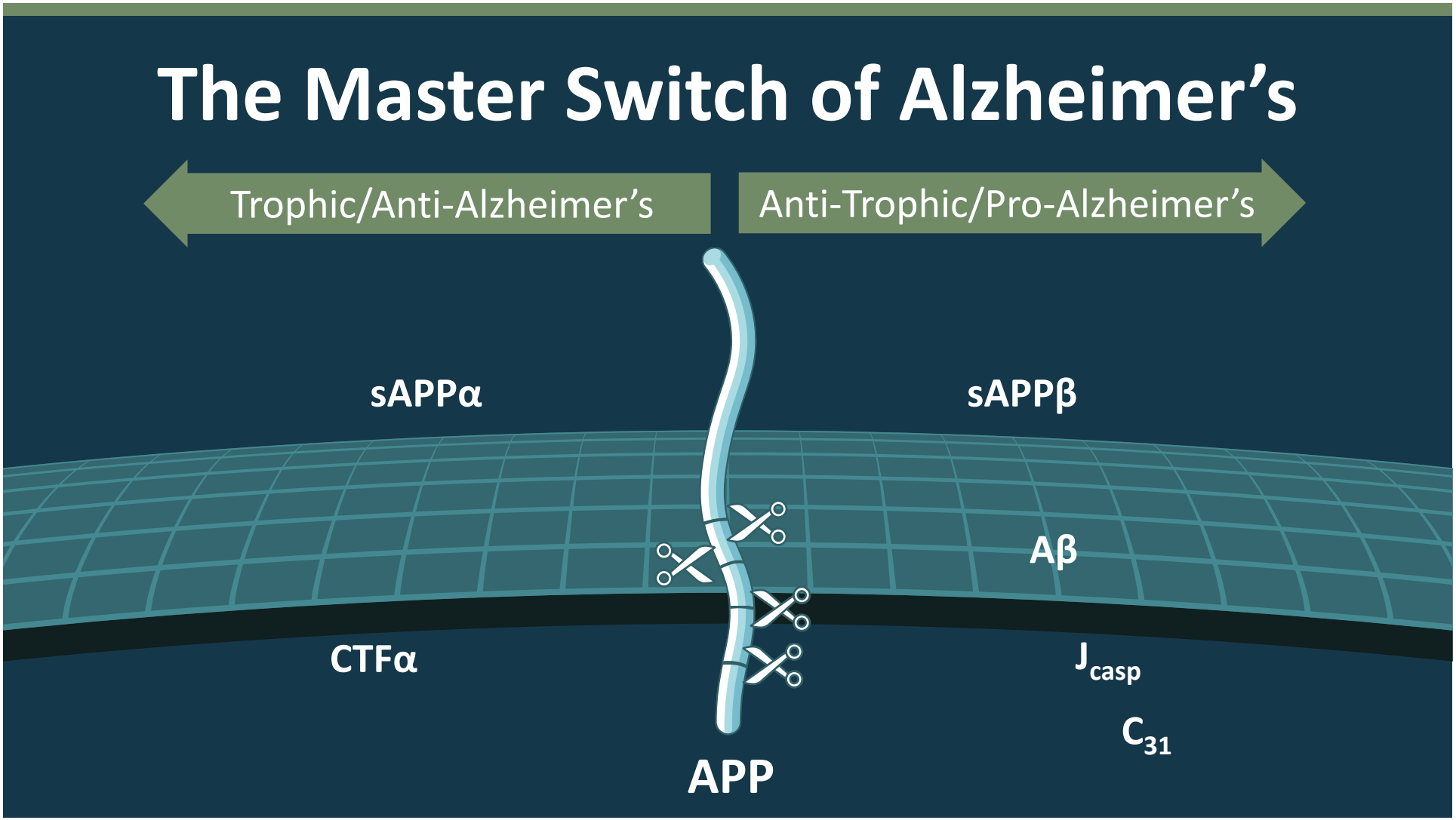
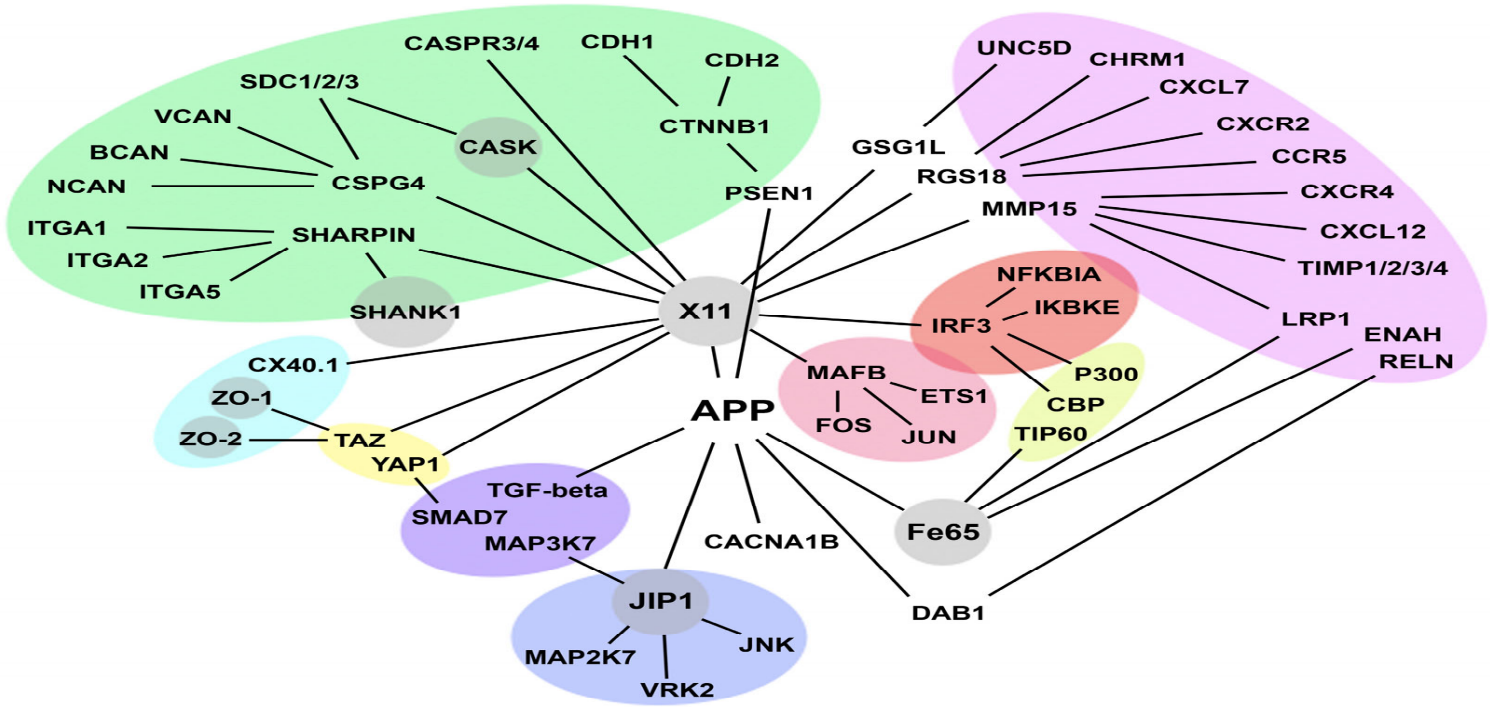
Synaptoclastic




The Master Switch of Alzheimer's
Trophic/Anti-Alzheimer's
Anti-Trophic/Pro-Alzheimer's
sAPPα
sAPPβ
Aβ
CTFα
J_{casp}
C_{31}
APP

The APP Interactome



- Recognition and coupling of extracellular environment to the cytoskeleton and intracellular signaling - slow remodeling/recycling
- Proliferation-and-migration: pathfinding, ECM remodeling, autocrine/paracrine signaling - fast remodeling/recycling
- The Hippo pathway: adhesions-to-nucleus signaling and EMT control
- Specialized cell junctions/synapses
- Stress-activated signaling
- TGF-beta signaling
- Scaffolds
- Histone acetylation and regulation of transcription
- Proto-oncogene signaling
- Inflammation and immune response; NF-kB signaling

A roof with 36 holes? Or ARLS?

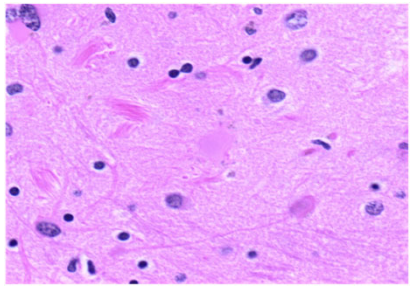
ARLS (Ascending Rate-Limiting Steps)

The 21st-century physician

Canonical Alzheimer's disease

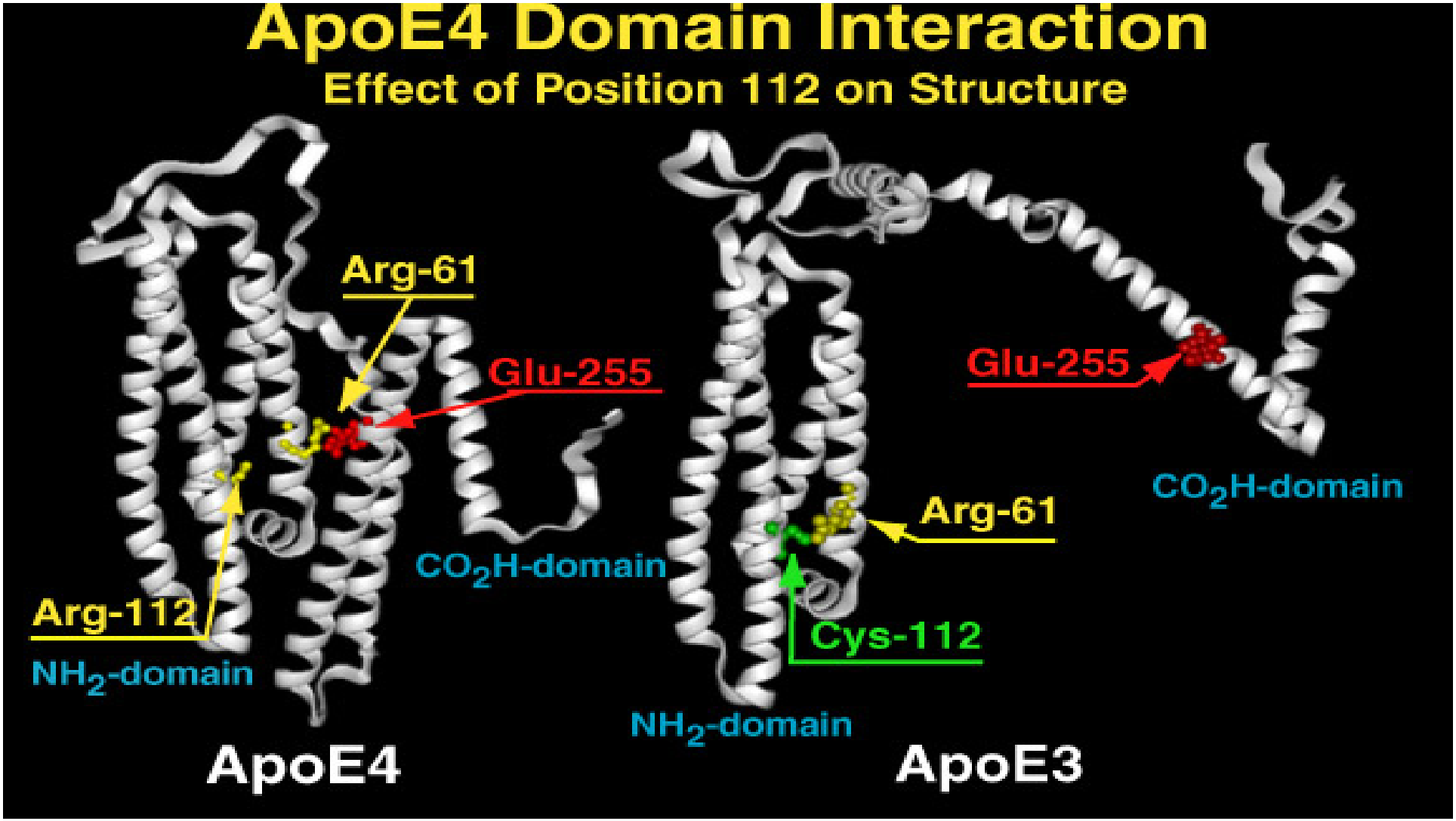
ApoE4 → ? → AD

(p-τ, Aβ, etc.)



The Chimp That Killed the Rhino

Evolution, Shortgevity, Alzheimer's, and the God Gene


ApoE4 Domain Interaction
Effect of Position 112 on Structure
Arg-61
Glu-255
CO_2H-domain
Arg-112
NH_2-domain
ApoE4
Glu-255
Arg-61
CO_2H-domain
Cys-112
NH_2-domain
ApoE3

The Chimp That Killed the Rhino

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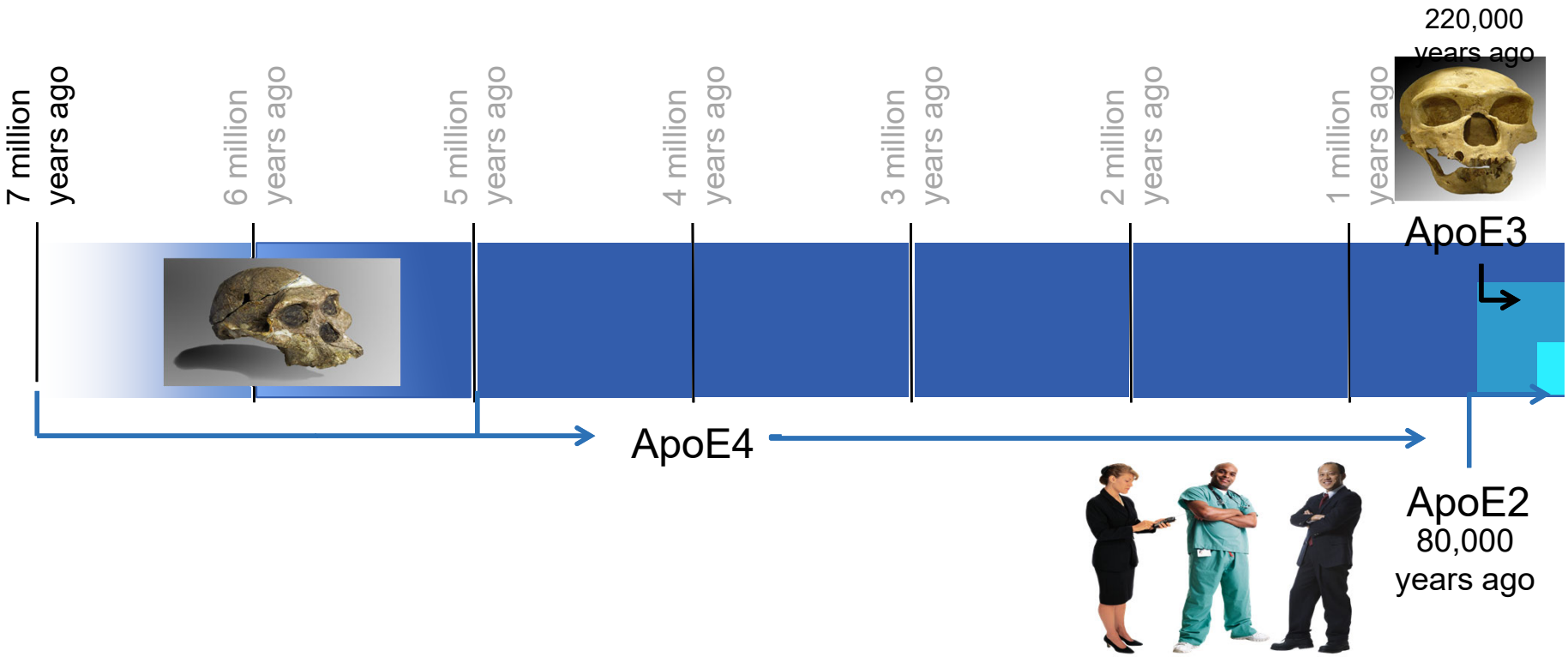
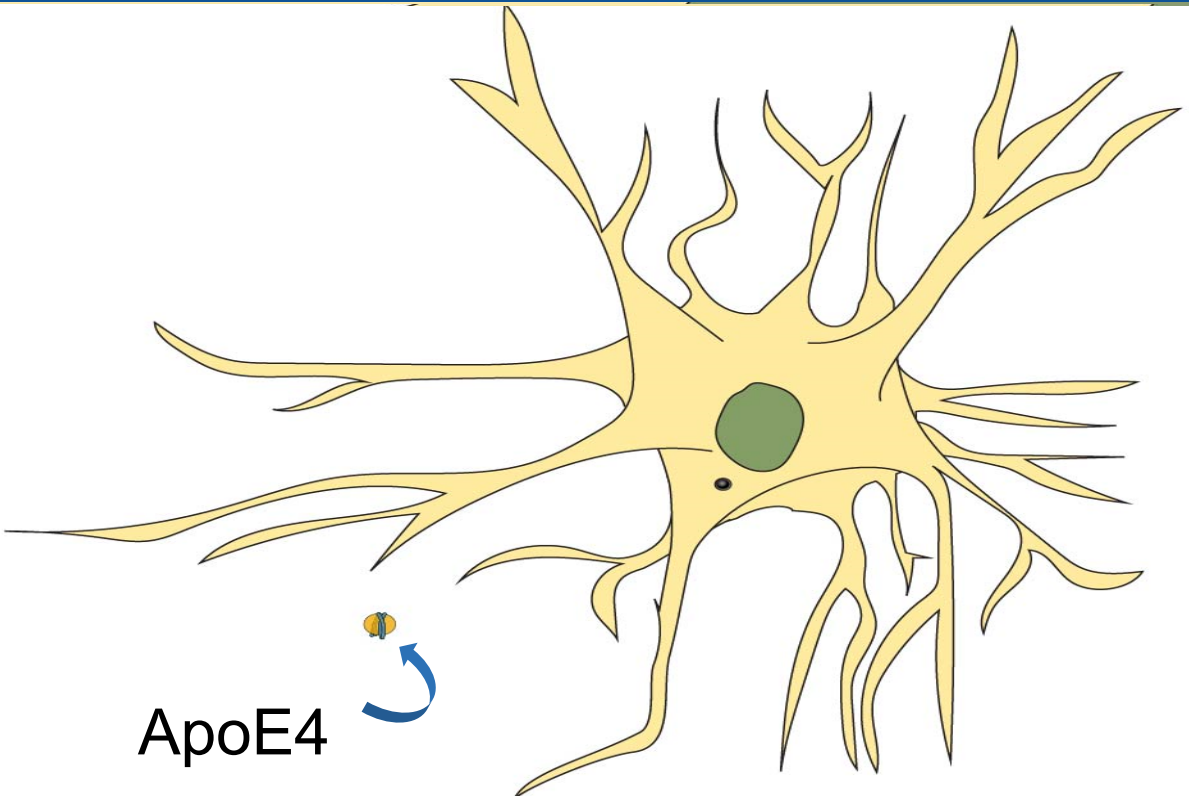
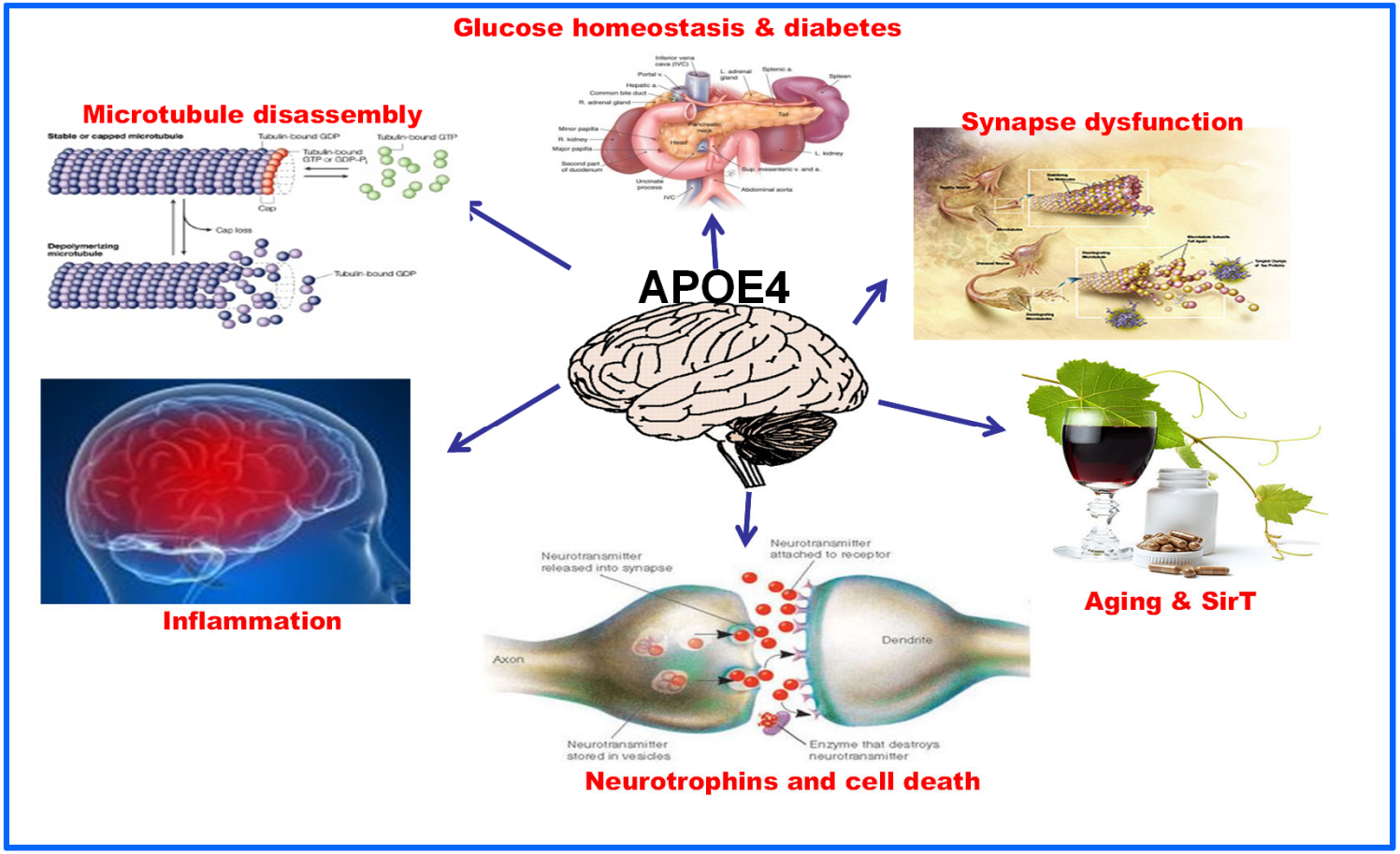


ApoE4—new mechanism

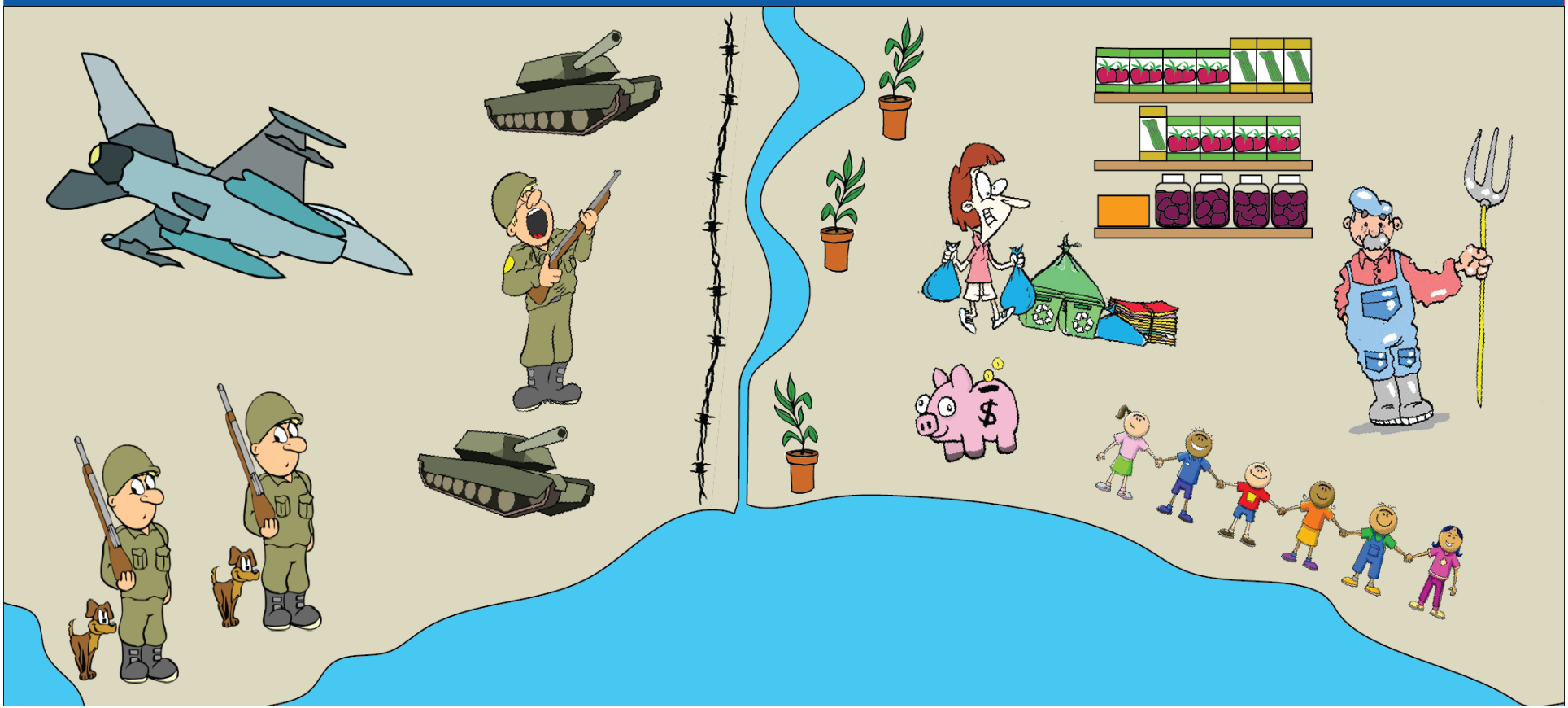


ApoE4-promoter interactions by ChIP-Seq



ApoE4:
RelA dominant

ApoE3:
SirT1 dominant



Standard of care vs. 21st century: standard

- Wait for symptoms to appear.
- Go to doctor; 10’; limited by system; passive; involvement of patient seen as interference.
- Tiny data set: sodium, potassium, etc. No algorithm or computation.
- Monotherapeutic with minimal effect.
- Unable to purchase long-term care insurance.
- Progress to nursing home; high expense.
- Destroy family’s finances.
- Die destitute.

Standard of care vs. 21st century: 21st century

- Active prevention, reversal, optimization.
- Central coordination of evaluation, program, social networking, insurance, neuroceuticals.
- Expert systems, larger data sets, closing complexity gap.
- Active insurance—dementia, then other chronic conditions, aging, general health.
- Continued optimization.
- Reduce global burden of dementia—a trillion-dollar effect.
- Combine the failure of the current system, the available and evolving programs, the increased data sets, and the programmatic approach to Rx, with the lever arm of the first reversals of cognitive decline, to establish superior model.

How to reverse cognitive decline in Alzheimer's

- **First determine what stage:**
- **Presymptomatic phase of disease (pathology +).**
- **SCI: subjective changes, cognitive tests "normal." May last a decade.**
- **MCI: subjective changes plus abnormal cognitive testing; ADLs unaffected. 5-10% convert to AD per year.**
- **AD: ADLs affected.**
- **Next, determine what subtype:**
- **Type 1: inflammatory ("hot").**
- **Type 2: atrophic ("cold").**
- **Type 1.5: glycotoxic ("sweet").**
- **Type 3: toxic ("vile").**
- **Type 4: vascular ("pale").**
- **Type 5: traumatic ("dazed").**

Goals of Treatment and Prevention

- **Energetics: ketosis (1.0-4.0 mM BHB or >7 ACEs), cerebral blood flow, oxygenation.**
- **Insulin sensitivity.**
- **Trophic support: growth factors, hormones, nutrients.**
- **Resolution of inflammation and prevention of further inflammation.**
- **Treatment of pathogens, optimization of microbiomes.**
- **Detoxification.**
- **Stimulation: light or magnetic stimulation, brain training.**
- **Improve adaptive immune system, reduce innate (inflamm).**
- **Reduce amyloid-beta.**
- **Regeneration, synaptogenesis.**

ReCODE Mobile App

- App Feature List
  - Integration with FitBit, Oura Ring, Apple Watch, Ketone Breathalyzer, and more…
  - Snapshot of daily and weekly progress.
  - Push notifications to keep participant on track and engaged.
  - Access to procured content and guides specific to the protocol.
  - Live forums for sharing and learning from fellow practitioners and participants.
  - Access to reports, history as well as results tracking of all other cognitive assessments.
  - Access to participant care teams.

How can we achieve these biochemical goals?

- **Energetics: ketosis (1.0-4.0 mM BHB or >7 ACEs), cerebral blood flow, oxygenation.**
- **→Endogenous or exogenous ketosis (ketone salts or esters? KE1?); KetoFLEX 12/3, exercise (Kaatsu, EWOT, strength training), sleep, stress reduction.**
- **→Cerebral blood flow: EWOT, optimize vascularity, minimize inflammation, nitric oxide, ginkgo, vinpocetine; if thrombotic tendency (by genomics or history), consider pycnogenol and nattokinase.**
- **→Oxygenation: nocturnal (SpO2 = 96-98%), diurnal (EWOT).**
- **→Mitochondrial support: ubiquinol, nicotinamide riboside, PQQ, ketones; methylene blue?**

How can we achieve these biochemical goals?

- **Insulin sensitivity (flip IRS-1 phosphorylation from S/T to Y):**
- **→KetoFLEX 12/3 diet: plant rich, high fiber, meat (grass-fed beef, pastured chicken) and fish (wild caught SMASH) optional, high choline, 12/3 fasting, high-good-fat, intermediate protein, low carbohydrate.**
- **→Strength training (muscle rich in insulin receptors).**
- **→Many options for support: Mg, Zn, vitamin D, chromium picolinate, Ceylon cinnamon, R-lipoic acid, berberine (vs. Metformin), NAC, bitter melon.**
- **→Pharmaceuticals such as Januvia or Victoza.**

How can we achieve these biochemical goals?

- **Trophic support:**
- **→Growth factors such as BDNF and NGF: WCFE, ALCAR, Hericium erinaceus, exercise, thymosin beta-4, cerebrolysin?, intranasal trophic factors (e.g., VIP, insulin, NGF, etc.).**
- **→Optimal hormones: estradiol, progesterone, testosterone, pregnenolone, DHEA, thyroid, cortisol, etc.**
- **→Optimal nutrients (cf. Dr. Paul Clayton re nutrients): vitamin B12, vitamin D, choline, omega-3, etc.**

How can we achieve these biochemical goals?

- **Resolution of inflammation and prevention of further inflammation:**
- **→Specialized pro-resolving mediators.**
- **→Anti-inflammatories such as omega-3, curcumin, ginger, etc.**
- **→Identify and remove cause(s) of inflammation such as leaky gut, periodontitis ("leaky gums"), chronic sinusitis, mycotoxins, pathogens, and lack of sleep (quantity, quality, and timing).**

How can we achieve these biochemical goals?

- **Treatment of pathogens, optimization of microbiomes:**
- **→Check Oral DNA; Dentalcidin toothpaste and mouthwash? Oral probiotics such as Revitin.**
- **→Identify and treat chronic pathogens such as Borrelia, Bartonella, Babesia, Ehrlichia, Anaplasma, mold species.**
- **→Heal gut (DGL, bone broth, etc.); Saccharomyces boulardi? Probiotics and prebiotics.**

How can we achieve these biochemical goals?

- **Detoxification from metals (e.g., mercury) and other inorganics (e.g., air pollution), organics (e.g., toluene, glyphosate), and biotoxins (e.g., trichothecenes, gliotoxin):**
- **→Basics: high fiber, filtered water, sauna, sweating, non-toxic soap, NAC/liposomal glutathione, sulforaphane, ascorbate.**
- **→Targeted detox for identified toxins such as mercury (Brewer Protocol).**
- **→Shoemaker or Nathan Protocol for biotoxins.**

How can we achieve these biochemical goals?

- **Brain stimulation:**
- **→Brain training such as BrainHQ or Sudoku or musical instrument or crosswords, etc.**
- **→Light stimulation, optimal 40 Hz (e.g., Vielight) or defocused laser; or magnetic (e.g., MeRT).**
- **→Increase neurotransmission: choline, nootropics, cAMP, huperzine A, etc.**
- **Others also in development, such as 40 Hz sound, microcurrent voltage.**

How can we achieve these biochemical goals?

- **Immune optimization (cf. COVID-19 immune defects):**
- **→Reduce the inflammation associated with activation of the innate immune system, while enhancing the adaptive immune system.**
- **→SPM, omega-3, optimize omega-6:3 ratio, omega-3 index, or AA:EPA ratio.**
- **→Vitamins A, C, D; Zn, quercetin, beta-glucan, alpha-lipoic acid, etc. Consider AHCC, high-dose echinacea.**
- **→Remove source(s) of inflammation!**

How can we achieve these biochemical goals?

- **Reduce amyloid-β (component of innate immune system):**
- **→Curcumin, cat's claw, resveratrol, vitamin D, etc.**
- **→This is where the anti-amyloid antibodies, which have failed in trials as monotherapies to date, may be useful. Same for BACE inhibitors.**
- **→High polyphenol diet such as plant-rich, mildly ketogenic diet with fasting (e.g., KetoFLEX 12/3).**
- **→Remove source(s) of inflammation!**

How can we achieve these biochemical goals?

- **Regeneration:**
- **→Optimize growth factors, hormones, nutrients, oxygenation, blood flow, ketosis, metabolic flexibility, stimulation.**
- **→Consider stem cells—autologous (e.g., ADRC) or heterologous (e.g., cord blood-derived).**
- **→Intermittent fasting, some foods such as berries and crucifers, sleep, exercise, senolytics such as quercetin.**
- **→Remove source(s) of inflammation and toxins!**

The EvantheaTrial

BUCK INSTITUTE FOR RESEARCH ON AGING

Drs. Ann Hathaway, Kat Toups, Deborah Gordon

- **First trial in which, instead of pre-determining a treatment, contributors are identified and targeted.**
- **Small, proof-of-concept "pre-trial" with 30 patients.**
- **Evanthea Foundation support; QuesGen CRO.**
- **Compares ReCODE protocol to historical outcomes from standard of care.**
- **Evaluations seek to identify contributors to cognitive decline: pathogens, toxins, genetics, nutrients/trophins/ hormones, immune response, etc.**

Troubleshooting

“I am not getting better—why?”

- How long on the protocol? Slow decline, stop decline, minor improvements, major improvements.
- How well documented is the problem? AD-related?
- Have the suboptimal lab values been optimized?
- Has mild ketosis been achieved? Good fats-based diet?
- How advanced was the process on presentation?
- Most common cause is lack of compliance; health coach?
- 2nd most common cause is type 3 AD.
- “Can’t be bothered syndrome.”

“I am not getting better—why?” (cont’d)

- Need a CIRS consultant?
- Undiagnosed sleep apnea?
- Regular brain training?
- Doing supplements only?
- Key is to exceed threshold; if not, keep tweaking.
- Continued exposure?
- Are the major underlying causes—inflammation, trophic withdrawal, insulin resistance, and toxic exposure—all addressed optimally?
- Behavior, purpose, joy, stress reduction.

Specific reasons for failure to improve

- **Failure to identify the various contributors to cognitive decline, such as organic toxins, tick-borne illnesses, or vascular insufficiency.**
- **Reduced SpO2 (association with nuclear atrophy); suboptimal sleep from any cause.**
- **Failure to achieve ketosis (1.0-4.0 mM BHB or 8-30 ACES).**
- **Failure to improve vascular flow (often undiagnosed vascular component), for example under-exercising.**
- **Failure to resolve inflammation and remove source (e.g., leaky gut, oral pathogens, biotoxin exposure, chronic sinusitis, tick-borne pathogens, etc.).**
- **Continued stress.**
- **Continued exposure to biotoxins or other toxins. Suboptimal detoxification.**
- **Failure to heal innate immune system to adaptive system mismatch.**
- **Failure to include BHRT.**
- **Not using a health coach; irregular follow-up. Doctor shopping. “Expert” input.**
- **Not continuing to optimize.**

Lessons from the patients

- 53 yo F with 4-year history of memory loss, learning difficulty, and prosopagnosia, along with MCAD.
- ApoE4/4.
- Treated with protocol, cognitive assessment increased from 35th percentile to 98th percentile. Subjectively back to normal.
- MCAD reduced but persisted; hypogammaglobulinemia appeared and progressed.
- Because of earlier prosopagnosia, recommended for CIRS labs.
- Markedly abnormal CIRS labs.
- Babesia discovered and treated; MCAD and hypogammaglobulinemia both improved.

Prevention and Reversal of Cognitive Decline

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Research Paper

Reversal of cognitive decline: A novel therapeutic program

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Abstract: This report describes a novel, comprehensive, and personalized therapeutic program that is based on the underlying pathogenesis of Alzheimer's disease, and which involves multiple modalities designed to achieve metabolic enhancement for neurodegeneration (MEND). The first 10 patients who have utilized this program include patients with memory loss associated with Alzheimer's disease (AD), amnestic mild cognitive impairment (aMCI), or subjective cognitive impairment (SCI). Nine of the 10 displayed subjective or objective improvement in cognition beginning within 3-6 months, with the one failure being a patient with very late stage AD. Six of the patients had had to discontinue working or were struggling with their jobs at the time of presentation, and all were able to return to work or continue working with improved performance. Improvements have been sustained, and at this time the longest patient follow-up is two and one-half years from initial treatment, with sustained and marked improvement. These results suggest that a larger, more extensive trial of this therapeutic program is warranted. The results also suggest that, at least early in the course, cognitive decline may be driven in large part by metabolic processes. Furthermore, given the failure of monotherapeutics in AD to date, the results raise the possibility that such a therapeutic system may be useful as a platform on which drugs that would fail as monotherapeutics may succeed as key components of a therapeutic system.

INTRODUCTION

Magnitude of the problem

Cognitive decline is a major concern of the aging population, and Alzheimer's disease is the major cause of age-related cognitive decline, with approximately 5.4 million American patients and 30 million affected globally[1]. In the absence of effective prevention and treatment, the prospects for the future are of great concern, with 13 million Americans and 160 million globally projected for 2050, leading to potential bankruptcy of the Medicare system. Unlike several other chronic illnesses, Alzheimer's disease prevalence is on the rise, which makes the need to develop effective prevention and treatment increasingly pressing. Recent estimates suggest that AD has become the third leading cause of death in the United States [2], behind cardiovascular disease and cancer. Furthermore, it has been pointed out recently that women are at the epicenter of the Alzheimer's epidemic, with 65% of patients and 60% of caregivers being women [3]. Indeed, a woman's chance of developing AD is now greater than her chance of developing breast cancer [4].

Failure of monotherapeutics

Neurodegenerative disease therapeutics has been, arguably, the field of greatest failure of biomedical therapeutics development. Patients with acute illnesses such as infectious diseases, or with other chronic illnesses, such as cardiovascular disease, osteoporosis, human immunodeficiency virus infection, and even cancer, have access to more effective therapeutic options than do patients with AD or other neurodegenerative diseases such as Lewy body

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Research Paper

Reversal of cognitive decline in Alzheimer's disease

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Abstract: Alzheimer's disease is one of the most significant healthcare problems nationally and globally. Recently, the first description of the reversal of cognitive decline in patients with early Alzheimer's disease or its precursors, MCI (mild cognitive impairment) and SCI (subjective cognitive impairment), was published [1]. The therapeutic approach used was programmatic and personalized rather than monotherapeutic and invariant, and was dubbed metabolic enhancement for neurodegeneration (MEND). Patients who had had to discontinue work were able to return to work, and those struggling at work were able to improve their performance. The patients, their spouses, and their co-workers all reported clear improvements. Here we report the results from quantitative MRI and neuropsychological testing in ten patients with cognitive decline, nine ApoE4+ (five homozygous and four heterozygous) and one ApoE4-, who were treated with the MEND protocol for 5-24 months. The magnitude of the improvement is unprecedented, providing additional objective evidence that this programmatic approach to cognitive decline is highly effective. These results have far-reaching implications for the treatment of Alzheimer's disease, MCI, and SCI; for personalized programs that may enhance pharmaceutical efficacy; and for personal identification of ApoE genotype.

INTRODUCTION

Alzheimer's disease is now the third leading cause of death in the United States, following only cardiovascular disease and cancer [1]. There are approximately 5.2 million Americans with AD, but this estimate ignores the many young Americans destined to develop AD during their lifetimes: given the lifetime risk of approximately 15% when including all ApoE genotypes, as many as 45 million of the 318 million Americans now living may develop AD during their lifetimes if no prevention is instituted [2].

Effective treatment of Alzheimer's disease has been lacking, but recently a novel programmatic approach involving metabolic enhancement was described, with promising anecdotal results [3]. This treatment is based on connectomic studies [4] and previous transgenic findings [5] as well as epidemiological studies of various monotherapeutic components of the overall program [6]. The approach is personalized, responsive to suboptimal metabolic parameters that reflect a network imbalance in synaptic establishment and maintenance vs. reorganization, and progressive in

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Case Report Open Access

Reversal of Cognitive Decline: 100 Patients

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Abstract

The first examples of reversal of cognitive decline in Alzheimer's disease and the pre-Alzheimer's disease conditions MCI (Mild Cognitive Impairment) and SCI (Subjective Cognitive Impairment) have recently been published. These two publications described a total of 19 patients showing sustained subjective and objective improvement in cognition, using a comprehensive, precision medicine approach that involves determining the potential contributors to the cognitive decline (e.g., activation of the innate immune system by pathogens or intestinal permeability, reduction in trophic or hormonal support, specific toxin exposure, or other contributors), using a computer-based algorithm to determine subtype and then addressing each contributor using a personalized, targeted, multi-factorial approach dubbed ReCODE for reversal of cognitive decline.

An obvious criticism of the initial studies is the small number of patients reported. Therefore, we report here 100 patients, treated by several different physicians, with documented improvement in cognition, in some cases with documentation of improvement in electrophysiology or imaging, as well. This additional report provides further support for a randomized, controlled clinical trial of the protocol and the overall approach.

Keywords: Alzheimer's; Mild cognitive impairment; Programmatics; ReCODE; Precision medicine; Amyloid precursor protein; Synaptoblastic; Synaptoclastic

Introduction

Alzheimer's disease is now the third leading cause of death in the United States [1-6], and the development of effective treatment and prevention is a major healthcare goal. However, clinical trials of drug candidates for Alzheimer's disease treatment have been almost uniformly unsuccessful. There may be several reasons for such repeated failure: (1) given the long pre-symptomatic period, treatment is typically initiated late in the pathophysiological process; (2) what is referred to as Alzheimer's disease is not a single disease, but rather exhibits several different subtypes [3,4]; (3) just as for other complex chronic illnesses such as cardiovascular disease, there may be many potential contributors to Alzheimer's disease, such as inflammation, various chronic pathogens, trophic withdrawal, insulin resistance, vascular compromise, trauma, and exposure to specific toxins. Therefore, a monotherapeutic, monophasic approach is likely to be suboptimal, and personalized, multiphasic programs based on each individual's genetics and biochemistry may be preferable. Indeed, such personalized programs may offer advantages in future clinical trials of drug candidates. (4) The model of Alzheimer's disease on which the drug targets (e.g., amyloid-β peptide) have been based may be an inaccurate or incomplete model of the disease.

We have argued for a fundamentally different view of Alzheimer's disease [1,2,5,7] in which APP, the amyloid precursor protein, functions as a molecular switch due to its activity as an integrating dependence receptor [8-10]: in the presence of sufficient support from trophic signaling, APP is cleaved at the alpha site, leading to the production of two synaptoblastic peptides, sAPPα and αCTF. In contrast, in the absence of sufficient support from trophic signaling, APP is cleaved at the beta, gamma, and caspase sites, leading to the production of four synaptoclastic peptides, sAPPβ, Aβ, Jcasp, and C31. In this model, inflammation exerts an anti-trophic effect on APP signaling, at least in part *via* the NF-κB (nuclear factor κ-light chain enhancer of B cells) induction of BACE (beta-amyloid cleaving enzyme) and gamma-secretase activity. Similarly, toxins such as divalent metals (e.g., mercury) also exert an anti-trophic effect on APP signaling, since these lead to a net increased production of the toxin-binding peptide, Aβ. This

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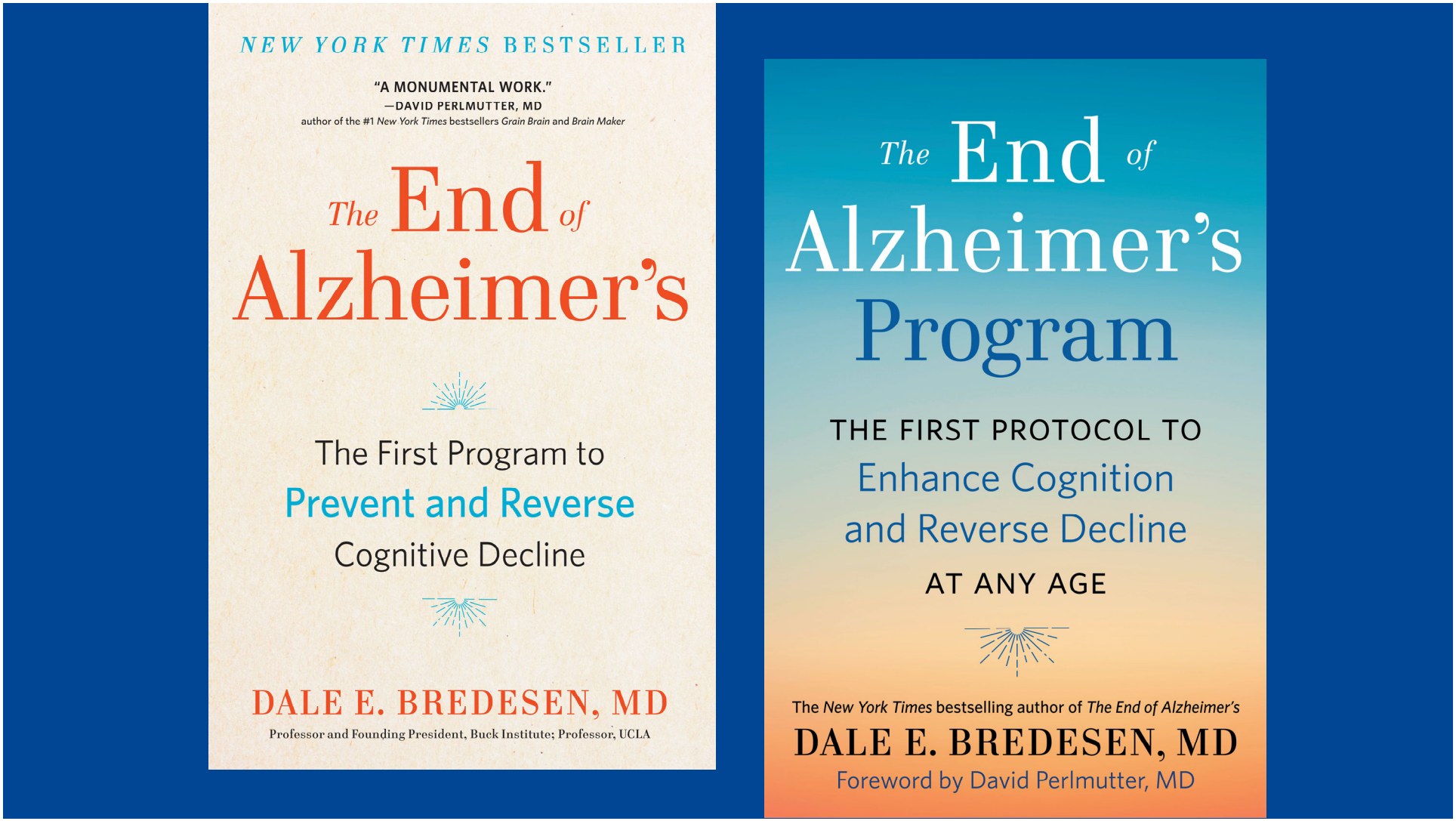
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The End of Alzheimer's
The First Program to
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DALE E. BREDESEN, MD
Foreword by David Perlmutter, MD

The potential for evaluation, prevention, and effective treatment of cognitive decline is far greater than ever before.

Summary: Alzheimer's should be a rare disease

- **What is referred to as "Alzheimer's disease" is the result of a *protective response* to 6 major metabolic and toxic perturbations: inflammation, insulin resistance/glycotoxicity, trophic withdrawal (trophic factors, hormones, nutrients), specific toxins (divalent metals, organic toxins, mycotoxins, et al.), vascular insufficiency (blood flow, oxygen delivery, substrate delivery), or trauma.**

- **There are 6 subtypes of Alzheimer's disease (and combinations of these 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; Bredesen et al., *JADP* 2018).**

- **This programmatic approach should be applicable to other neurodegenerative illnesses, as well as other complex chronic illnesses.**

- **We should be able to reduce the global burden of dementia markedly (and chronic illness), and increase the global cognitive ability, through metabolic profiling, larger data sets, prevention and early reversal, patient-researcher partnerships (PRPs), and personalized, programmatic approaches to cognitive (and overall) health.**

Just as for leprosy and polio, Alzheimer's *shall* become a former scourge.