



Changing Our Understanding of Alzheimer's Disease from inevitable, untreatable, and incurable, to preventable, treatable and curable.

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Overview

Alzheimer's disease and related disorders (AD), then, now and imagine....

Musings of physician-scientist engaged in AD research for 30+ years.

Provide insight into the progress made with respect to our understanding of AD over the last 30 years and why I am cautiously optimistic that this increased understanding will enable be translated into therapies that benefit patients in the not to distant future

Convey the importance of public policy changes and parternships that are needed to insure we actually accomplish this translation.





Alzheimer's Disease 117 years ago Dr. Alois Alzheimer's and August D



What is Alzheimer's Disease?

- From Dr. Alzheimer's monograph:
 - "On Nov 25th 1901 Auguste D was admitted to the Frankfurt hospital where she was examined by Dr. Alzheimer. She had a striking cluster of symptoms that included reduced comprehension and memory, as well as aphasia, disorientation, unpredictable behavior, paranoia....."
- By far the most common cause of dementia in the elderly
 - ~2/3 of dementia in patients >60 years old
- Typically begins with subtle memory loss and progresses relentlessly --typically over 7 to 10 years
- Ultimately involves most higher cognitive functions leading to complete incapacitation and death



Dr. Alois Alzheimer

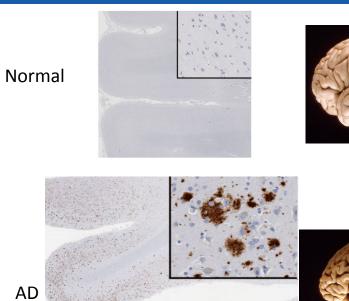


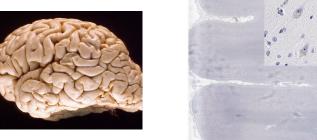
Auguste D

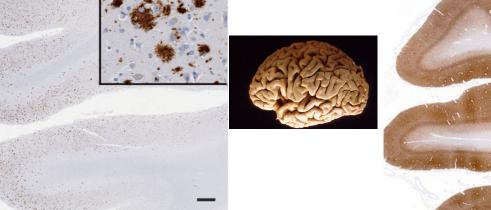


Plaques, Tangles and Degeneration











Plaques/A β

Tangles/tau

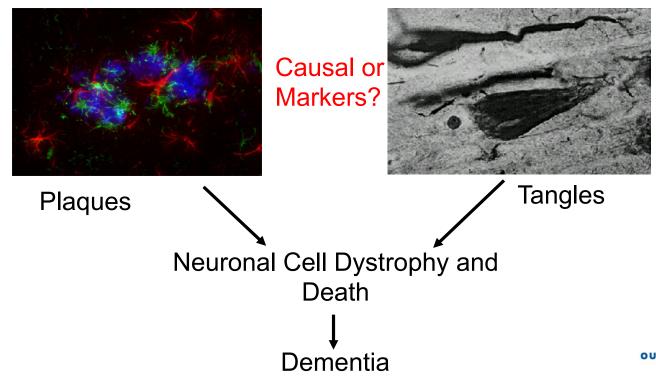


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Cause and Effect Alzheimer's Disease Circa 1990? Searching in the Dark



Uncertain roles of $A\beta$ and tau in AD Uncertain Nosology

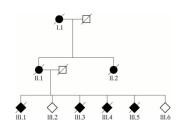




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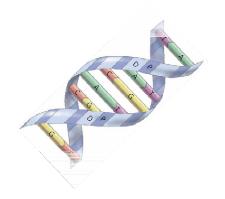
Genetics, Causality and Alzheimer's Disease







- In rare families AD is heritable (genetic) and we have identified most of the genes causing deterministically heritable forms of AD
- All genetic forms of AD alter $A\beta$ in a manner that will increase the likelihood that it will aggregate
- $A\beta$ is only harmful when it aggregates



- Analogous to cholesterol and heart disease
 - Families with heritable high cholesterol levels and histories of cardiovascular disease have genetic alterations in genes that control cholesterol and lipid metabolism. These genetic findings provided key rationale for development of cholesterol lowering therapies (statins).





A simple framework of Alzheimer's Disease

The Aβ aggregate cascade hypothesis of AD

Prevent this and Prevent AD?

Aβ aggregation and plaque formation

Tau aggregation, tangle formation, Inflammation, other downstream pathologies

Brain Cell Loss and Dysfunction

Dementia/Brain Organ Failure

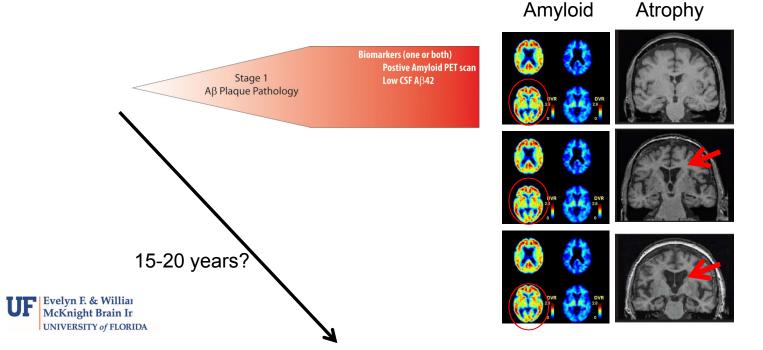


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We can now visualize the progression of AD in living humans the progression of AD in living huma

The Natural History of Alzheimer's Disease in Humans

 In Humans Alzheimer's Disease Pathology Precedes Clinical Symptoms by many years



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From then to now



- Real, tangible progress in our understanding of what AD is, the sequencing of events as AD progresses, and the ability to detect these events in living humans
 - But still many gaps in our knowledge...
- Development of a variety of interventions that can target the underling pathologies
- Development of modestly effective therapies that impact symptoms of disease, but hundred of failed therapeutic studies
- Still no disease modifying therapy
- Huge unmet medical need remains.



AD finally has captured the public attention and public policy has changed dramatically





HIV positive 1991

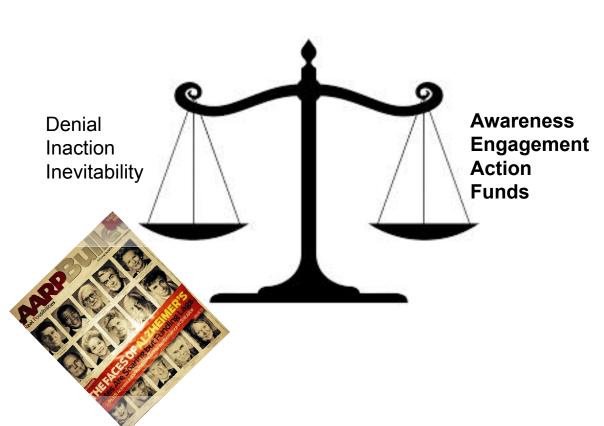


Alzheimer's Disease <u>diagnosed</u> in 1994



The Balance Has shifted





Evelyn F. & William L. McKnight Brain Institute

UNIVERSITY of FLORIDA

The NIH budget for AD research has increased ~ 4-fold in the last 5 years

Philanthropy is increasing

The State of Florida now supports AD research

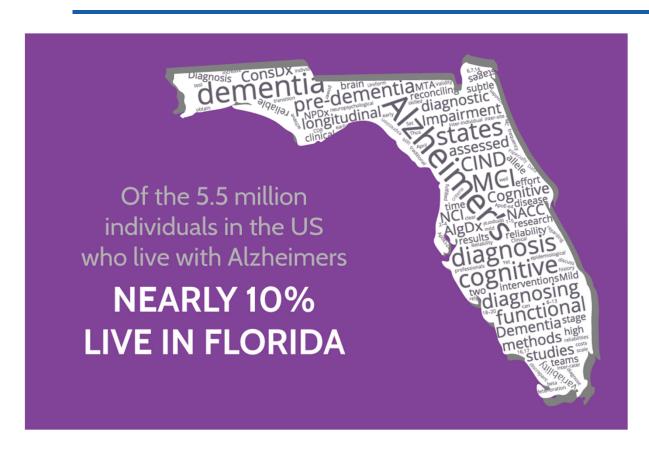
Thank you State legislators
Former Representative Matt Hudson
Senators Bill Galvano, Manny Diaz,
Lizbeth Benacquisto, Keith Perry, Rob
Bradley

All legislators at the National level

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These funds and awareness impact us locally in neurodegenerative disease











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Much of what we know about AD and related disorders comes form the study of Caucasians of Northern European decent







A consortium of Florida institutions helping to change the current understanding of Alzheimer's disease and related dementias from being incurable, inevitable and largely untreatable to a new reality in which these diseases are curable, preventable and treatable.

Our goals

Elucidate markers that define the earliest stages of cognitive impairment

Understand predictors of cognitive and functional decline in Hispanic and non-Hispanic individuals

Test **novel therapies** for AD and related dementias in a population that is increasingly more representative of the elderly in the US

Contribute tools, data, resources to support AD research

Provide unique community and professional training and educational opportunities relevant to AD and related dementias.

Develop paradigms to help recruit and <u>retain</u> diverse research participants in the earliest asymptomatic stages of disease



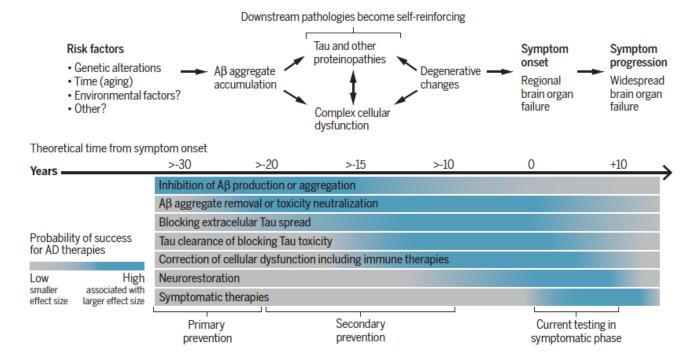
Now: Why don't we have better treatments? We have either tested the wrong drugs or the right drug at the wrong time!



NEURODEGENERATION

Alzheimer's disease: The right drug, the right time

Lessons from failed clinical trials can improve the development of Alzheimer's disease–modifying therapies





Now: We can overcome the streetlight effect!

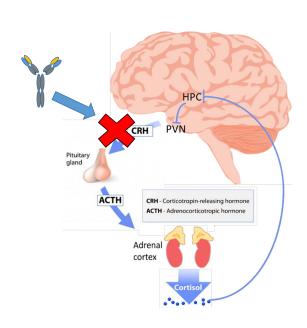


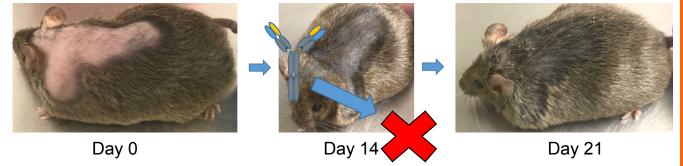




Working in the shadows targeting stress pathways with antibodies













Sooner rather than later the right drug at the right time, we may even be doing it right now!



But in the meantime what can you do to help

Be a polite but aggressive advocate at all levels

- Contact your State and National Legislators tell them that you support efforts to maintain and even further increase funding for Alzheimer's disease
- Participate and Support Research Efforts Locally and Nationally

Imagine: Together we will change our understanding of Alzheimer's Disease from inevitable, largely untreatable, and incurable, to preventable, treatable and curable



To find out more

- Websites
 - Alzforum.org
 - Alz.org
 - 1FLORIDA ADRC.org
- If you are worried about your own, a family members, or a friend's cognitive health, contact us and we will help you get a timely referral

