

Down syndrome biobank Consortium

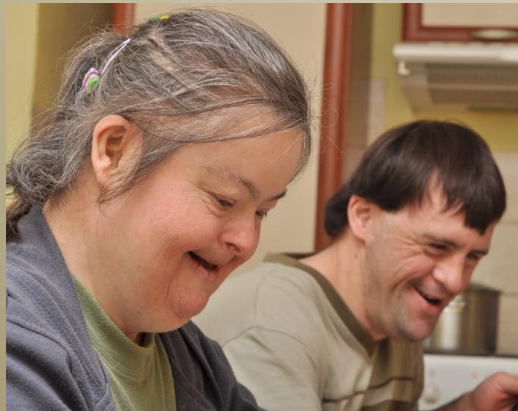
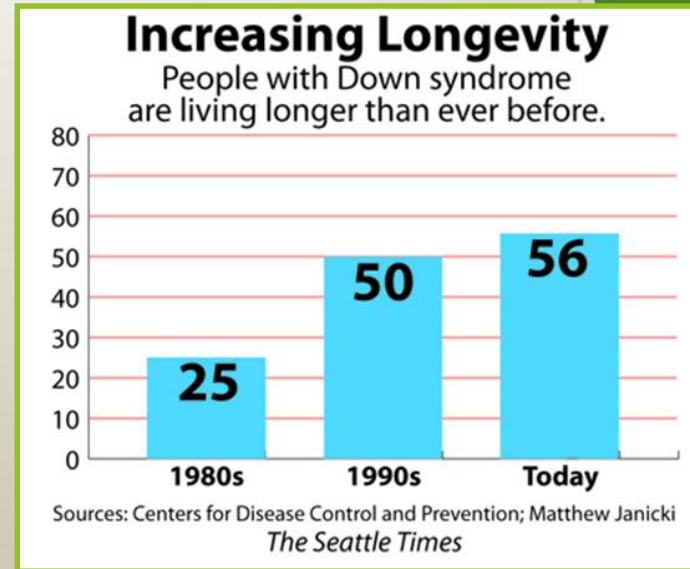
**Knoebel Institute for Healthy Aging
Karolinska Institutet NVS**



**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

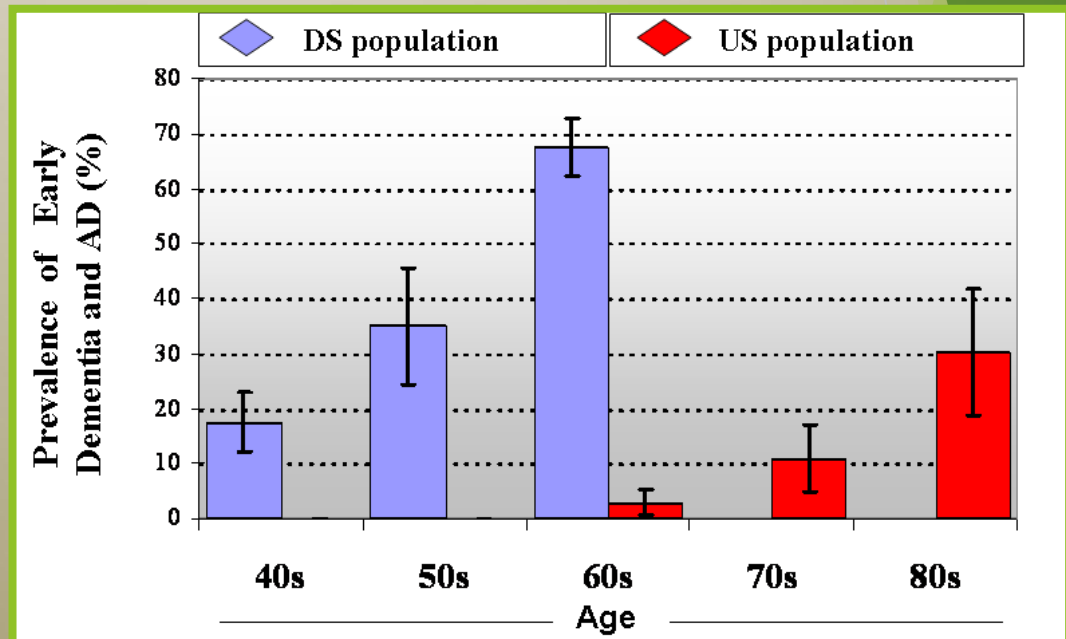
Accelerated aging in some body systems

Down syndrome and Alzheimer's

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

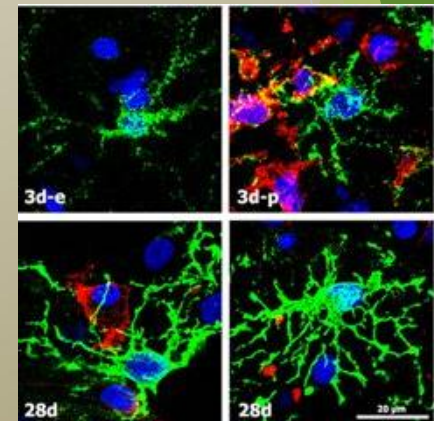
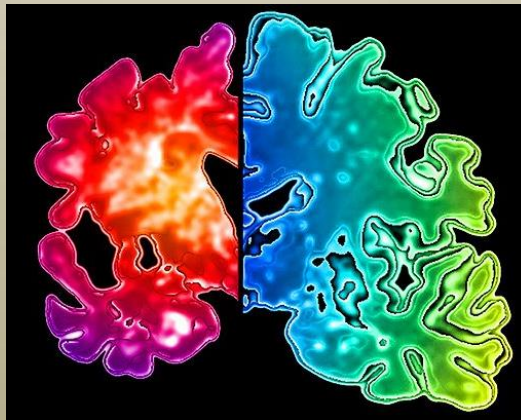
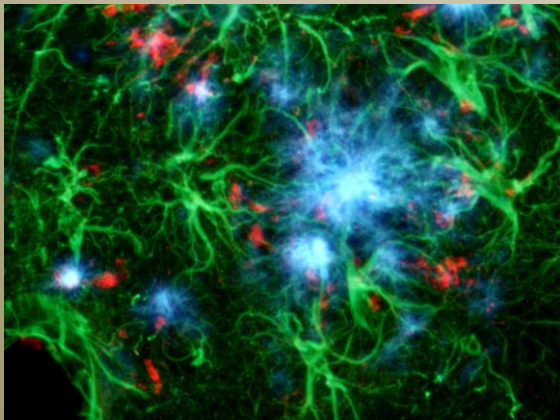


Hamlett et al., 2016



Biological correlates of dementia

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



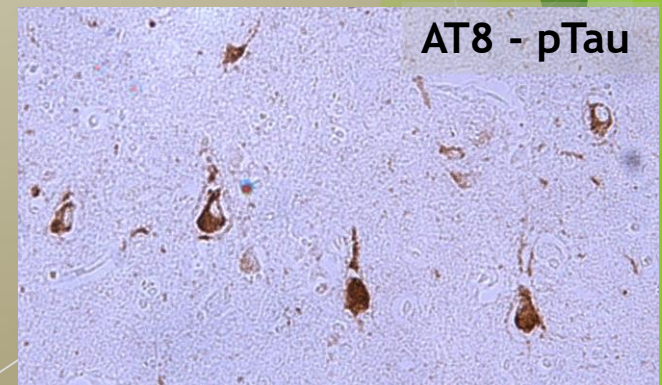
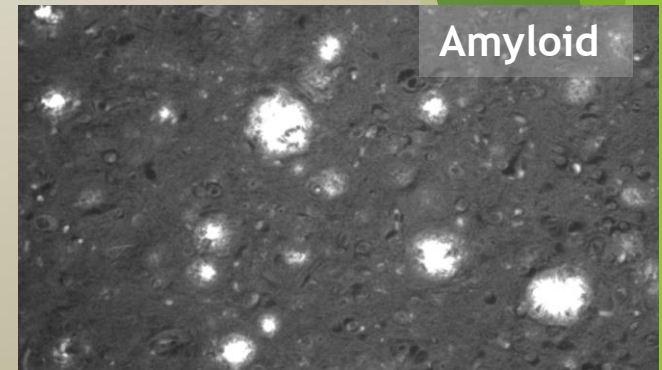
Neuropathology in DS-AD

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

Control 63 yrs

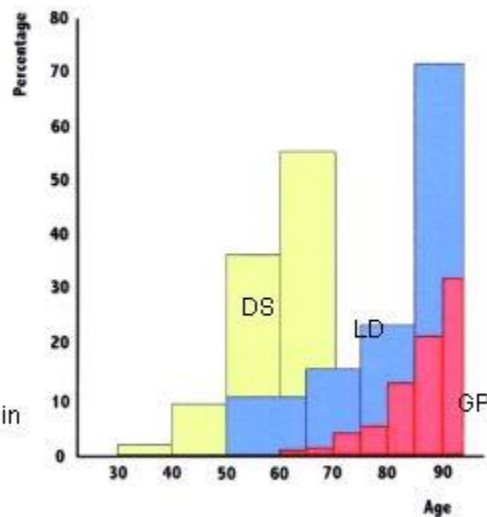


DS+AD 61 yrs



Variable dementia onset: need good biomarkers

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



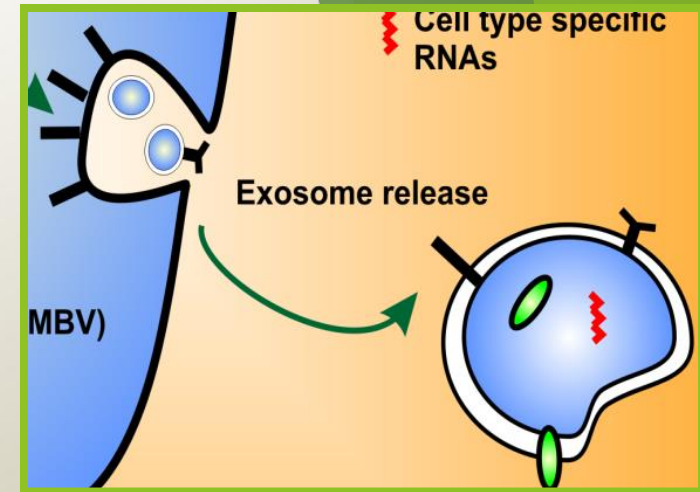
Cooper (reproduced in
BPS/RCP Guidance
2009)



Image courtesy of the Down's Syndrome Association

What is a biomarker?

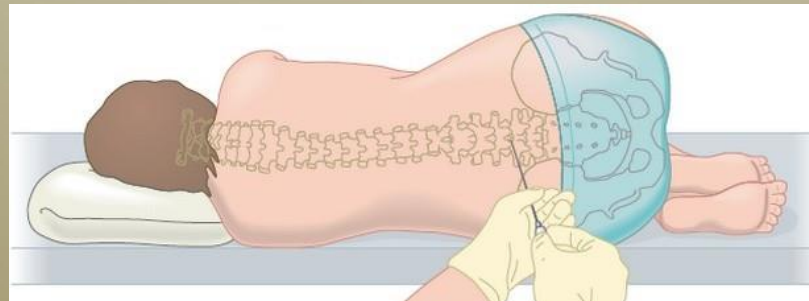
- ▶ MRI or PET imaging
- ▶ Proteins in blood or CSF
- ▶ Exosomes in blood containing markers
- ▶ Studies of brain tissue *post mortem*



**Pre mortem
Blood/CSF**

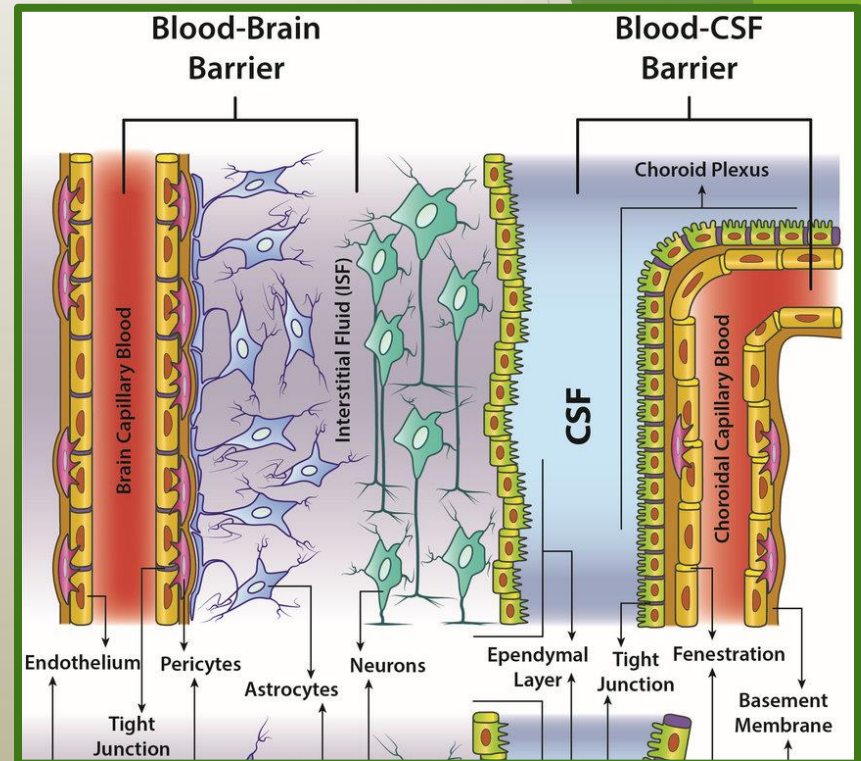


**Post mortem
Blood/CSF/Brain**



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

The diagram illustrates the role of exosomes in intercellular communication and clearance of neurodegenerative markers. It shows a **Donor cell** on the left and a **Receptor cell** on the right.

Donor Cell:

- MVB (Multivesicular Body):** Contains **ILVs (Intraluminal Vesicles)** and **proteopathic seeds**. Specific markers shown include α -syn, SOD1, PrP, RNA, and cytokines/enzymes.
- Secretory pathway (ER, Golgi):** Leads into the MVB.
- Endocytic pathway:** Also leads into the MVB.
- Degradation:** Indicated by an arrow pointing away from the MVB.
- Release:** An arrow points from the MVB to the **EXOSOME**.

EXOSOME:

- Marked with surface proteins: **CD9**, **CD63**, **CD81**, and **HSC70**.

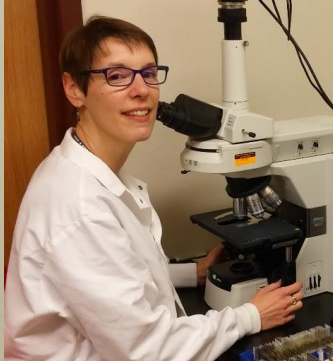
Receptor Cell:

- clathrin-mediated endocytosis:** A vesicle containing an exosome is shown being internalized.
- pinocytosis:** Another pathway for exosome uptake is shown.

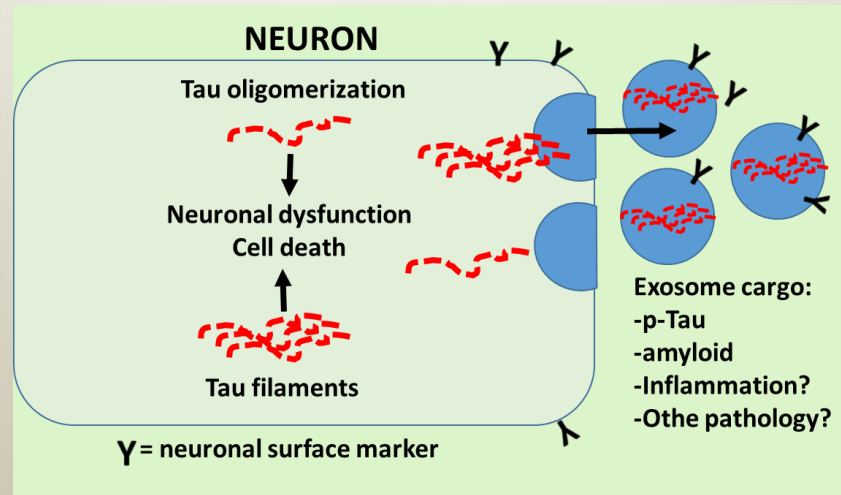
Interactions and Outcomes:

- Intercellular communication:** A red box highlights the transfer of signals between cells via exosomes.
- Clearance:** A green arrow points from an exosome to a **Microglia** cell, which is shown engulfing a **β -amyloid** deposit.

Neuron-derived exosomes



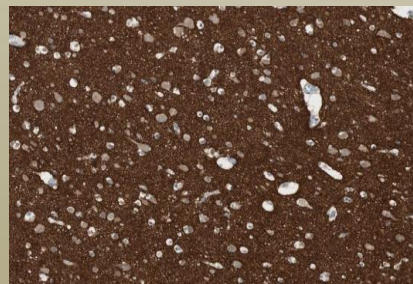
Aurelie Ledreux



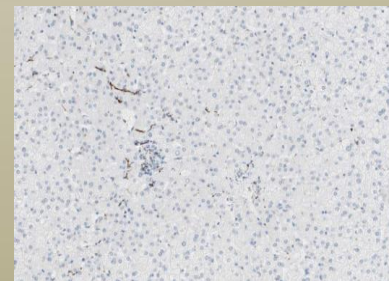
Eric Hamlett

Neuron-derived: L1CAM

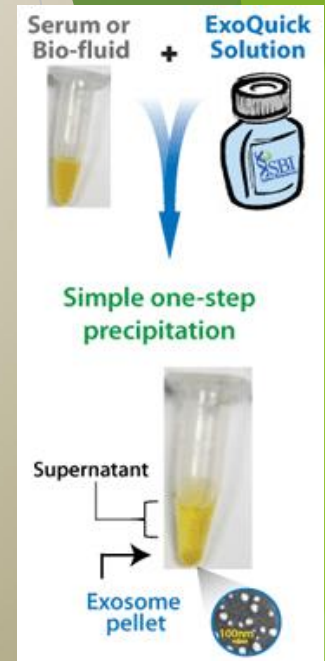
A. Brain cortex



B. Liver

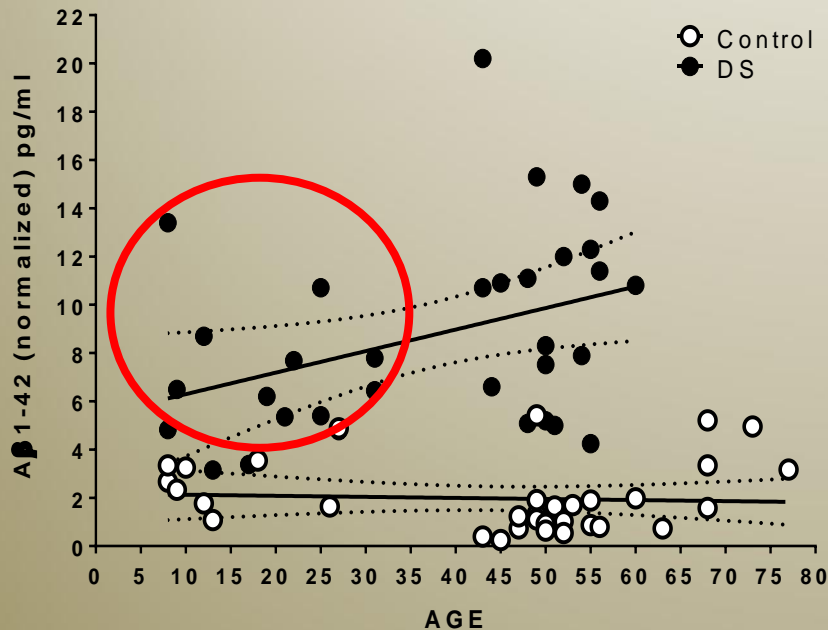


Photos: Human Protein Atlas licensed under the Creative Commons Attribution-ShareAlike 3.0 International License (thus not copyrighted). From (Uhlen et al., 2015).

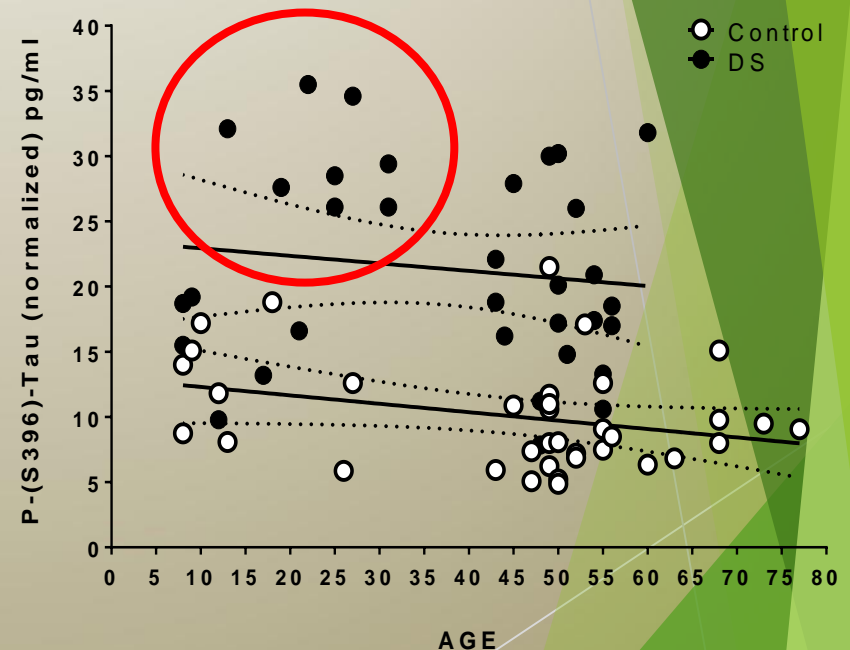


Exosomal biomarkers in a population with Down syndrome

AB1-42 levels by Age



P-(S396)-Tau levels by Age



● Down syndrome

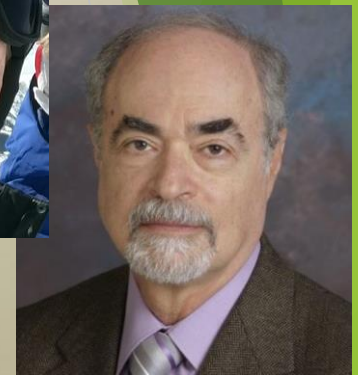
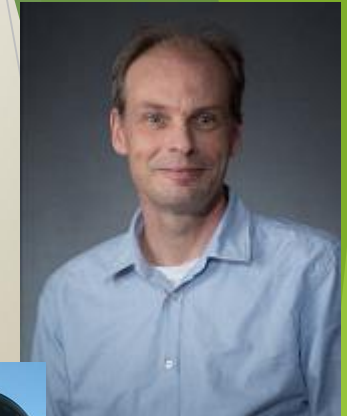
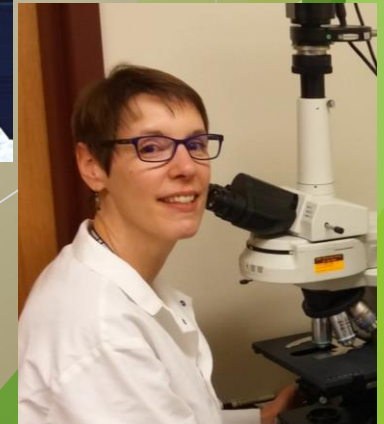
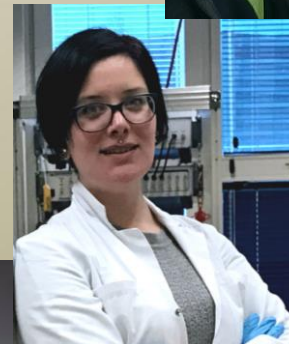
○ Controls

Tau pathology in DS

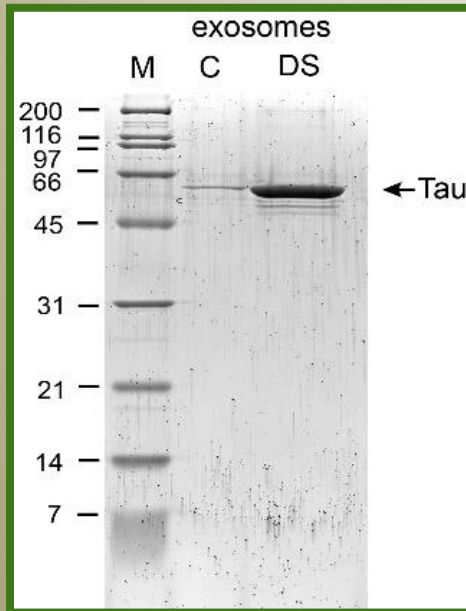
- ▶ New 5-year NIH grant
- ▶ Spread of tau pathology in mouse brain
- ▶ Aggregation properties of tau *in vitro*
- ▶ Mouse, human, and cell models



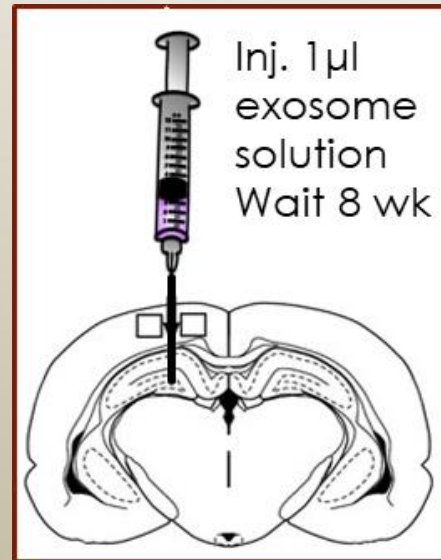
University of Denver
Karolinska Institutet
Barrow Neurological Institute
Sant Pau Hospital Barcelona
UC Irvine
MUSC



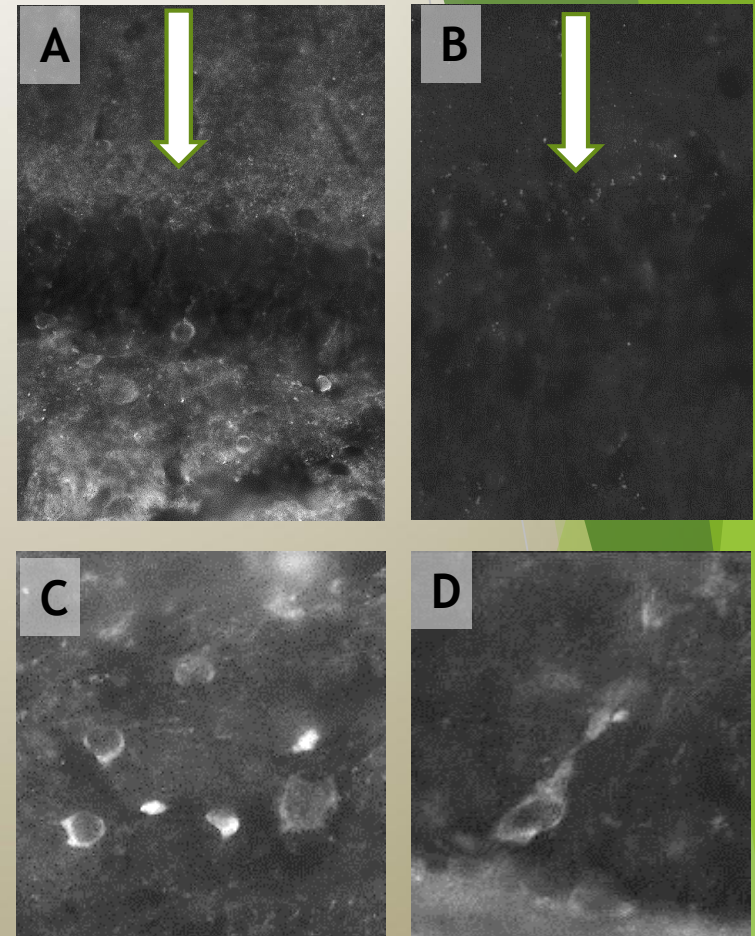
Propagation of Tau via exosomes



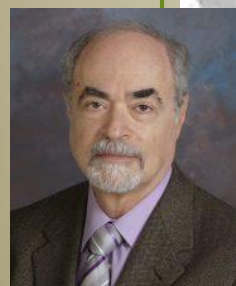
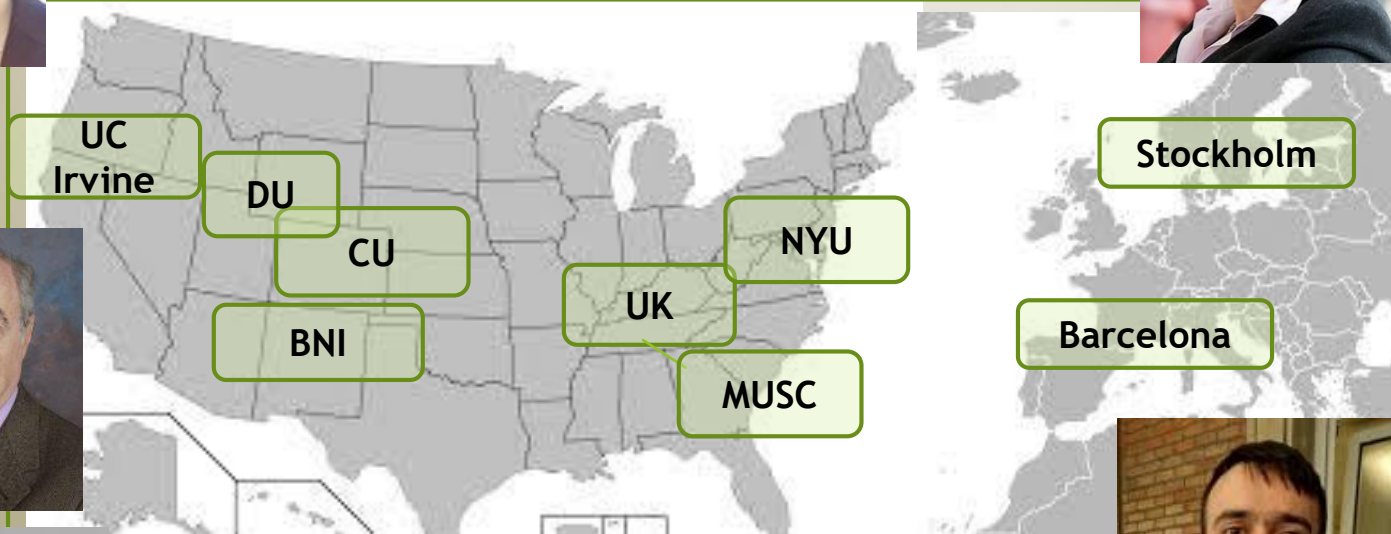
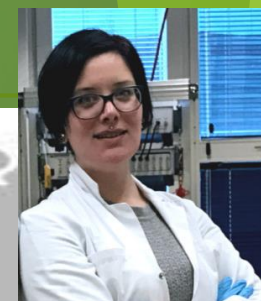
Amplification of Tau fibrils from exosomes from DS but not control



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



Barcelona



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

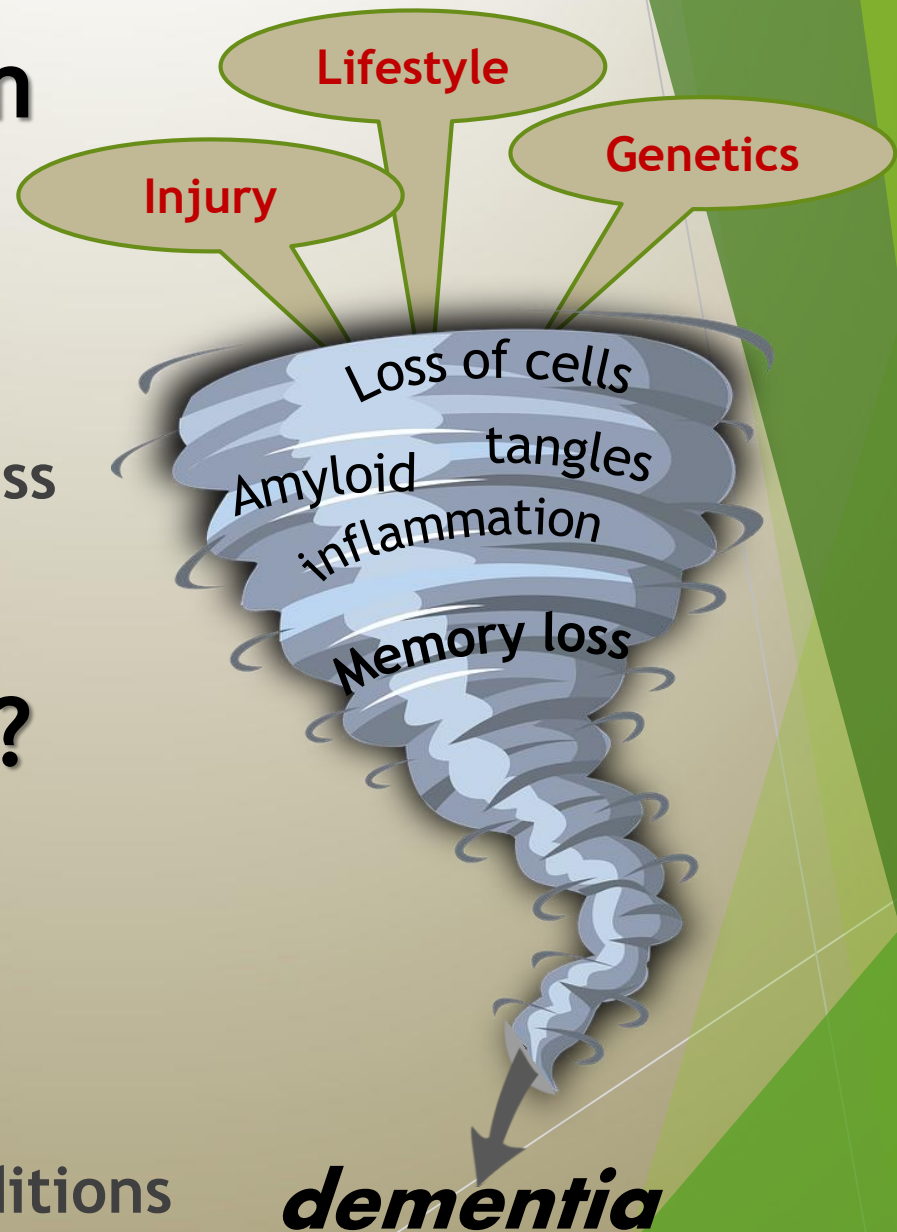


The perfect storm

- ▶ 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

Summit of
Mt. Neuroscience

Elevation 14,130 feet

CERULEAN & CHOLINERGIC

Neuronal Forests

Thank you!