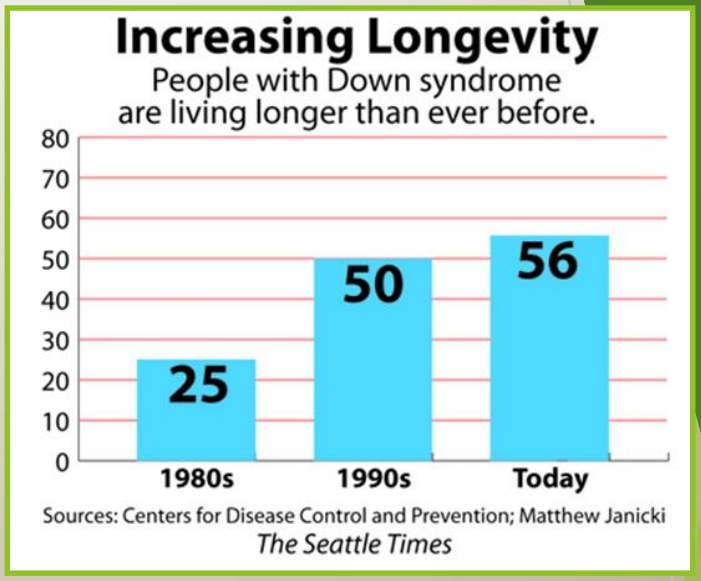
Down syndrome biobank Consortium

Knoebel Institute for Healthy Aging
Karolinska Institutet NVS

Lotta Granholm
Knoebel Institute for Healthy Aging
University of Denver

Down syndrome



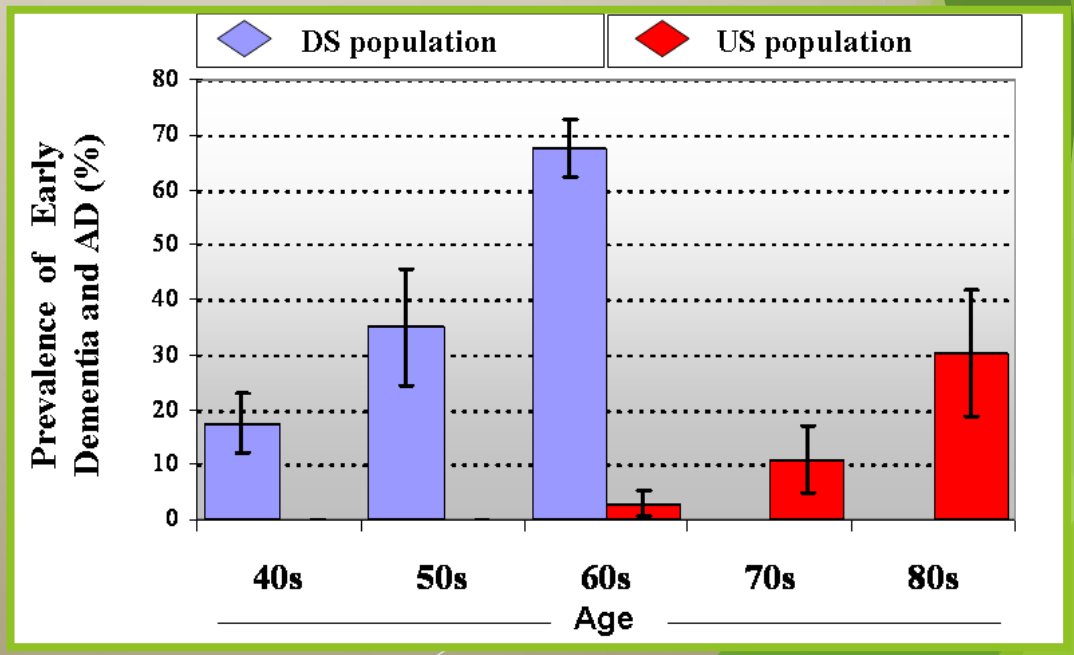
From: Matt Janicki

- Most: extra copy of Chr 21 from mother
- In < 5% of cases extra copy of Chr 21 from the father
- Remaining cases, the error occurs after fertilization

Accelerated aging in some body systems

Down syndrome and Alzheimer's

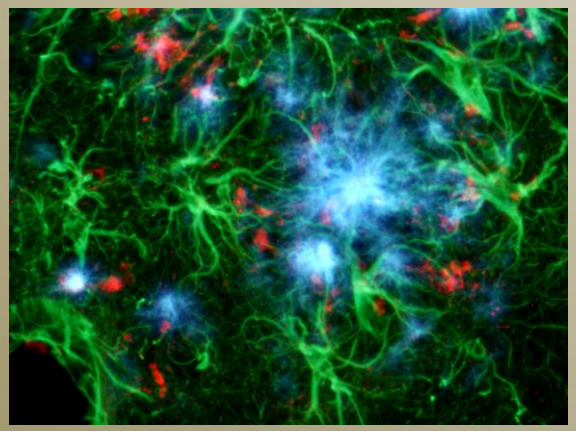
- Equal in all ethnic groups
- Increased risk and earlier onset
- 80% eventually develop dementia

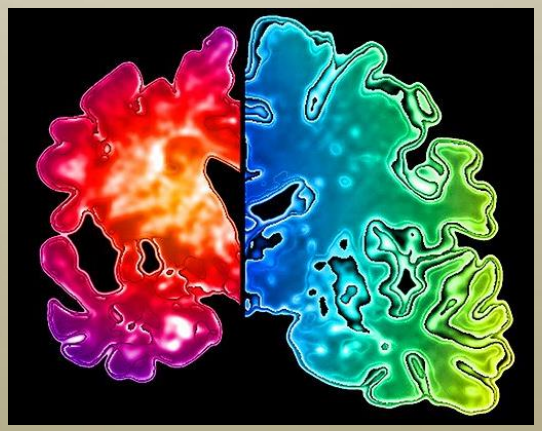


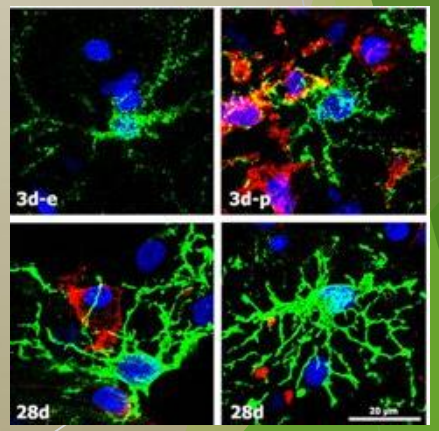
Hamlett et al., 2016

Biological correlates of dementia

- Protein aggregation - Amyloid and Tau
- Nerve cell (neuronal) Loss
- Inflammation
- Oxidative stress





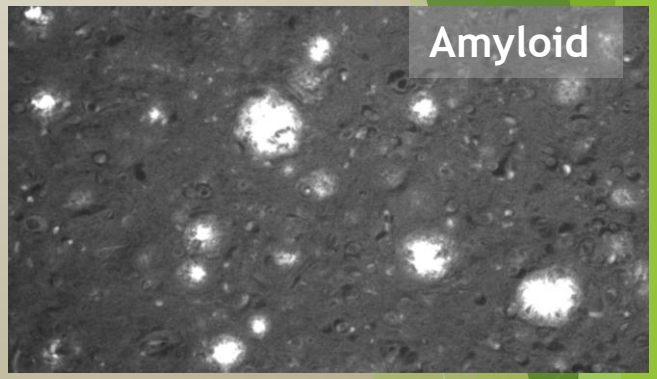


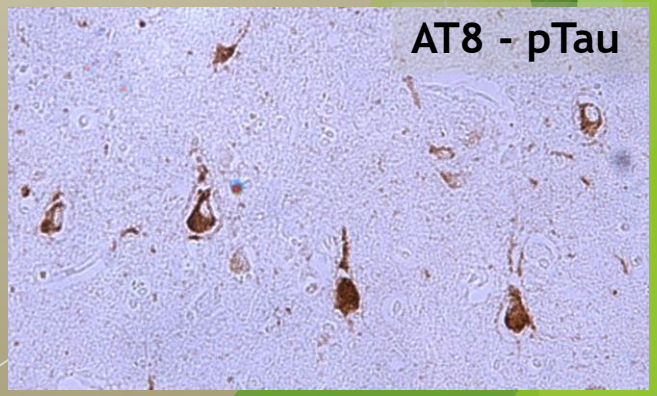
Neuropathology in DS-AD

- Accumulation of both **plaques** and **tangles**
- Similarities to Alzheimer pathology
- Oxidative stress, inflammation

Control 63 yrs

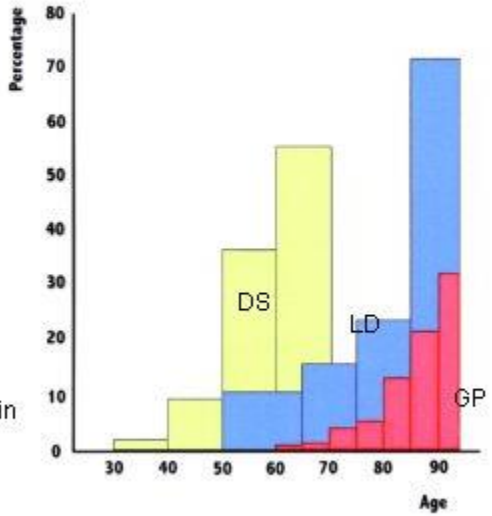
DS+AD 61 yrs





Variable dementia onset: need good biomarkers

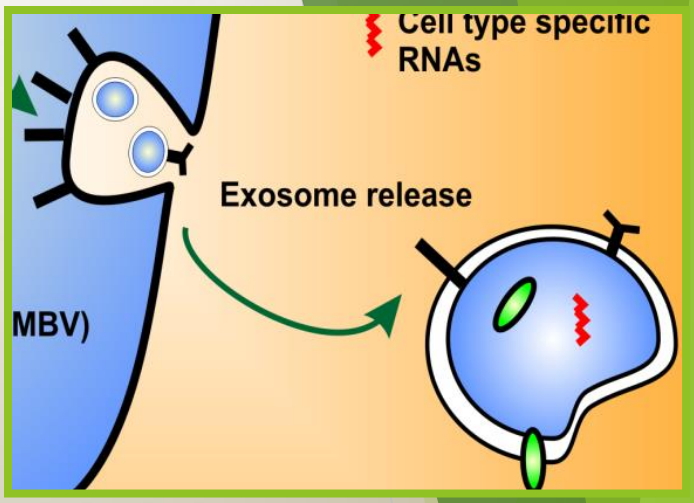
Comparative Rates of Dementia -
Down's syndrome, Learning disabilities, General Population



Cooper (reproduced in BPS/RCP Guidance 2009)

Image courtesy of the Down's Syndrome Association

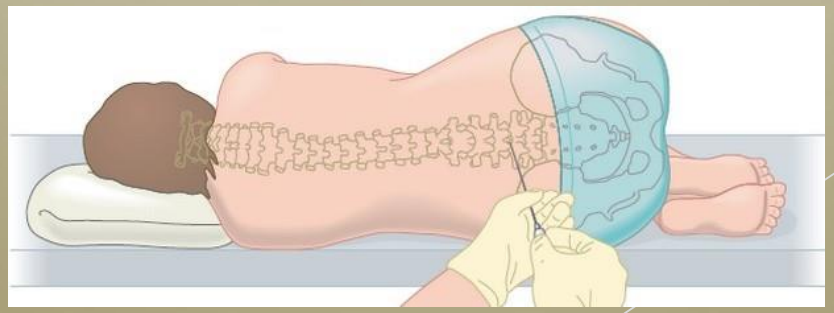
What is a biomarker?



- MRI or PET imaging
- Proteins in blood or CSF
- Exosomes in blood containing markers
- Studies of brain tissue *post mortem*

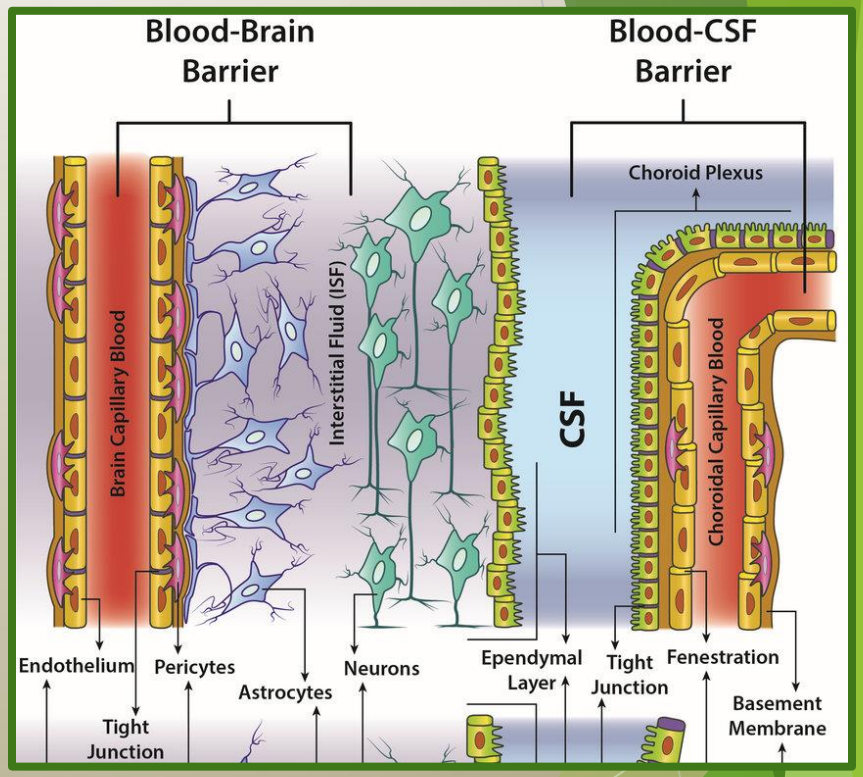
Pre mortem
Blood/CSF

Post mortem
Blood/CSF/Brain



Why do we need post mortem studies?

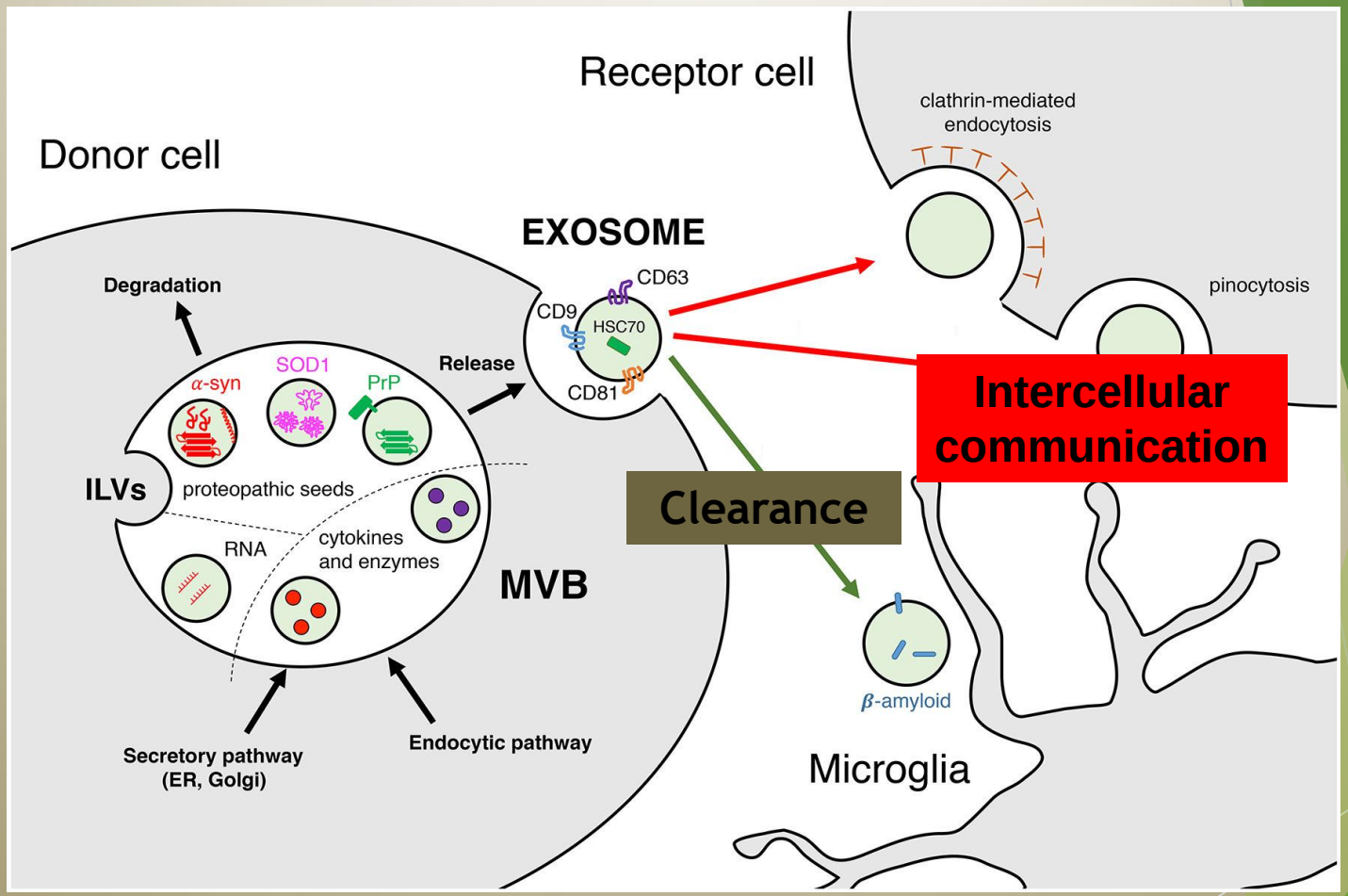
- Hard to diagnose dementia in live persons
- We still don't know the biological mechanisms for DS-related Alzheimer's
- Family members would like to know diagnose
- **Do blood or CSF biomarkers correlate with processes in the brain?**



D'Agata Molecules 23(1):9 · December 2017

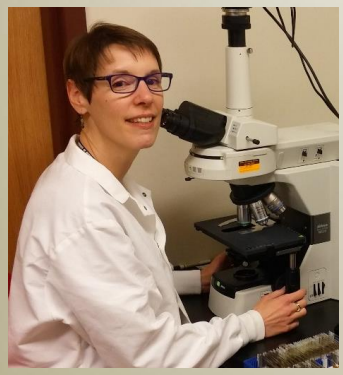
DOWN SYNDROME BIOBANK CONSORTIUM

The role of exosomes

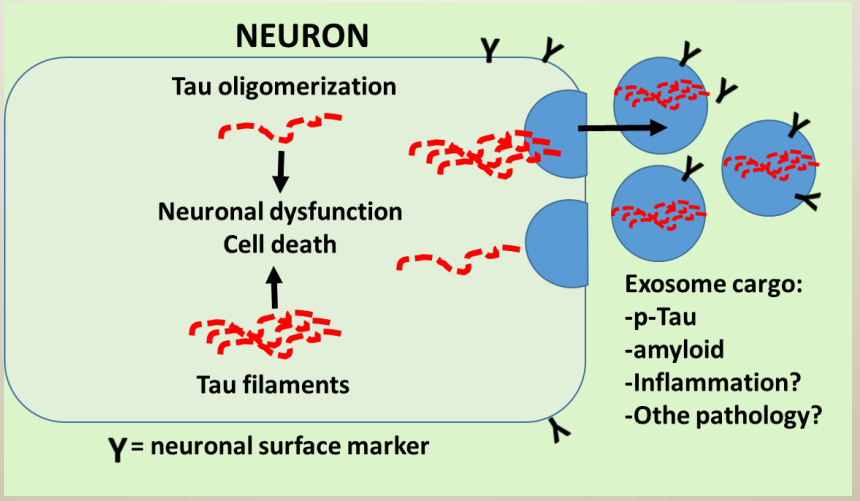


Soria et al. 2017 Front. Neurosc.

Neuron-derived exosomes



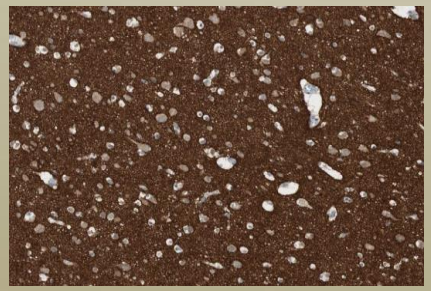
Aurelie Ledreux



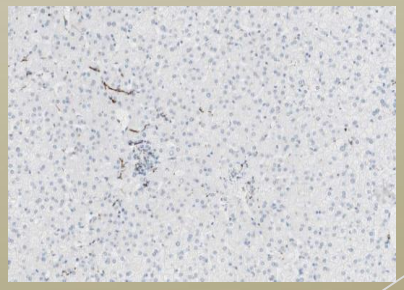
Eric Hamlett

Neuron-derived: L1CAM

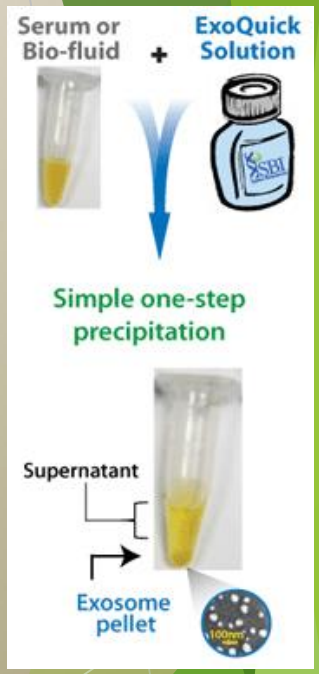
A. Brain cortex



B. Liver

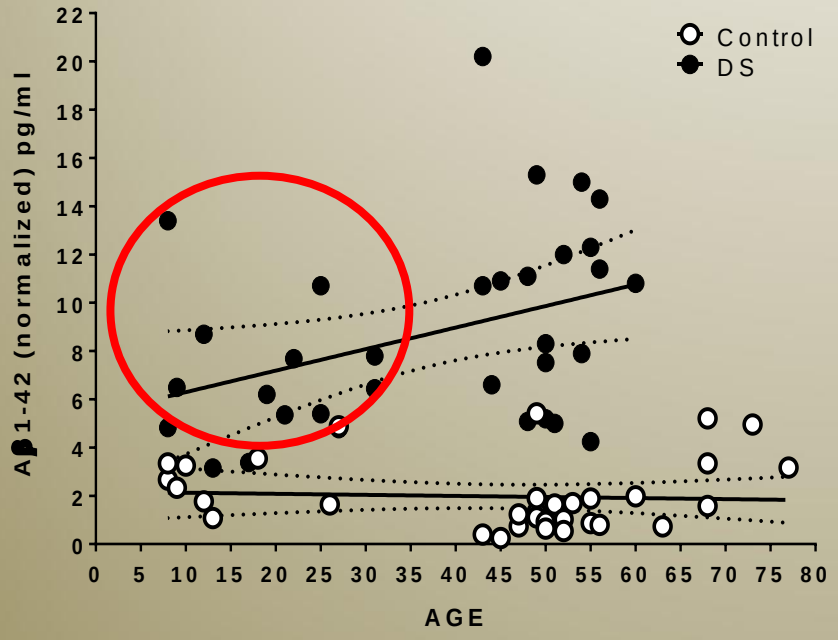


Photos:Human Protein Atlas licensed under the Creative Commons Attribution-ShareAlike 3.0 International License (thus not copyrighted). From (Uhlen et al., 2015).

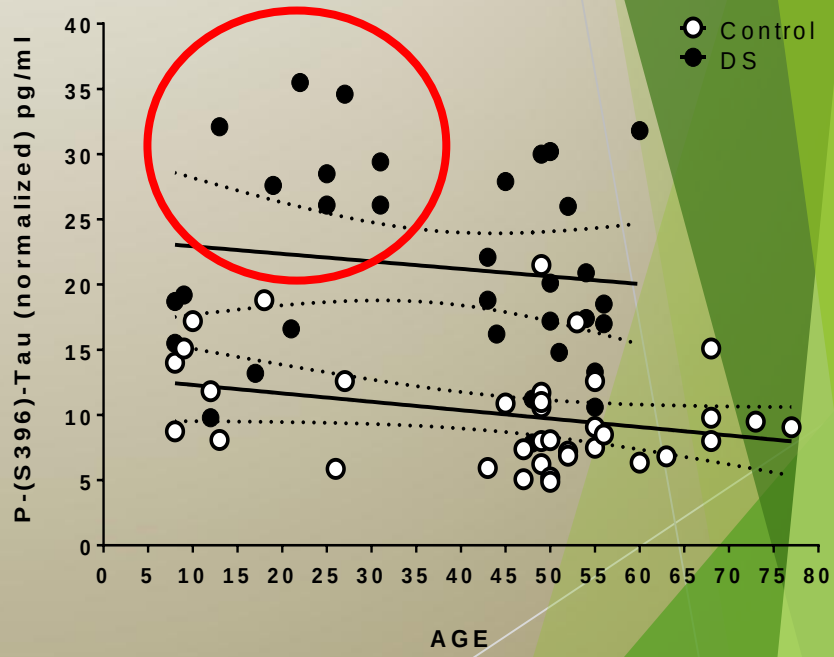


Exosomal biomarkers in a population with Down syndrome

Aß1-42 levels by Age



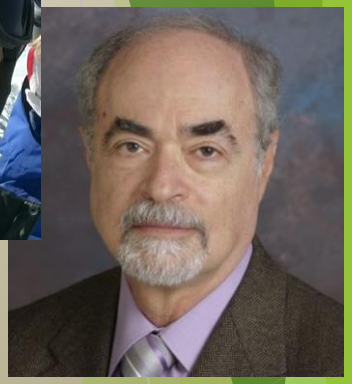
P-(S396)-Tau levels by Age

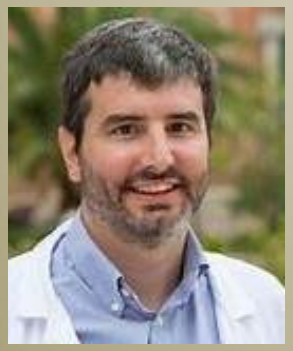


● Down syndrome ○ Controls

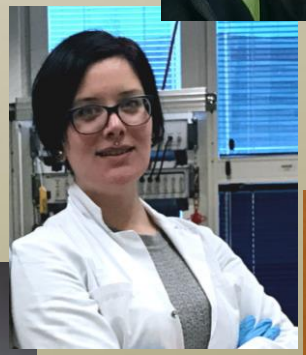
Tau pathology in DS

- New 5-year NIH grant
- Spread of tau pathology in mouse brain
- Aggregation properties of tau *in vitro*
- Mouse, human, and cell models

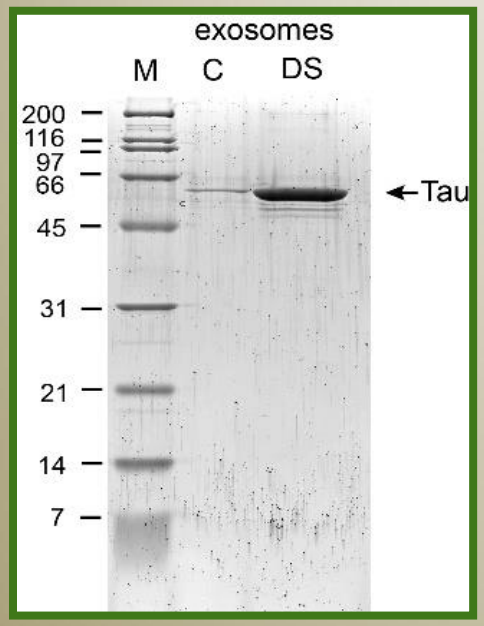




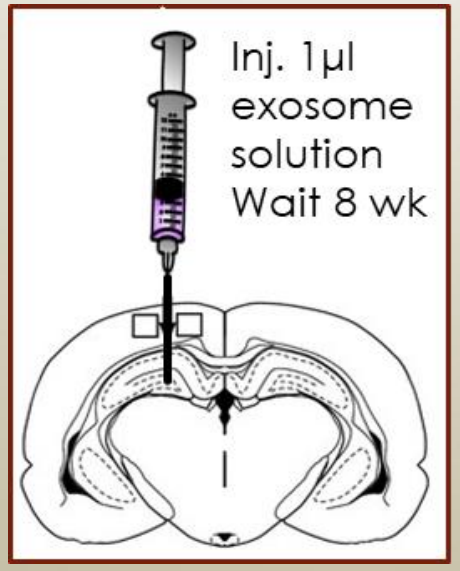
University of Denver
Karolinska Institutet
Barrow Neurological Institute
Sant Pau Hospital Barcelona
UC Irvine
MUSC



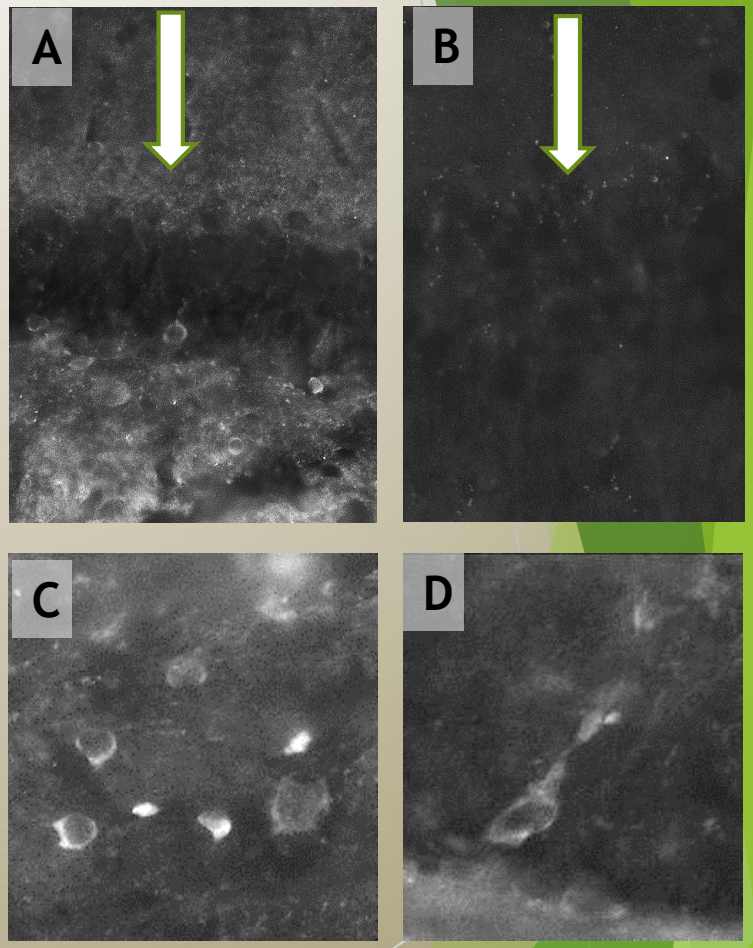
Propagation of Tau via exosomes



Amplification of Tau fibrils from exosomes from DS but not control

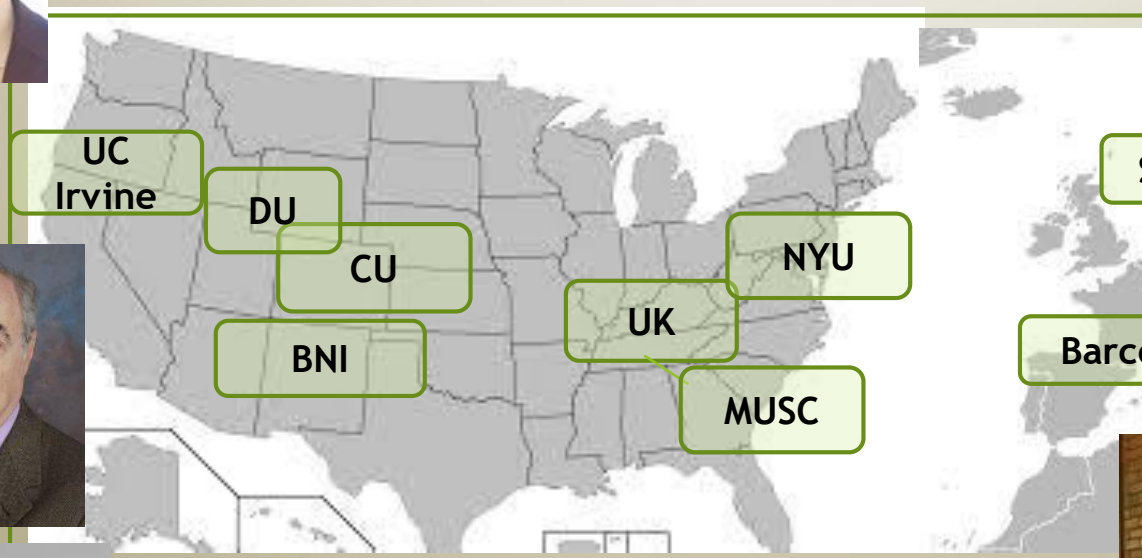


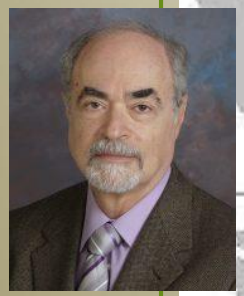
Can Tau pathology spread between species/individuals?

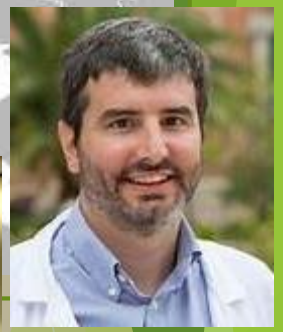


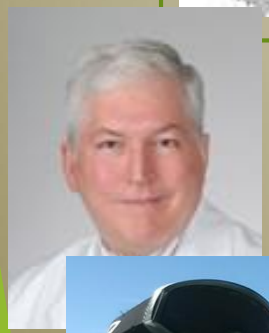
P-Tau antibodies Invitrogen polyclonal ab derived from a region of human Tau that contains s396 Conserved in mouse and rat

DOWN SYNDROME BIOBANK CONSORTIUM









- Provide tissues and biofluids
- Neuropathology staging
- Advocate for brain donation

BrightFocus™ Foundation
Cure in Mind. Cure in Sight.

The perfect storm

- Memory loss
- Protein aggregation
- Nerve cell (neuronal) Loss
- Inflammation

What can we do?

- Exercise/diet
- Reduce stress
- Battle inflammation
- Reduce systemic conditions

Together we can stop Alzheimer's

Thank you!