



Alzheimer's
Disease Center

at the Sanders-Brown Center on Aging

Update on AD Clinical Trials at the University of Kentucky

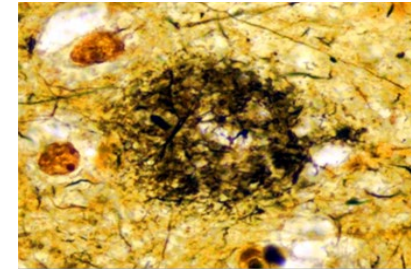
Greg Jicha, MD, PhD

McCowan Endowed Professor of Neurology

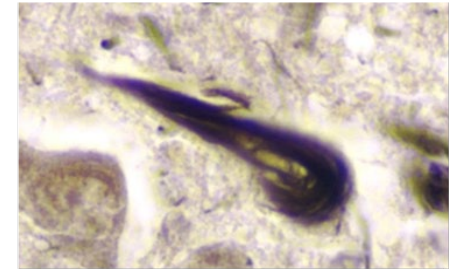
University of Kentucky ADRC

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



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

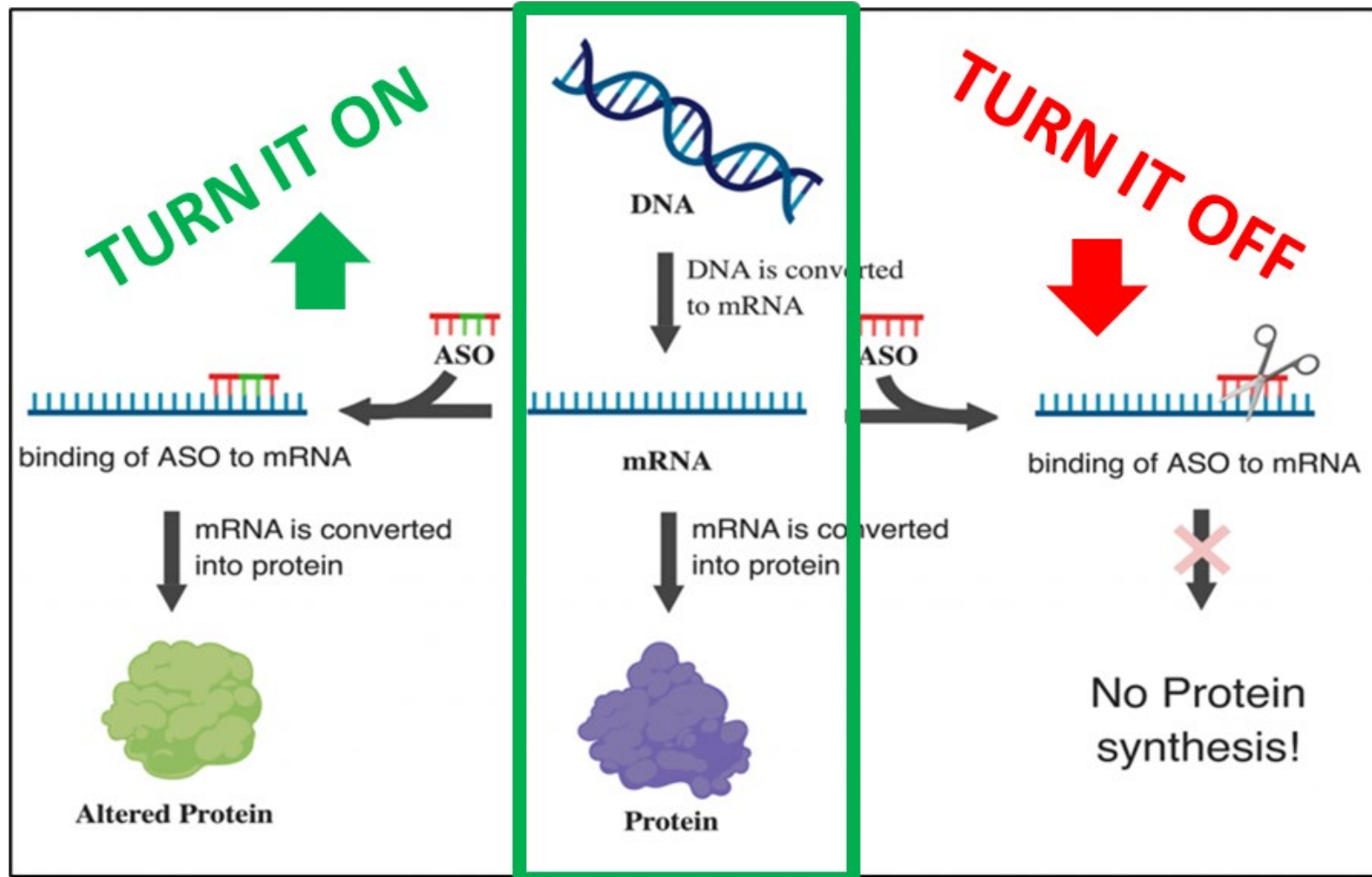


**Antisense mRNA
therapies: fixing the
underlying biological
problem!**

**But, as my wife likes to
remind me...**

***Even a broken clock is
right twice a day!***

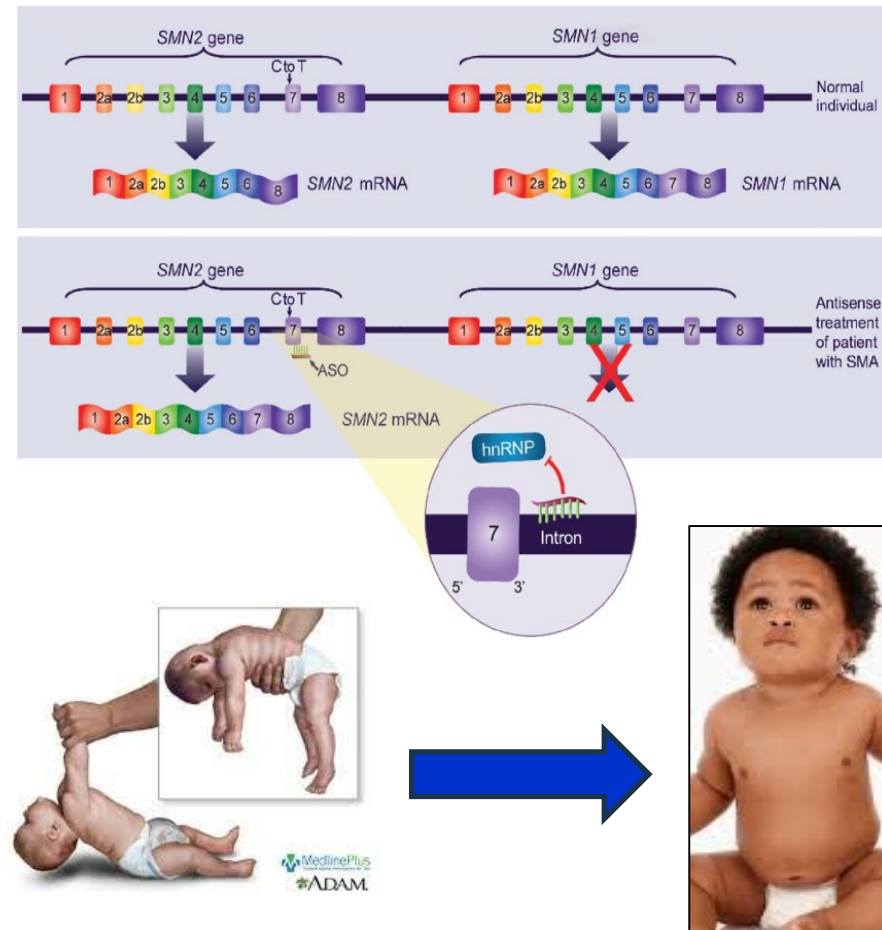
Let's take a look at how antisense therapies work...



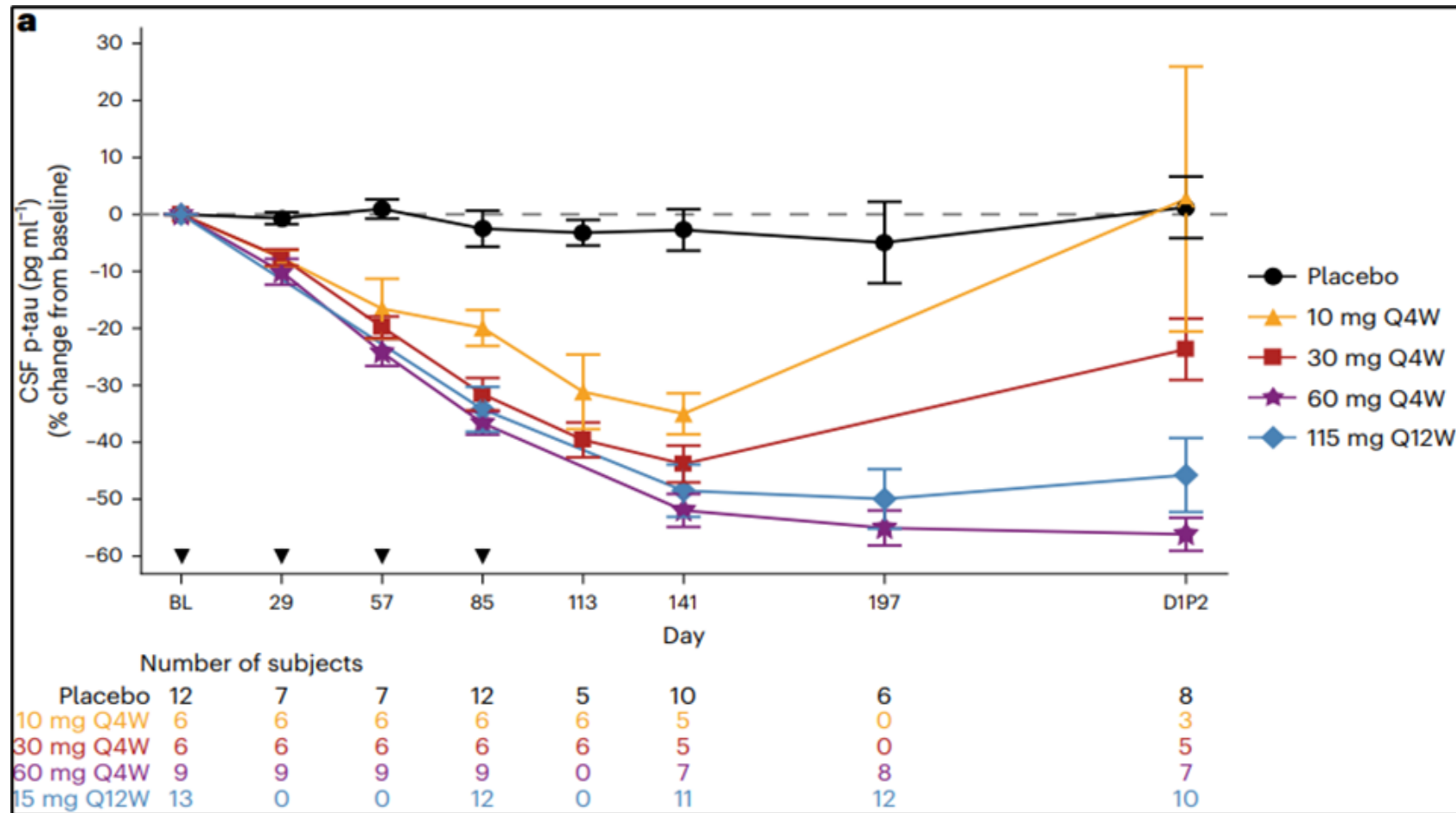
- If the mRNA makes dysfunctional proteins because of genetic mutation, we can deliver mRNA, increasing expression and restore normal function
- Or if we make too much protein and that is bad, we can stop the mRNA from making too much protein
- We can turn it on & turn it off to make it just right!

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



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



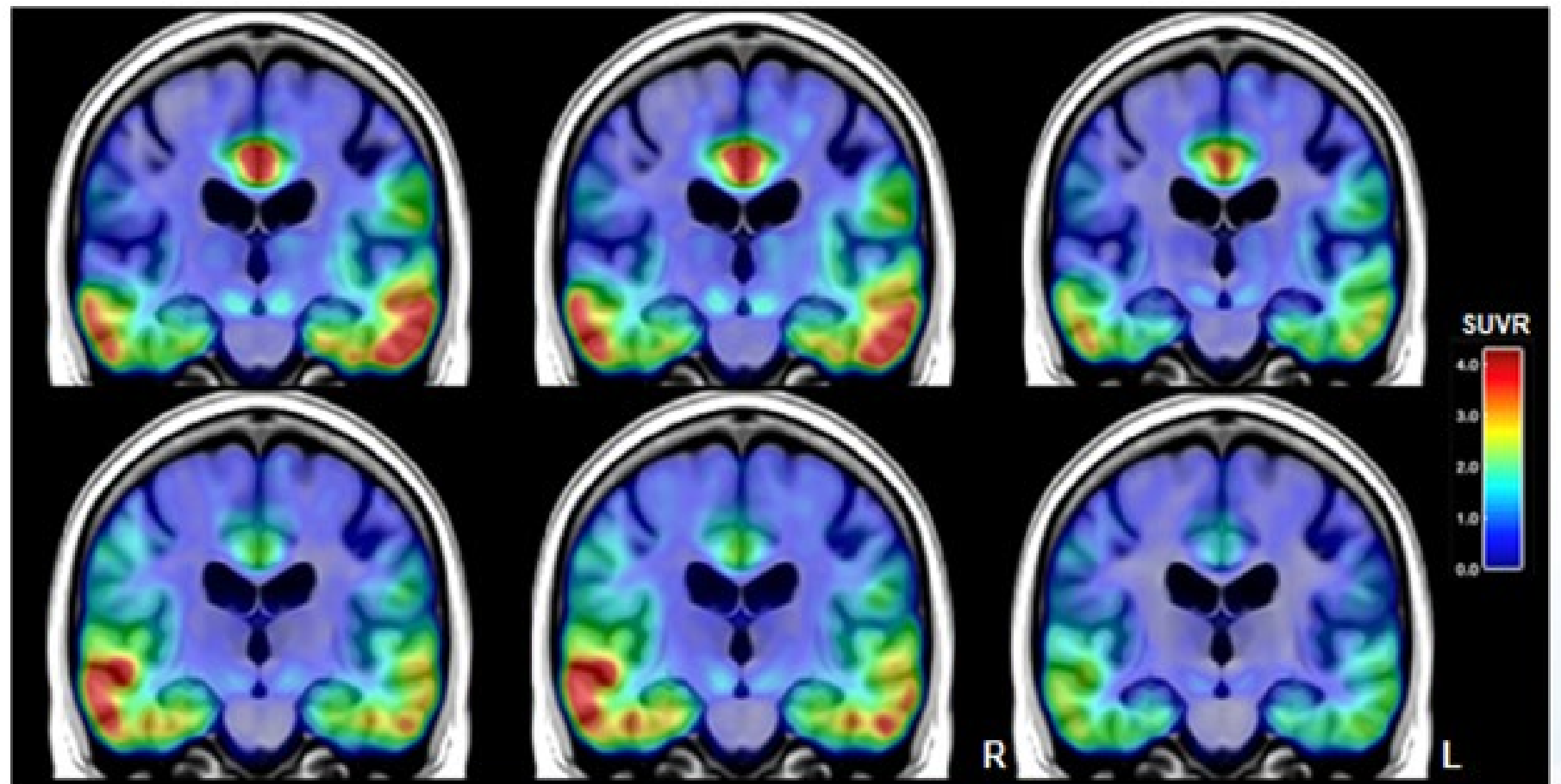
Mummery et al. Nat Med. 2023 Jun;29(6):1437-1447.

- 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

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

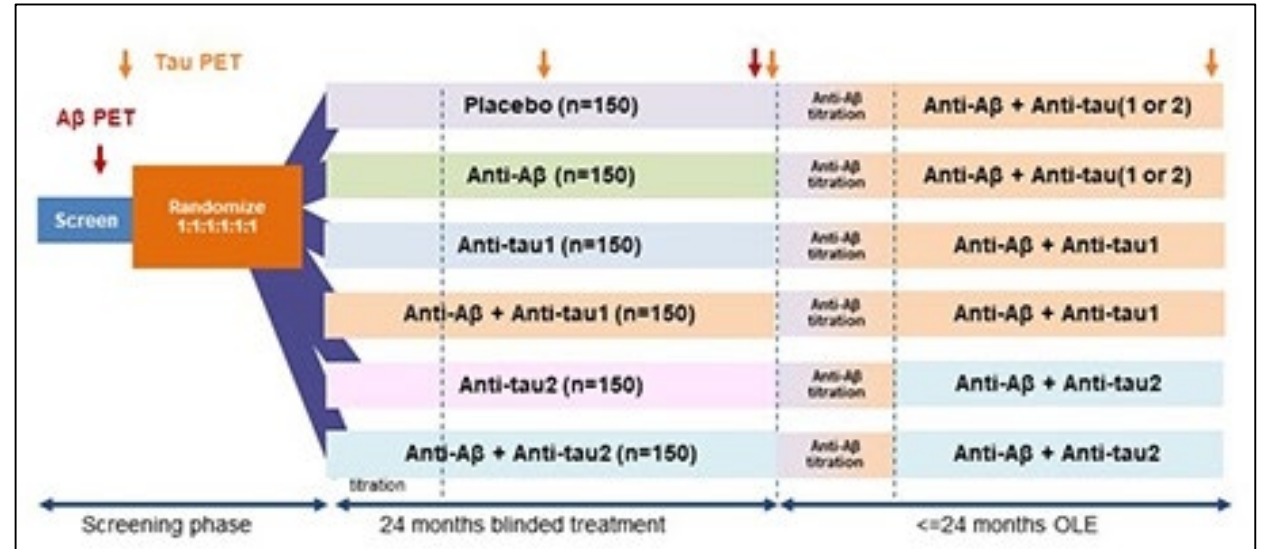
6 mos untreated

After 1 year of treatment

ACTC Tau Platform Trial

- 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.

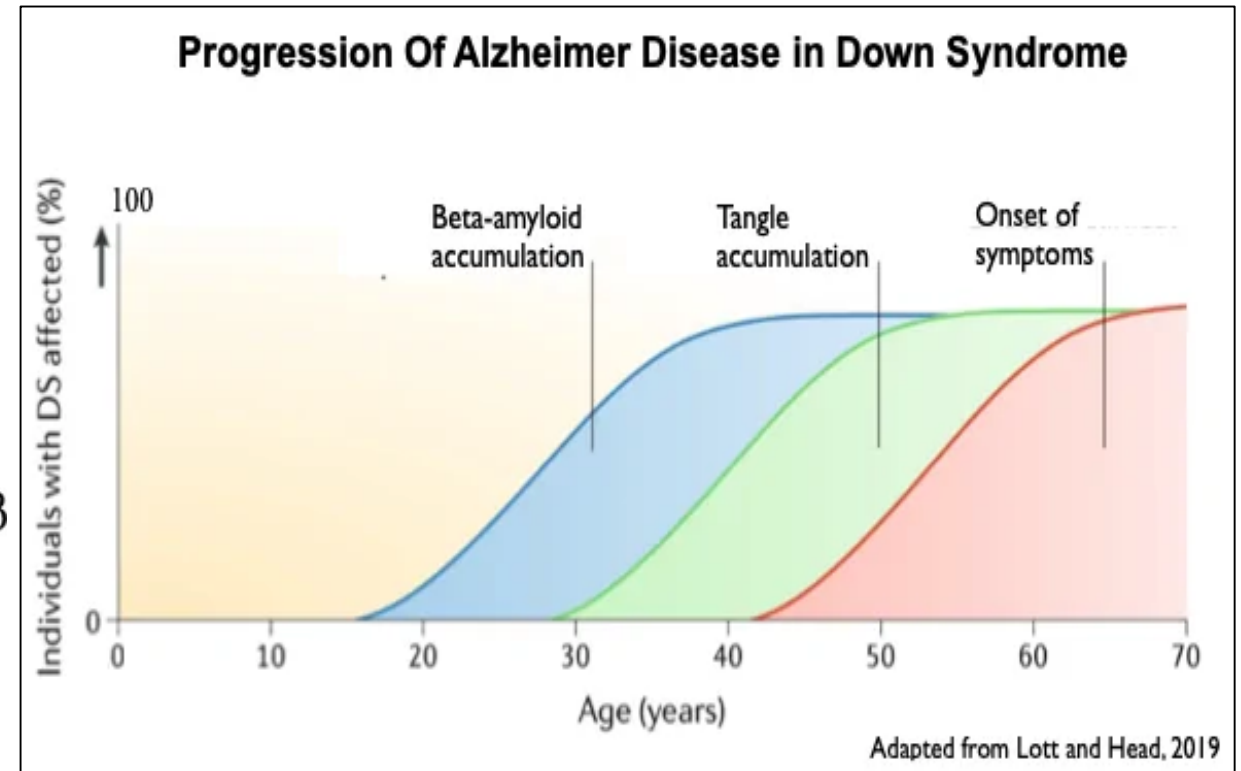
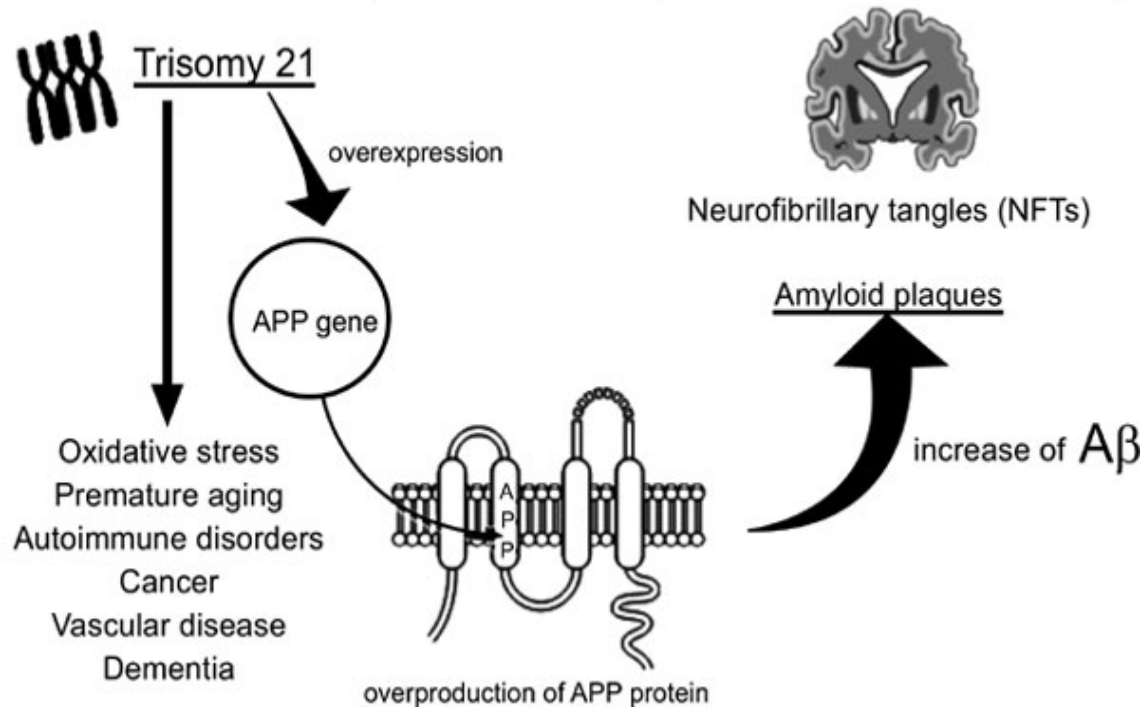
ACTC tau Platform Trial: n=900, 17% placebo, 5 active arms



COMING SOON

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

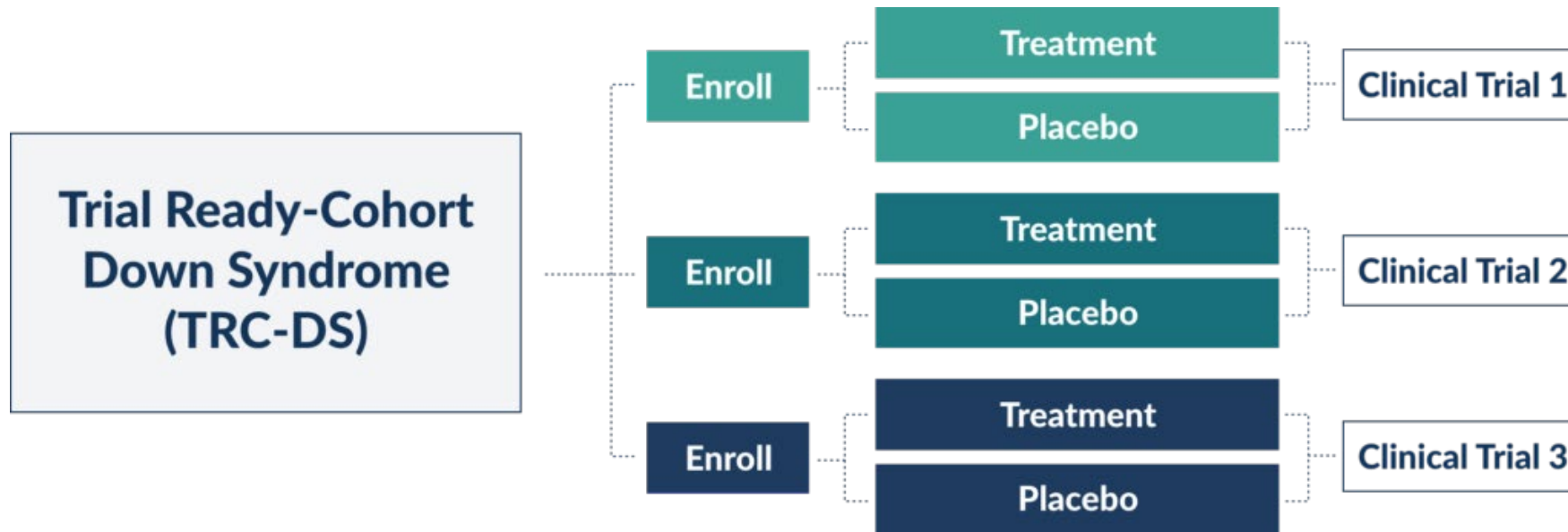
Down syndrome -----> Alzheimer's disease



- 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



Amyloid antisense therapy



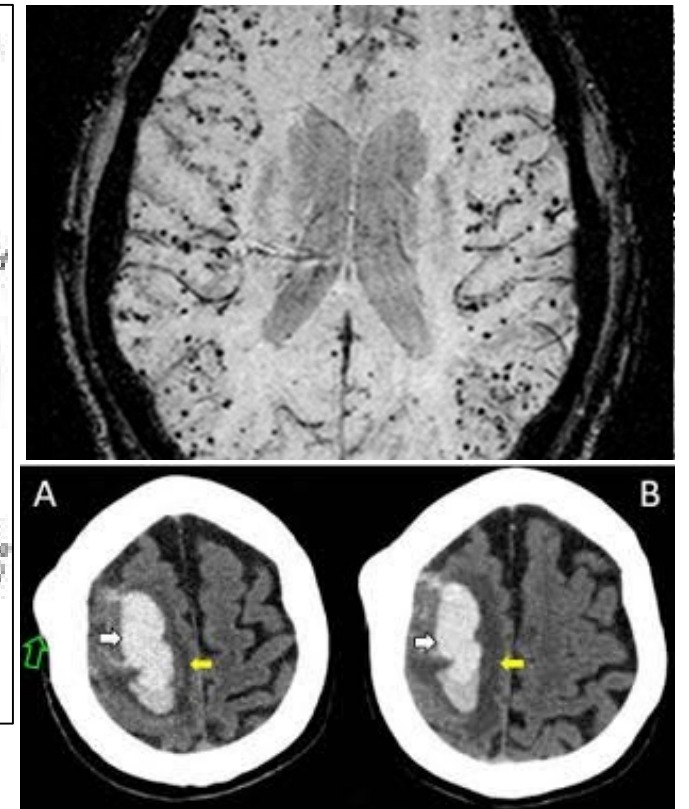
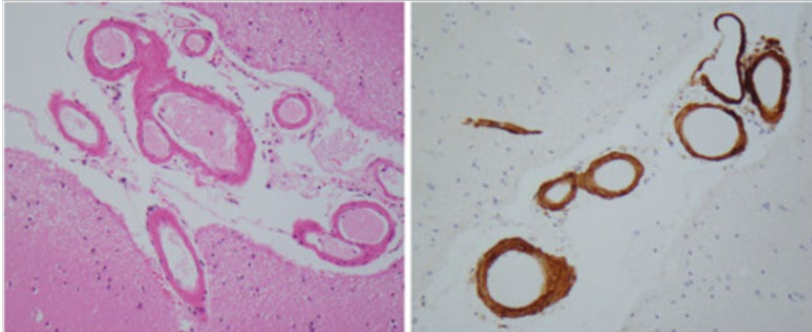
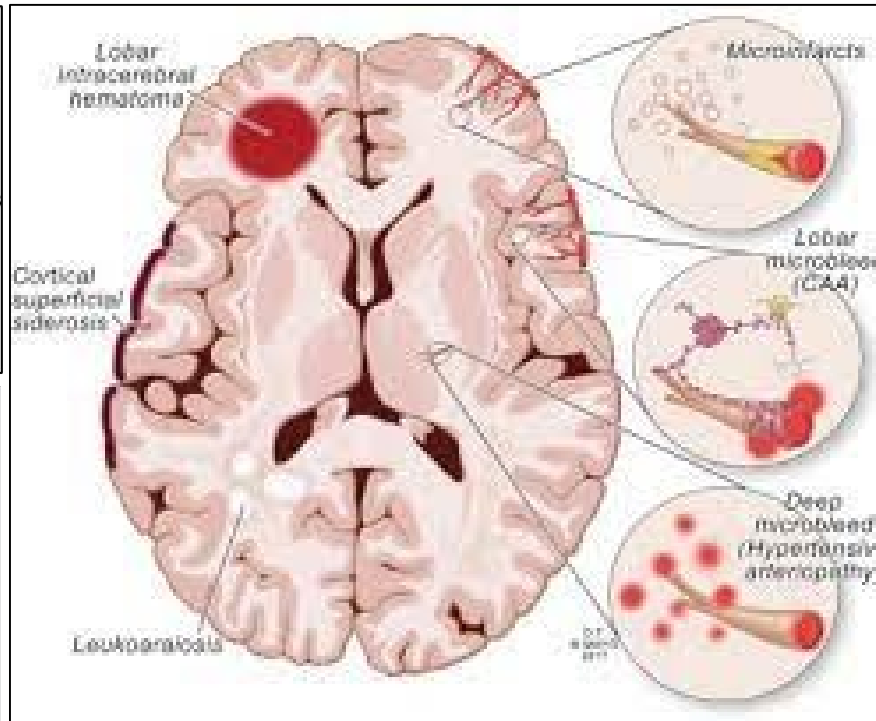
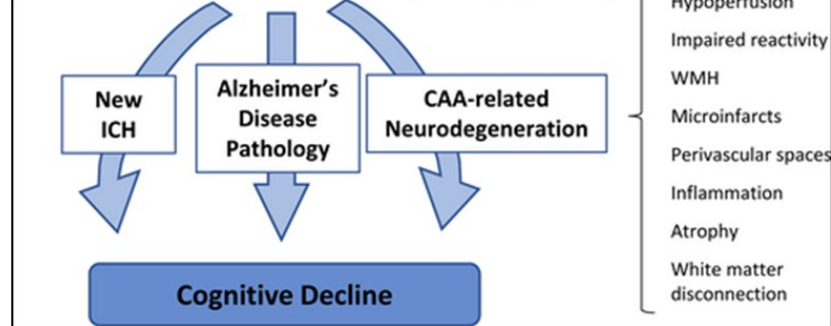
- Amyloid antisense mRNA can reduce amyloid expression caused by trisomy 21
- Trial is in start up at UK currently!





Cerebral Amyloid Angiopathy

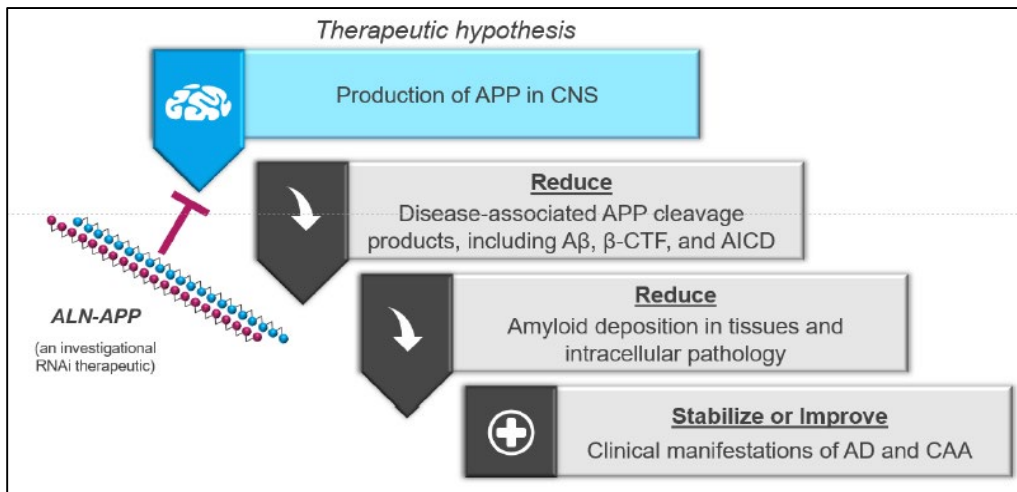
Cerebral Amyloid Angiopathy (CAA)



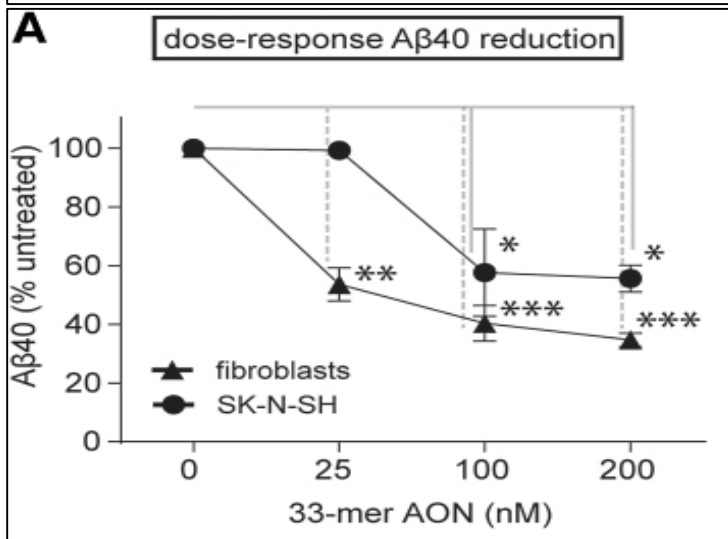
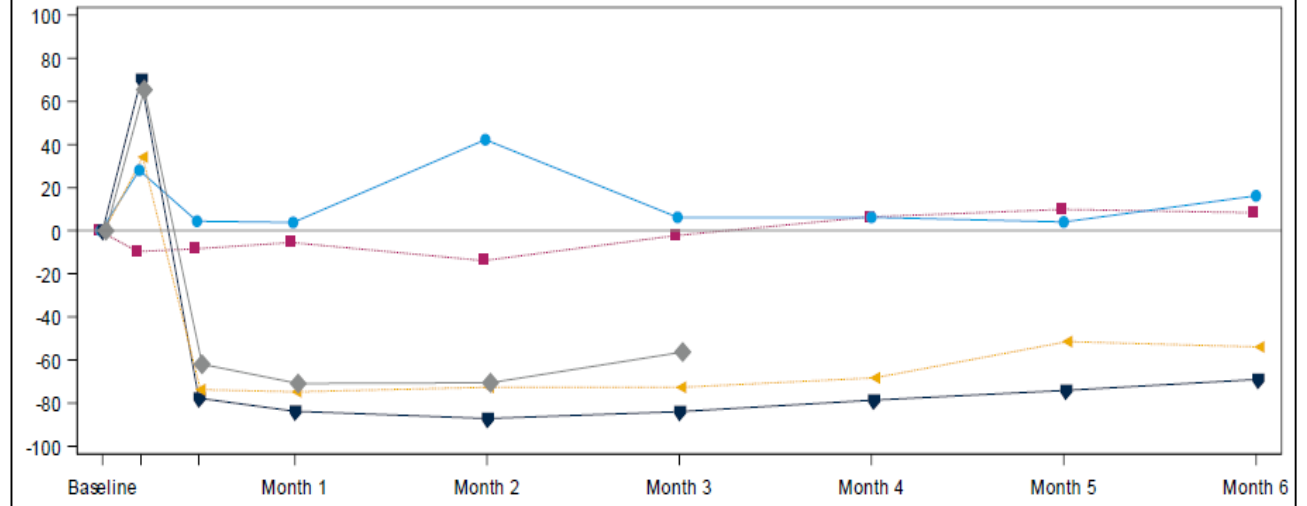
- CAA is caused by A β 1-40 in blood vessels
- 16% AD cases have CAA and are not eligible for anti-amyloid therapy (lecanemab)
- There is currently no effective and safe treatment for this devastating disease



Amyloid antisense therapy



Mean change in CSF A β 1-40



- 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!

COMING SOON

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



ADRC Consortium for Clarity in ADRD Research Through Imaging

Imaging Studies



Pills to slow Alzheimer's



BenfoTeam
Supervitamins & Nutrients

**Healthy Eating
Habits**



Cardiovascular risks



**Improving sleep for
brain health**



Behavioral approaches



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!