Alzheimer's Disease Center
at the Sanders-Brown Center on Aging

Update on AD Clinical Trials at the University of Kentucky

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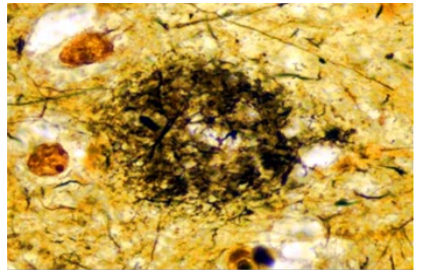
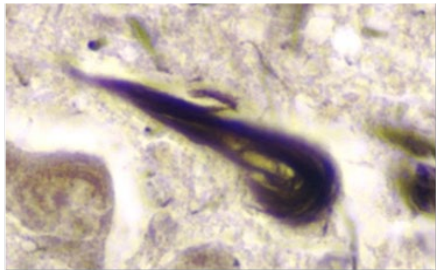
Amyloid makes plaques… & tau makes tangles…

- Sometimes we make too little good protein and that is bad
- Sometimes we make too much of a good protein and that can also be bad
- What if we could better control how much bad and good proteins we make?



Amyloid plaques



Tau makes tangles

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So let's take a look at one of the most promising approaches for treating neurodegenerative disease states IMHO…

Antisense MRNA therapies: fixing the underlying biological problem!

But, as my wife likes to remind me…

Even a broken clock is right twice a day!

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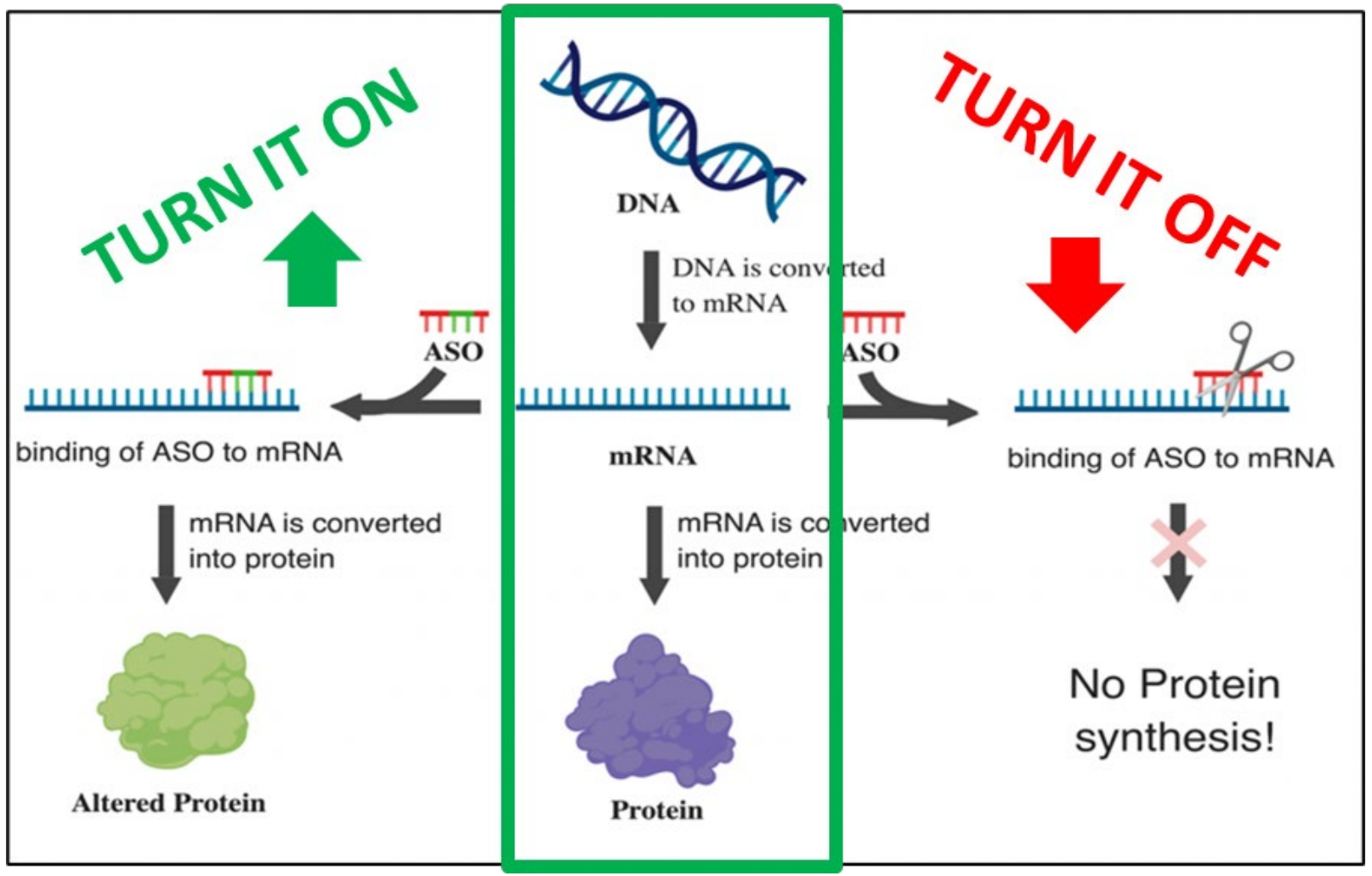
Let's take a look at how antisense therapies work…



- If the mRNA makes dysfunctional proteins because of genetic mutation, we can deliver mRNA, increasing expression and restore normal function
- Or if we make too much protein and that is bad, we can stop the mRNA from making too much protein
- We can turn it on & turn if off to make it just right!

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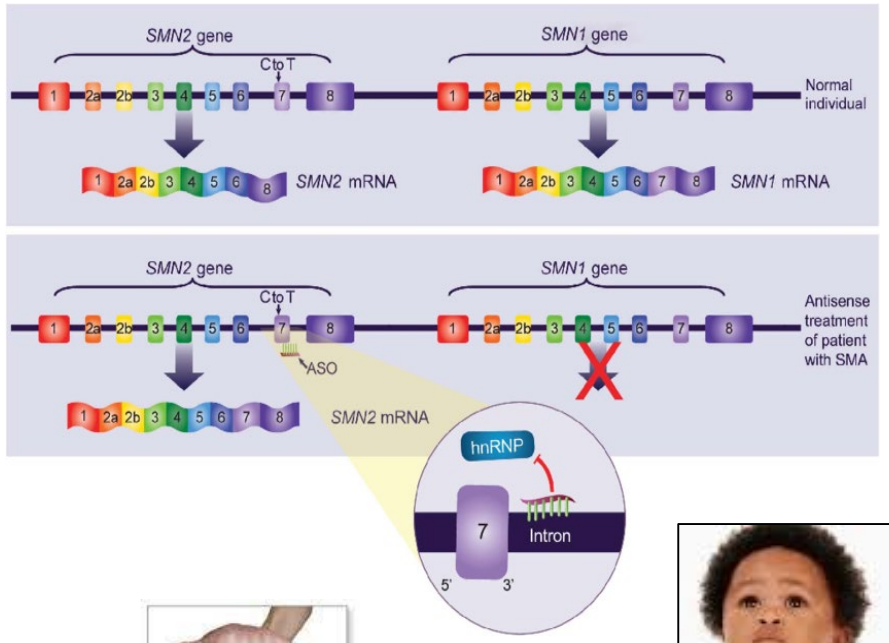
mRNA therapy successes…

Spinal Muscular Atrophy

- Lethal disease affecting children
- Newborns present with severe weakness, hypotonia, and heart defects and can die by age 6 months
- Chromosome 5 SMA is caused by a deficiency of a motor neuron protein called SMN, for "survival of motor neuron."
- Nusinersin is an antisense therapy approved in 2016 that is 71% effective delivered intrathecally
- This has led to a new gene therapy Zolgensma that is a one-time dose that is 100% effective



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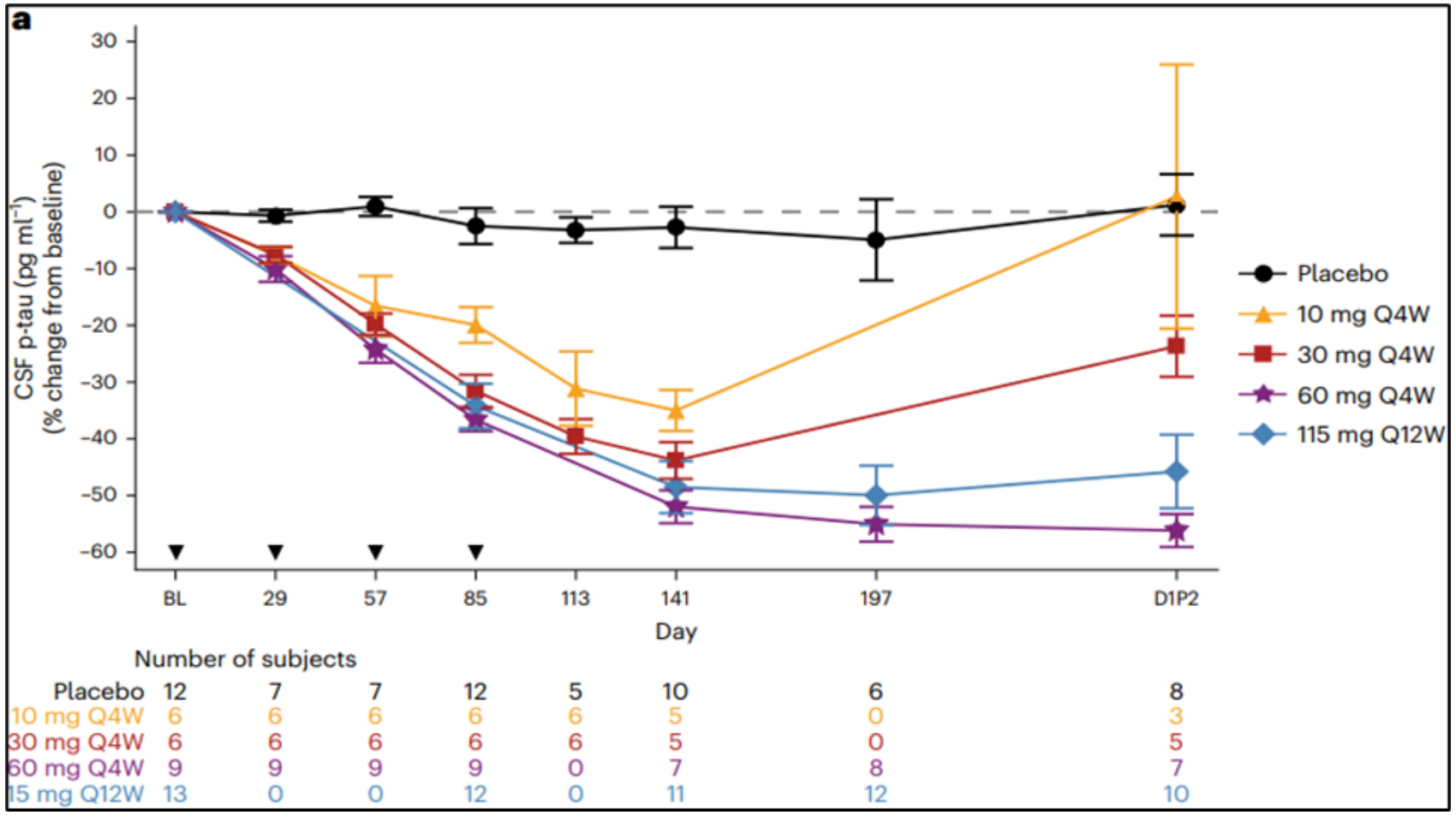
Can we block too much production of tau and slow or reverse AD?



Mummery et al. Nat Med. 2023 Jun;29(6):1437-1447.

- A randomized, double-blind, placebo-controlled, multiple-ascending dose phase 1b trial evaluated the safety, pharmacokinetics & target engagement of MAPTRx
- This study sought to inhibit MAPT expression with a tau-targeting antisense oligonucleotide (MAPTRx) and reduce tau levels in patients with mild AD

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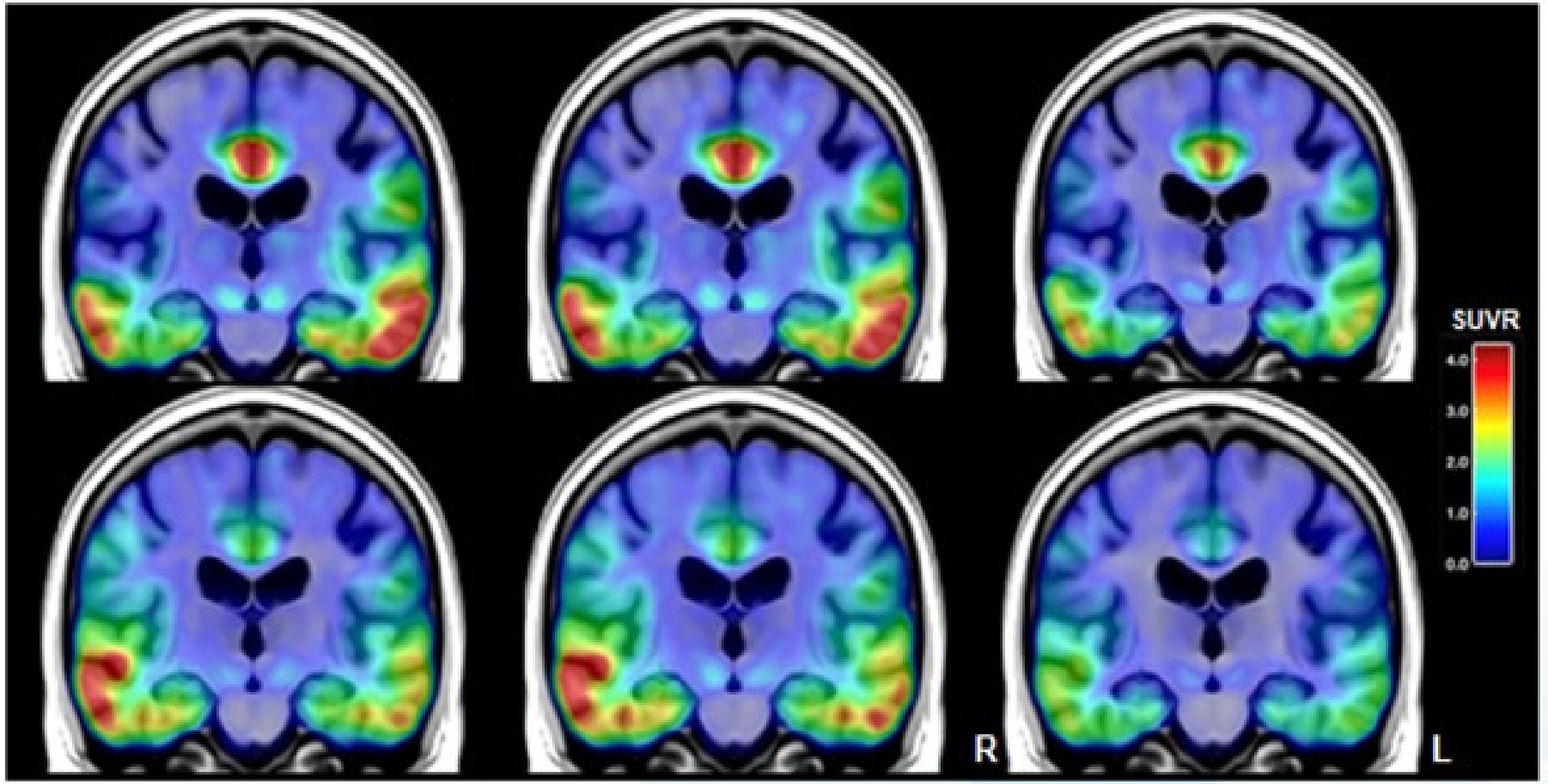
Tau antisense might stop progression, but can it reverse it?

Bye Bye Tangles

- **BIIB080 data presented at CTAD 2023**
- **In two people with mild AD (left), tangles (red) worsened over six months on placebo (middle), but cleared up during a year of tau ASO treatment (right). [Courtesy of Dominic Walsh, Biogen for Alzforum.]**



Baseline **6 mos untreated** **After 1 year of treatment**

https://www.alzforum.org/news/conference-coverage/first-hit-aggregated-tau-antisense-oligonucleotide-lowers-tangles

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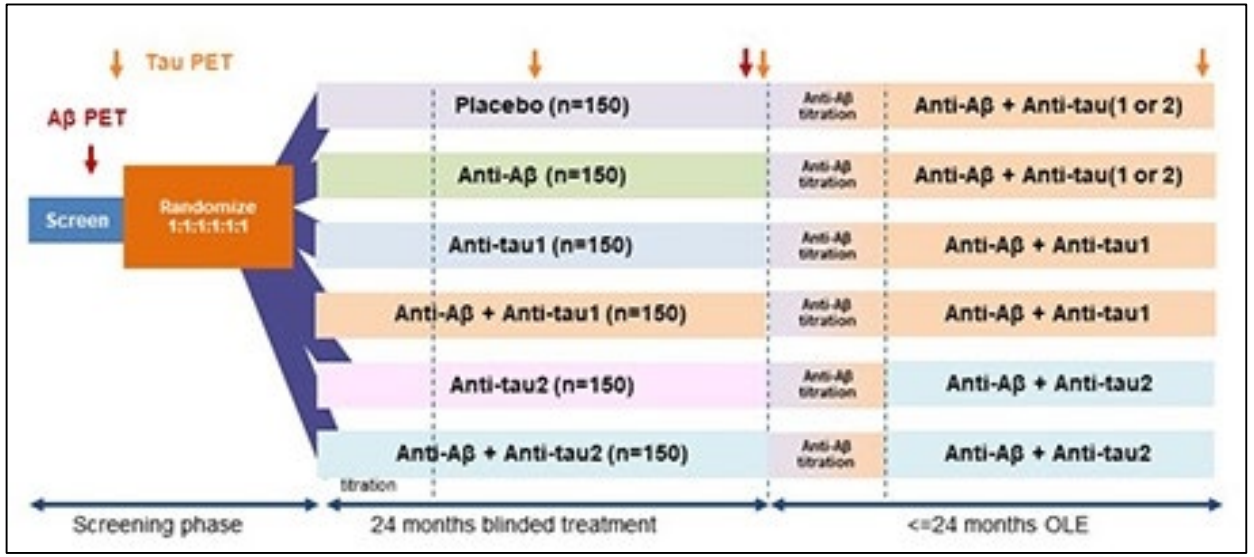
ACTC Tau Platform Trial

ACTC ALZHEIMER'S CLINICAL TRIALS CONSORTIUM

- The goal of the Alzheimer's Tau Platform (ATP) trial is to conduct a randomized, placebo controlled, Phase 2 platform trial in preclinical-prodromal AD
- This trial will test 5 therapeutic hypotheses involving combinations of 3 drugs versus placebo: Two tau therapies will be studied in a 2 x 3 factorial design (placebo vs. anti-amyloid [n=2] x two tau therapies or placebo [n=3]) for 24 months, in six parallel arms.
- 900 participants at ~100 ACTC sites over 24 months, randomize them 5:1 drug:placebo for 24 months of blinded treatment, followed by a 24-month open label extension.

ACTC tau Platform Trial: n=900, 17% placebo, 5 active arms



COMING SOON

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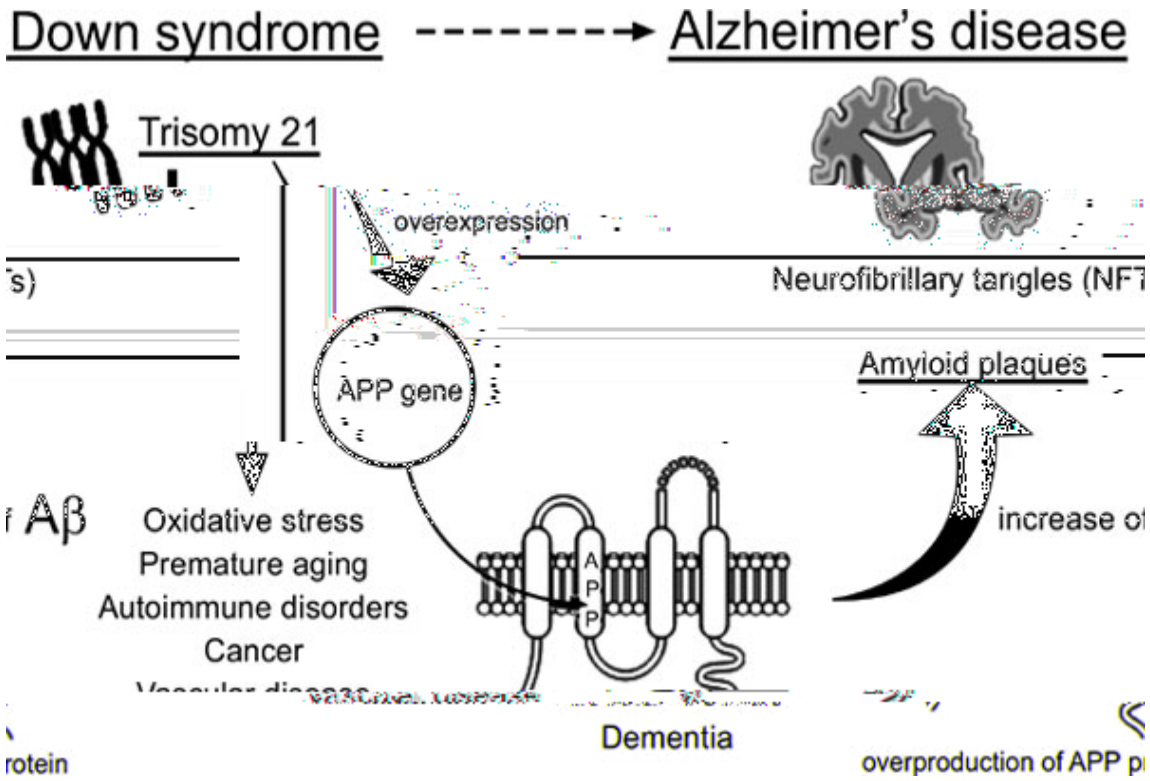
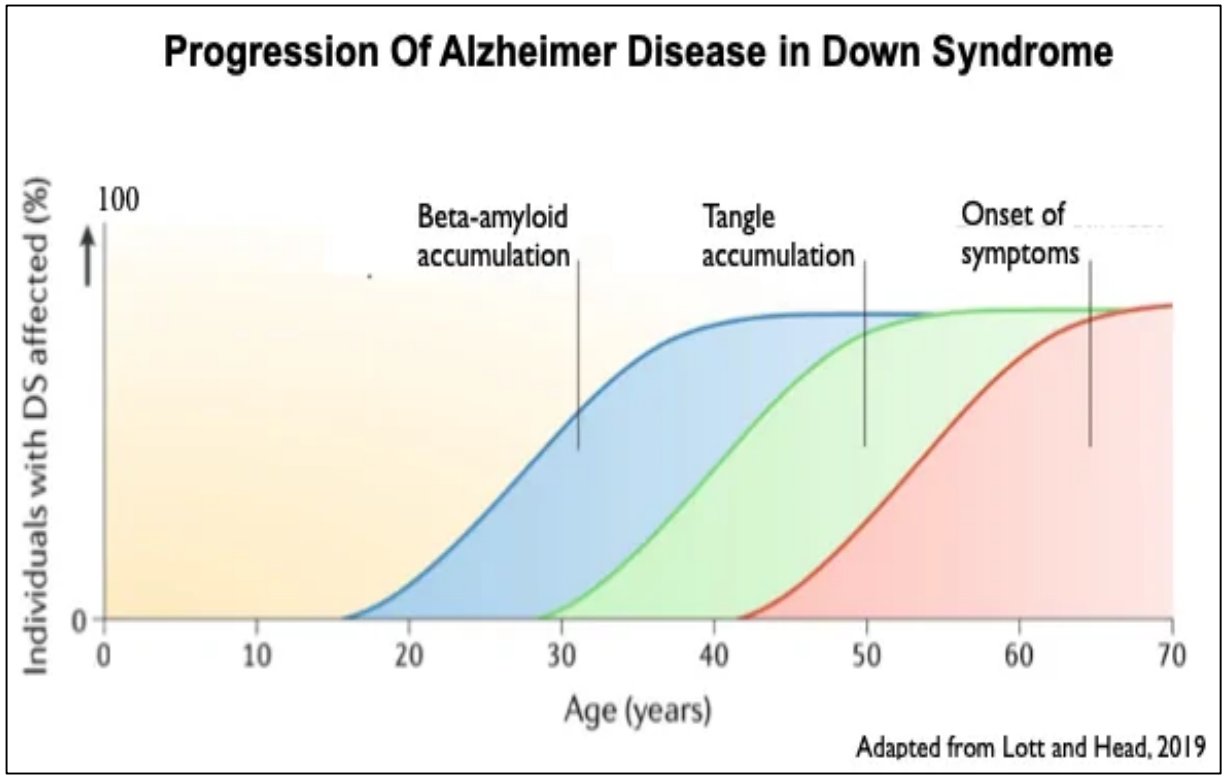
Adults with Down Syndrome are at high risk for Alzheimer's





ACTC-DS
Alzheimer's Clinical Trials Consortium
Down Syndrome

- DS has a 95% lifetime risk of AD
- #1 cause of death is AD
- Onset 20 years earlier than sporadic AD in non-DS persons

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Amyloid antisense therapy

ACTC-DS
Alzheimer's Clinical Trials Consortium
Down Syndrome

- Amyloid antisense mRNA can reduce amyloid expression caused by trisomy 21
- Trial is in start up at UK currently!

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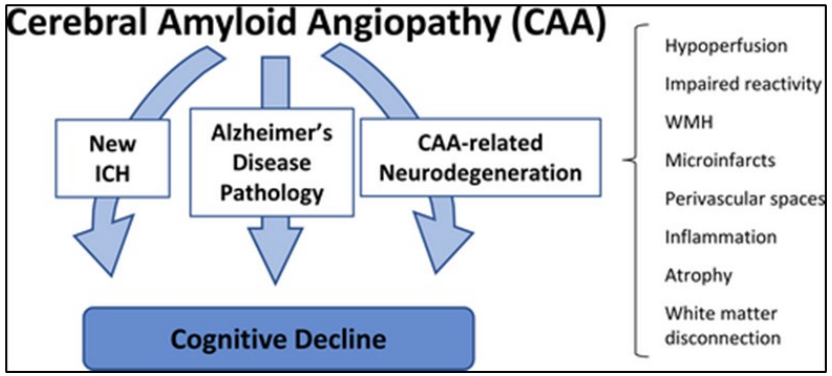
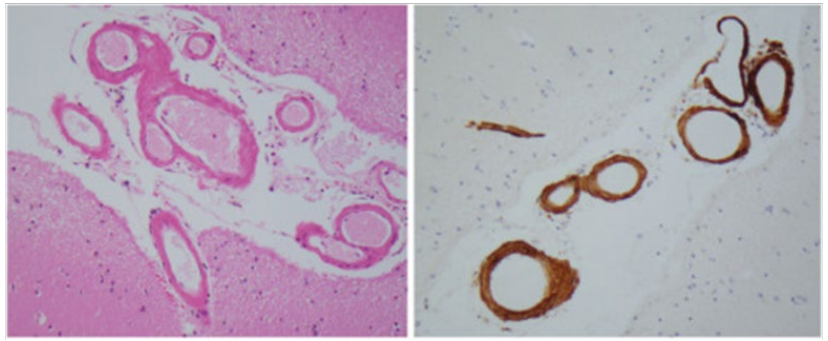
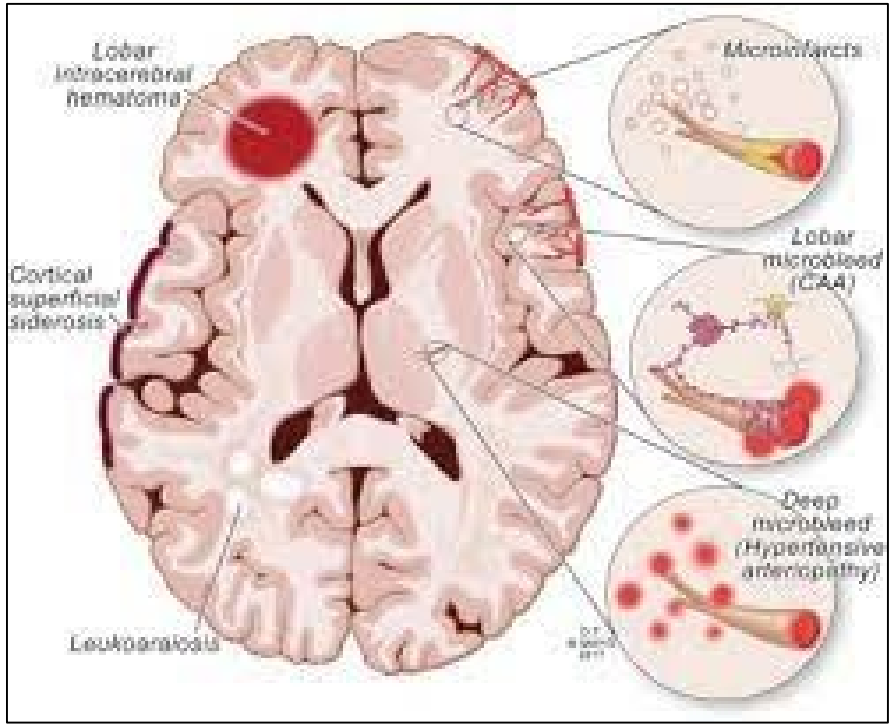
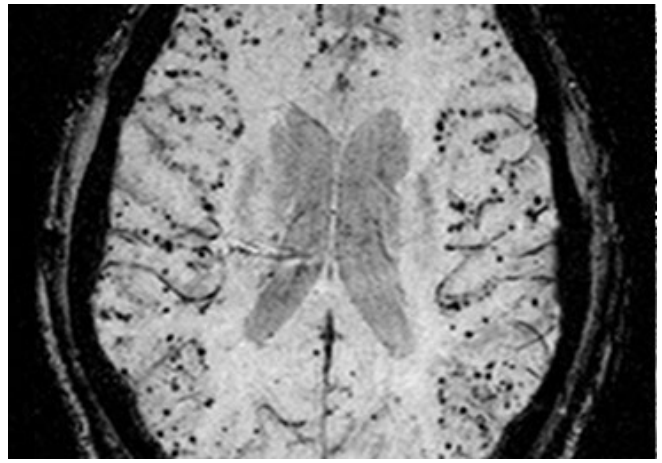
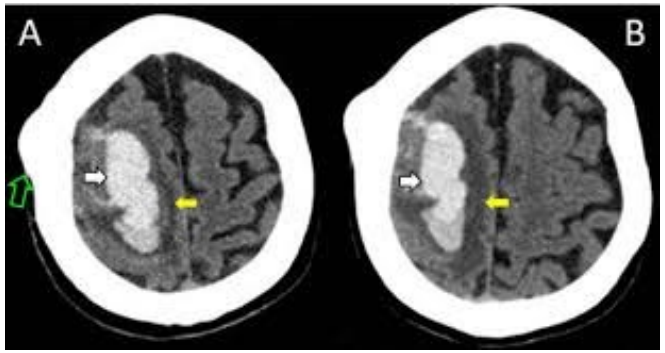
Cerebral Amyloid Angiopathy











- CAA is caused by Aβ 1-40 in blood vessels
- 16% AD cases have CAA and are not eligible for anti-amyloid therapy (lecanemab)
- There is currently no effective and safe treatment for this devastating disease

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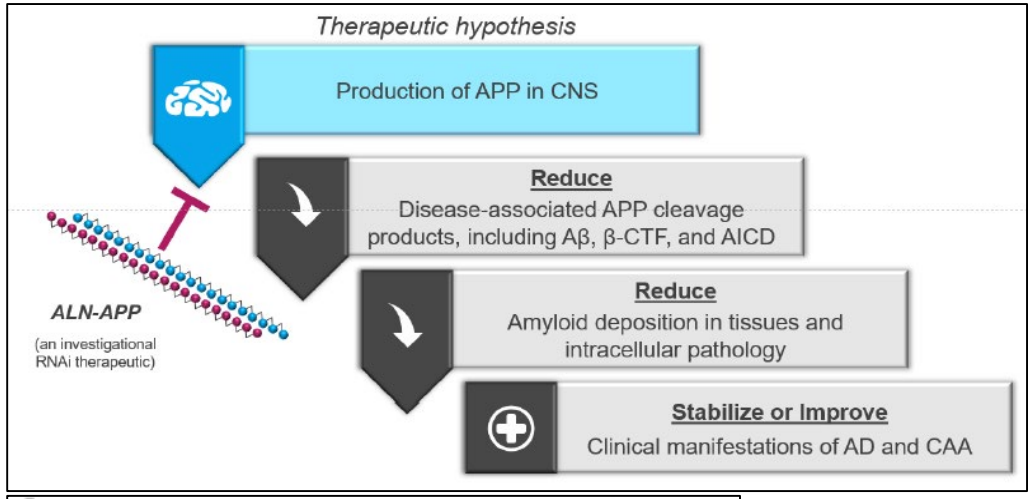
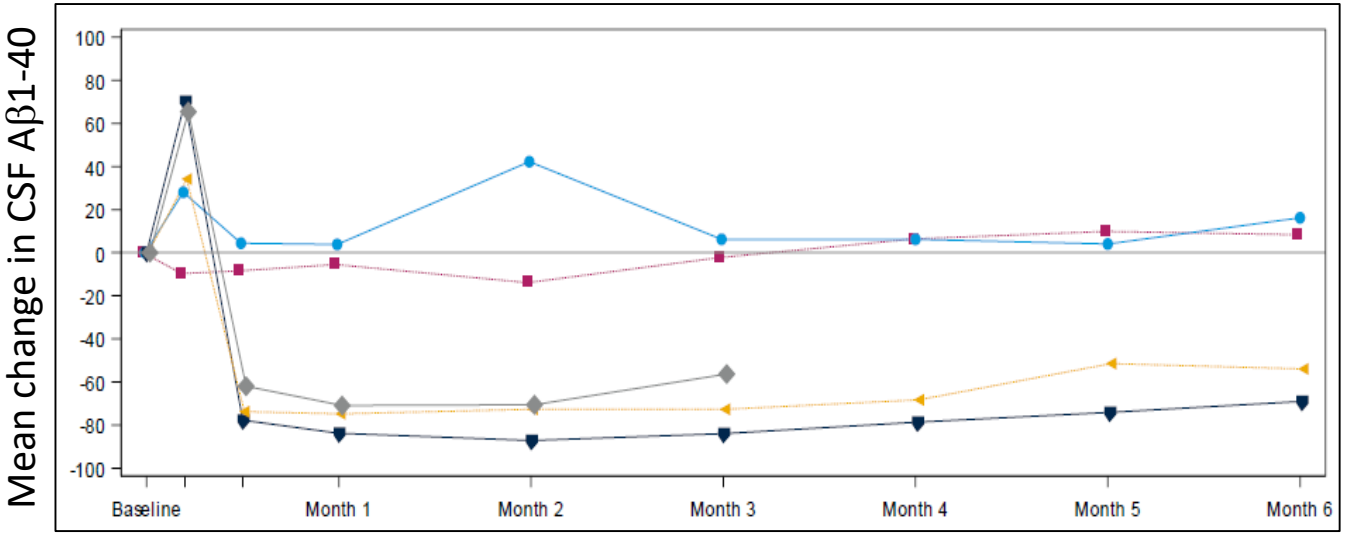
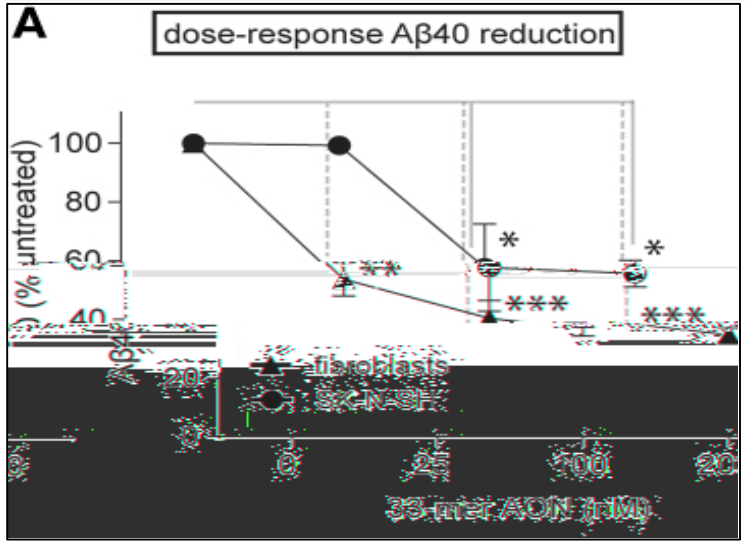
Amyloid antisense therapy







- This strategy appears incredibly promising for CAA
- It may work for AD too!
- The trial is enrolling persons with CAA irrespective of whether they have AD or not!

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There are many different ways to help and one may be right for you?

CLARiTI
ADRC Consortium for Clarity in ADRD Research Through Imaging

Imaging Studies

START

Pills to slow Alzheimer's

BenfoTeam

Supervitamins & Nutrients

Healthy Eating Habits

Diverse VCID

Cardiovascular risks

Improving sleep for brain health

Behavioral approaches

LiBY
Life's end Benefits of cannaBidiol (CBD) and tetrahYdrocannabinol (THC)

Palliative Care in the later stages

Call (859) 323-5550 if you would like to explore these & other ways to get involved!