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Dementia Discovery Fund

Update and scientific deep-dive with Bill Gates

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Agenda

- **DDF update**
- **Portfolio overview**
- Scientific deep dive into current prioritised areas of scientific focus for DDF
    1) Microglia, the role of glia in synaptic health, lead by Professor Beth Stevens
    2) Mitochondrial dynamics and their role in dementia, lead by Professor Daria Mochly-Rosen
- DDF summary

Global burden of dementia

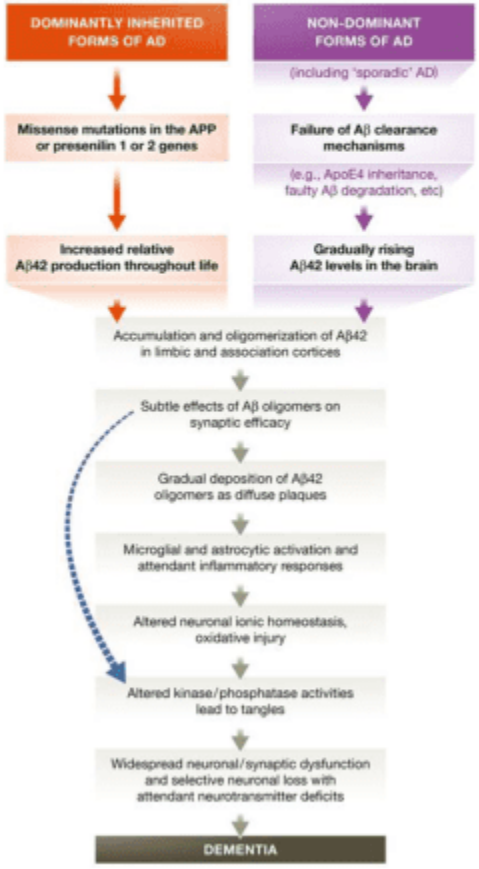
- By 2030, there will be 75 million people with Alzheimer's disease globally, costing $2 trillion
- No drugs that have any effect on the course of diseases of dementia have been developed yet
- To discover disease-modifying new drugs, we need different approaches to those tried historically
- The DDF is committed to investing in new biological approaches (outside amyloid β) to develop a range of safe, clinically effective drugs which can prevent or slow down the course of dementia
  - Taking a long-term approach to funding new approaches to treat dementia
  - Supporting start-ups considered too risky by regular venture capital firms

The market for dementia drugs is massive and finding a way to open it up is an investment opportunity worth getting right

Dementia Discovery Fund: Update

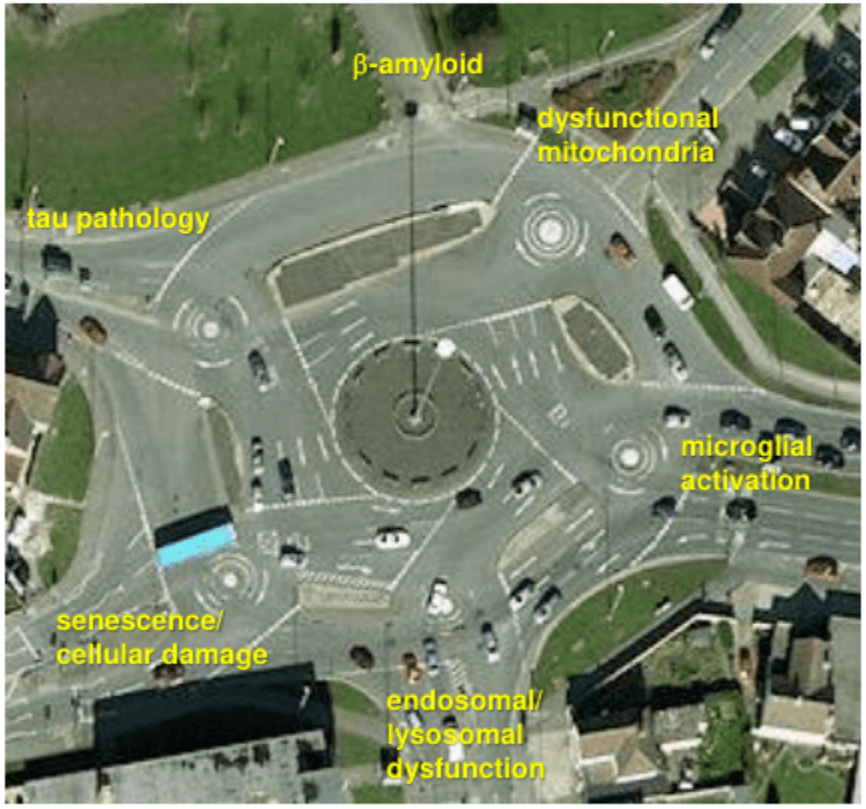
- Dementia represents a massive unmet medical need with huge associated costs of care
- Launched in October 2015 as a result of the G8 Summit and World Dementia Council meetings, the DDF is the world's first dementia-focused venture capital fund - the first time charity, government and pharma have joined forces with a venture firm on this scale
- Our vision is to demonstrate compelling disease-modifying clinical efficacy and safety data for 2-3 novel drugs in dementia patients by 2025, and expanded dramatically the range of treatment options in drug discovery and development
- We have privileged access to global CNS pharma experts through our Scientific Advisory Board
  - Provide advice, share knowledge and offer insights on different approaches and historical failures
  - The pharma companies have no commercial or decision making rights though they will be well positioned to acquire/license DDF-developed drugs/companies in due course
- DDF has raised ~£100M to date from strategic investors, and Woodford Investment Management (to close in April). DDF is now seeking an additional £130M to reach its target

A roundabout, not a cascade



The amyloid cascade hypothesis at 25 years, Selkoe and Hardy, EMBO 2016

DDF perspective on dementia pathogenesis (The Magic Roundabout):



DDF scientific strategy

- We have prioritized four key scientific areas initially, supported by human genetic and pathological data for near term, proactive investment, whilst remaining open to compelling opportunities outside of these key areas:

Microglial biology & inflammation

Mitochondrial dynamics

Trafficking and membrane biology

Synaptic physiology & function

Opportunistic

DDF investments map on to scientific strategy

- DDF investments range from DDF-led research projects to investments in established companies
- Current and near future (---) investments are shown:

Microglial biology & inflammation:

ALECTOR

Neuroinflammation Project

TIAKI THERAPEUTICS

Mitochondrial dynamics:

Rheostat

Mitoconix

Synaptic physiology & function:

Scholar Rock TGFβ Project

autifony THERAPEUTICS

cerevance

Trafficking and membrane biology:

Membrane Contact Sites Project

Opportunistic:

DDF ChemCo

gen2

Parkinson's Dementia Target Project

DDF Investment Criteria

Disease modifying impact

- We invest in drug discovery opportunities that have the potential to prevent or slow the course of dementia

Scientific opportunity

- We invest in biological mechanisms that have already demonstrated clinical impact in diseases outside dementia, as well as new mechanisms which can be proven in stratified patient groups

Filling the gaps

- We invest in targets and mechanisms too early for pharma and too high risk for most venture funds
- We deploy long-term and flexible capital to fund key scientific milestones that overcome critical hurdles in the development of dementia therapies by working with our world-class, global network of experts

Leveraging DDF investments

- We invest in projects and companies with potential to attract funds from sources beyond the DDF and its investors

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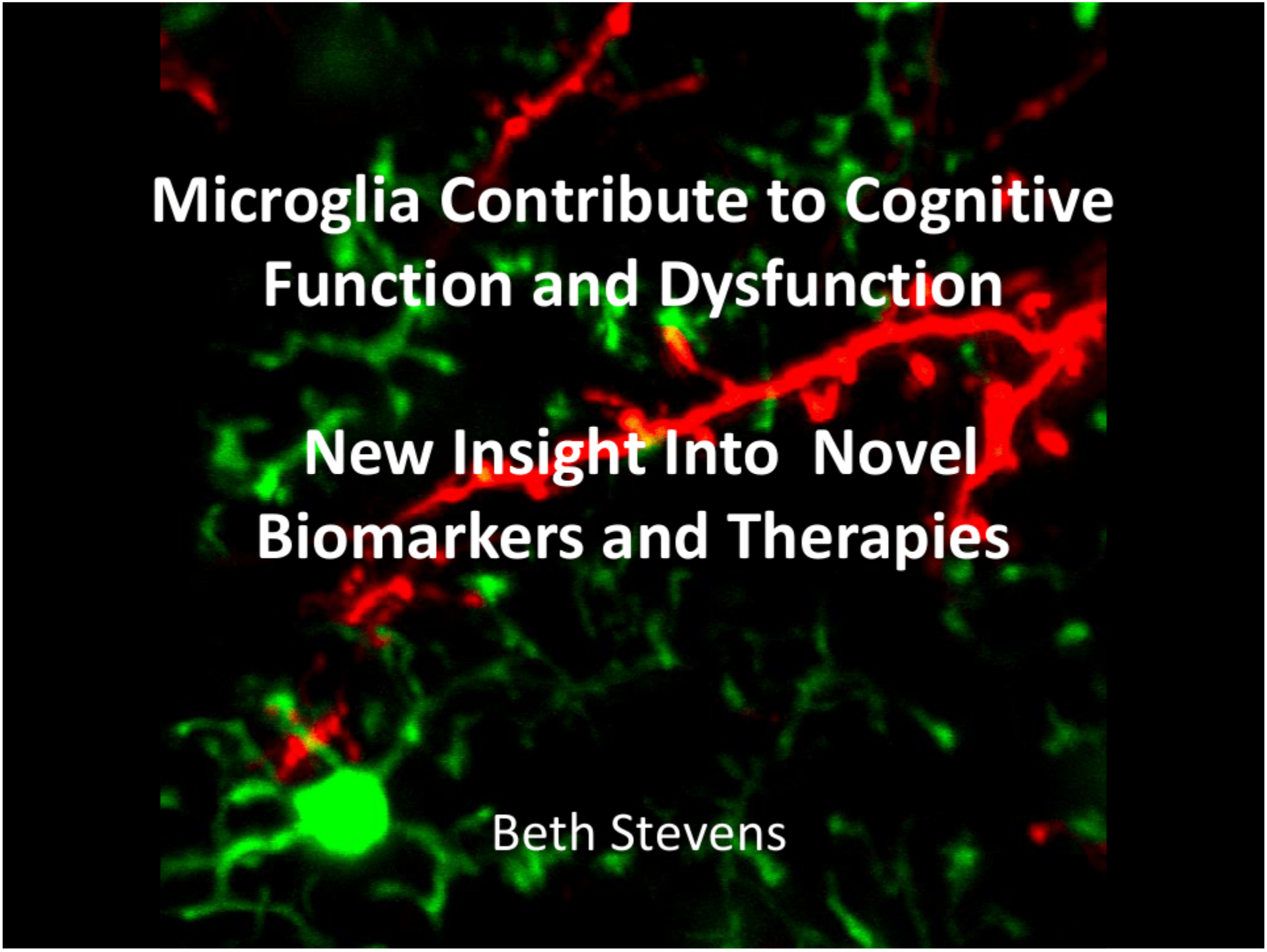
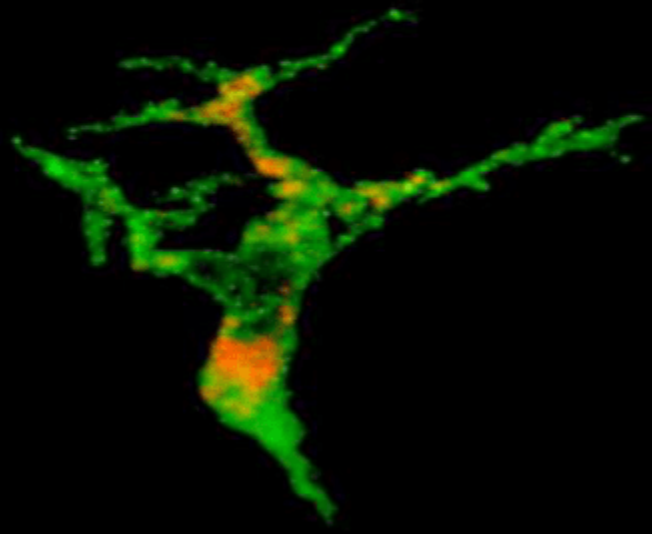

Microglia Contribute to Cognitive Function and Dysfunction
New Insight Into Novel Biomarkers and Therapies
Beth Stevens

Established Roles of Microglia: Both Harm and Protect the Brain

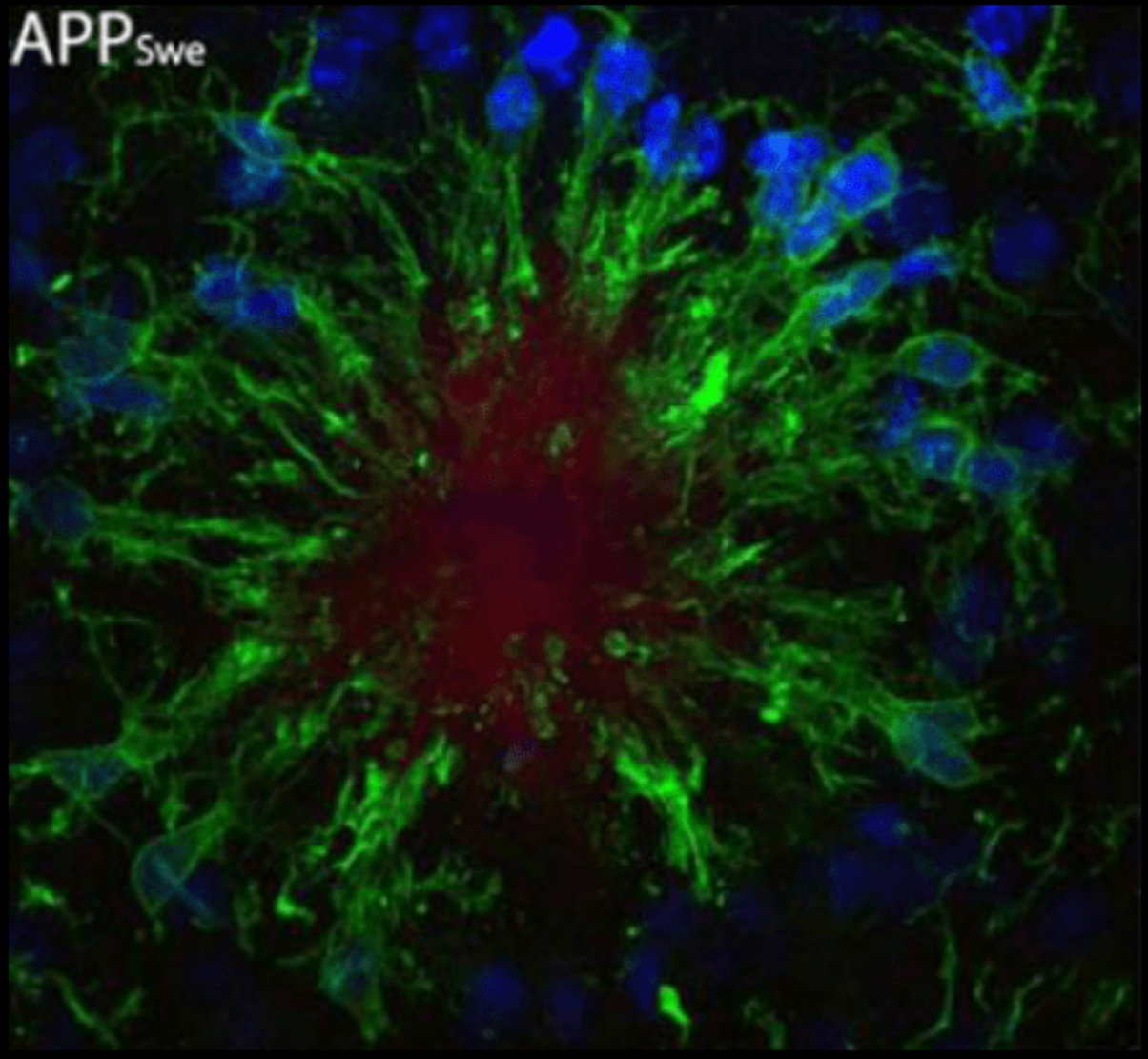
1. Neuroinflammation

2. Clear pathogens and debris

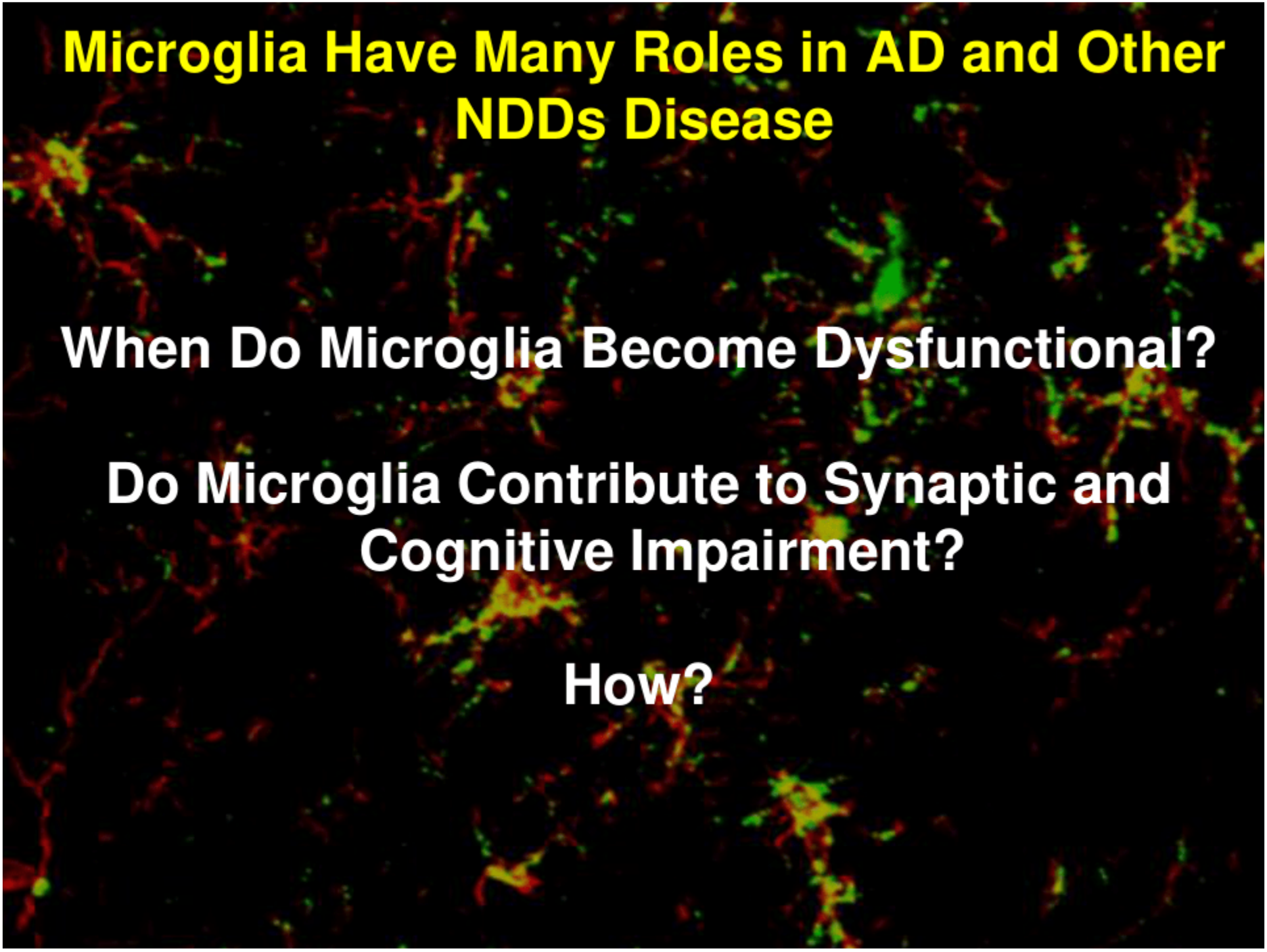
3. Remove toxic proteins



Activated Microglia Surround Plaques in Alzheimer's Disease Brain



Microglia Have Many Roles in AD and Other NDDs Disease



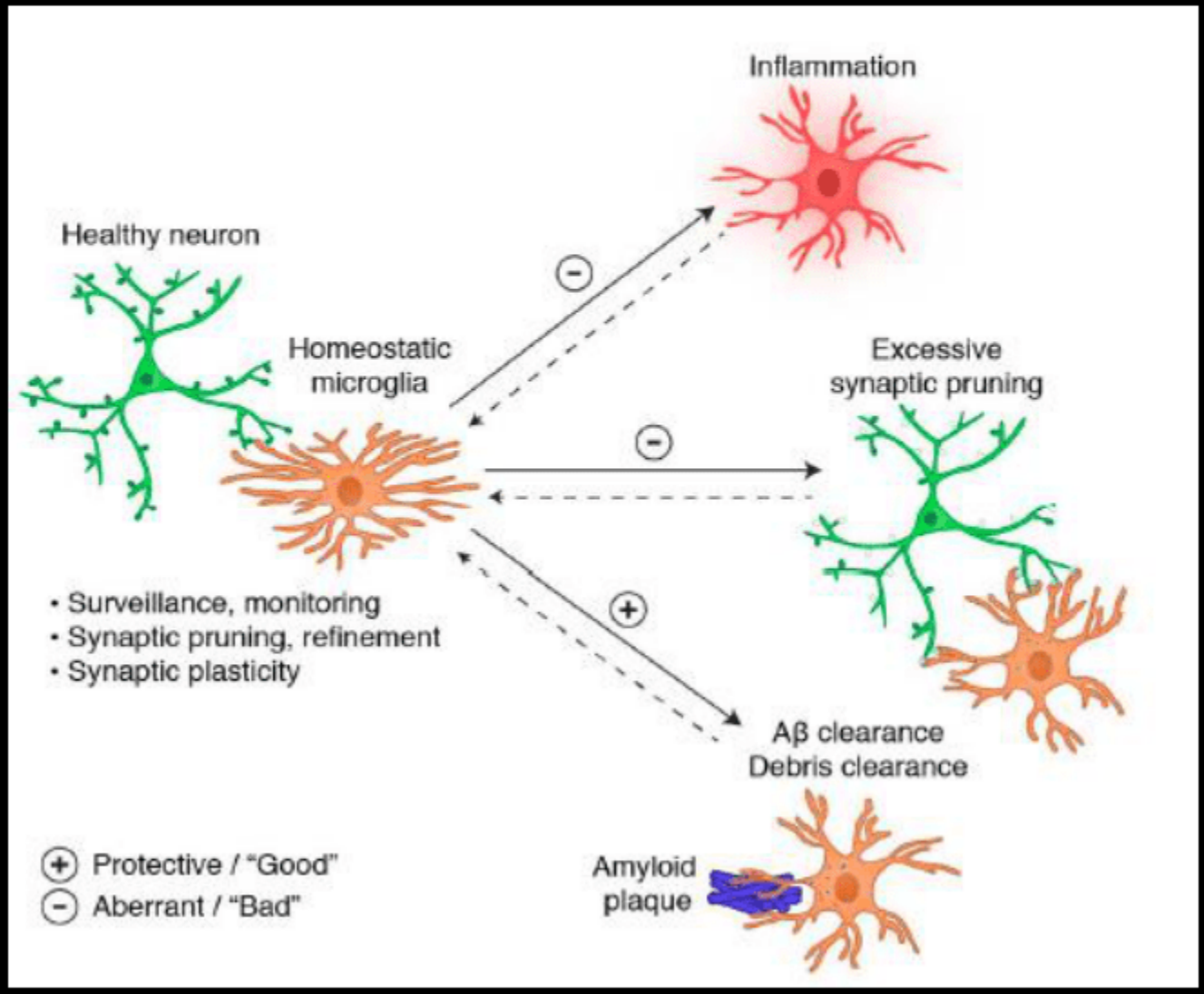
When Do Microglia Become Dysfunctional?

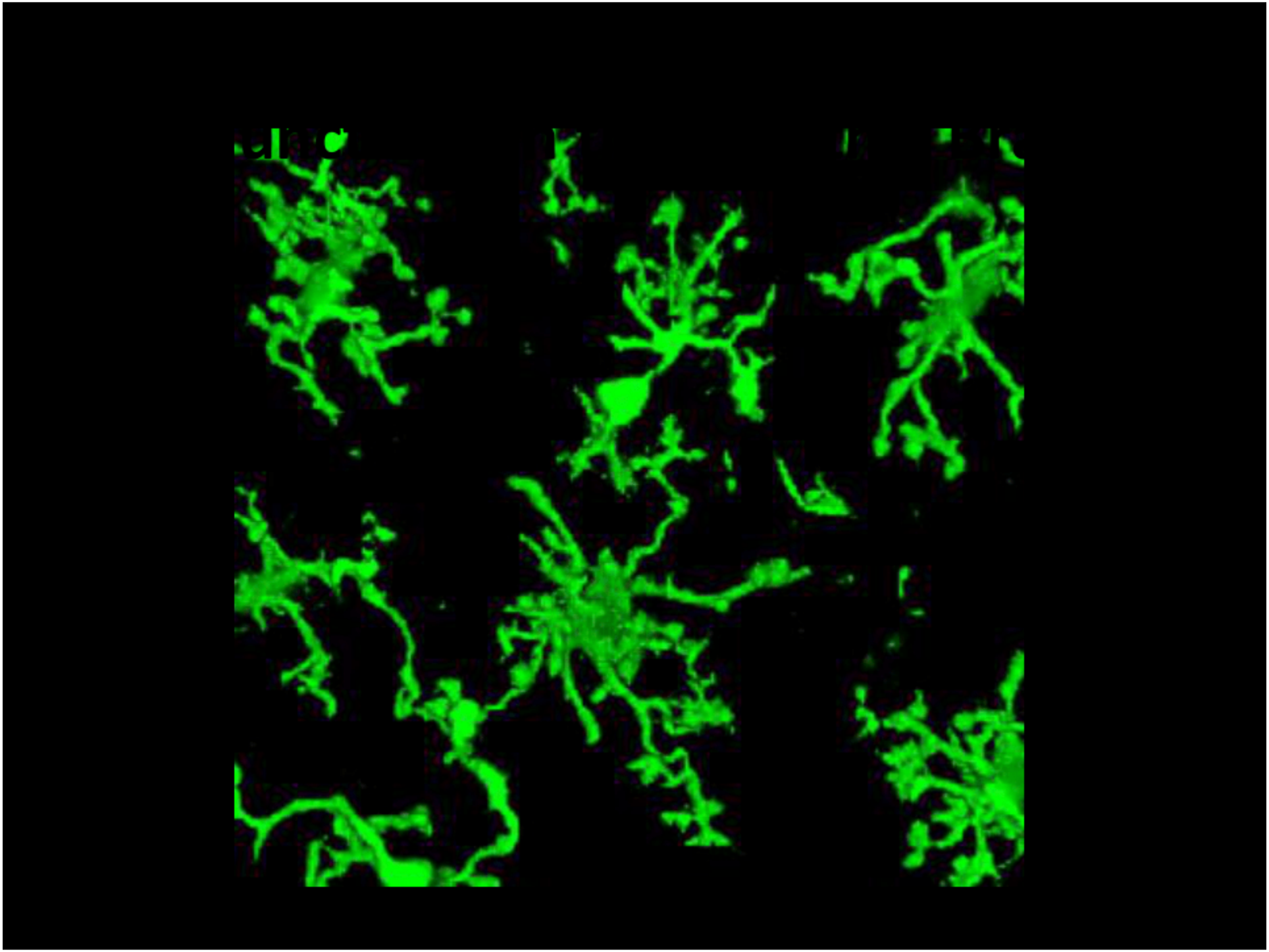
Do Microglia Contribute to Synaptic and Cognitive Impairment?

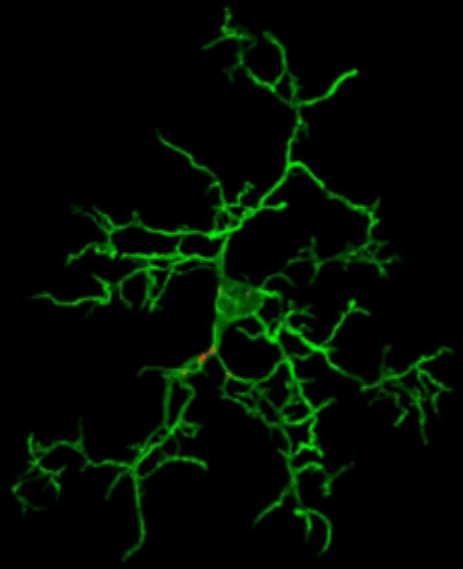
How?

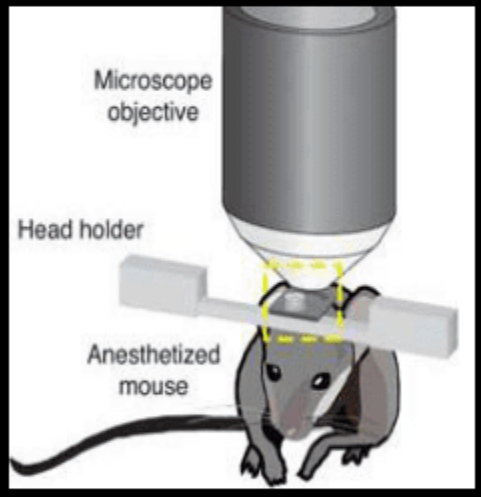
Microglia Have Many Roles in Neurodegenerative Disease

Understanding Microglia Biology and Specific Mechanism is Critical



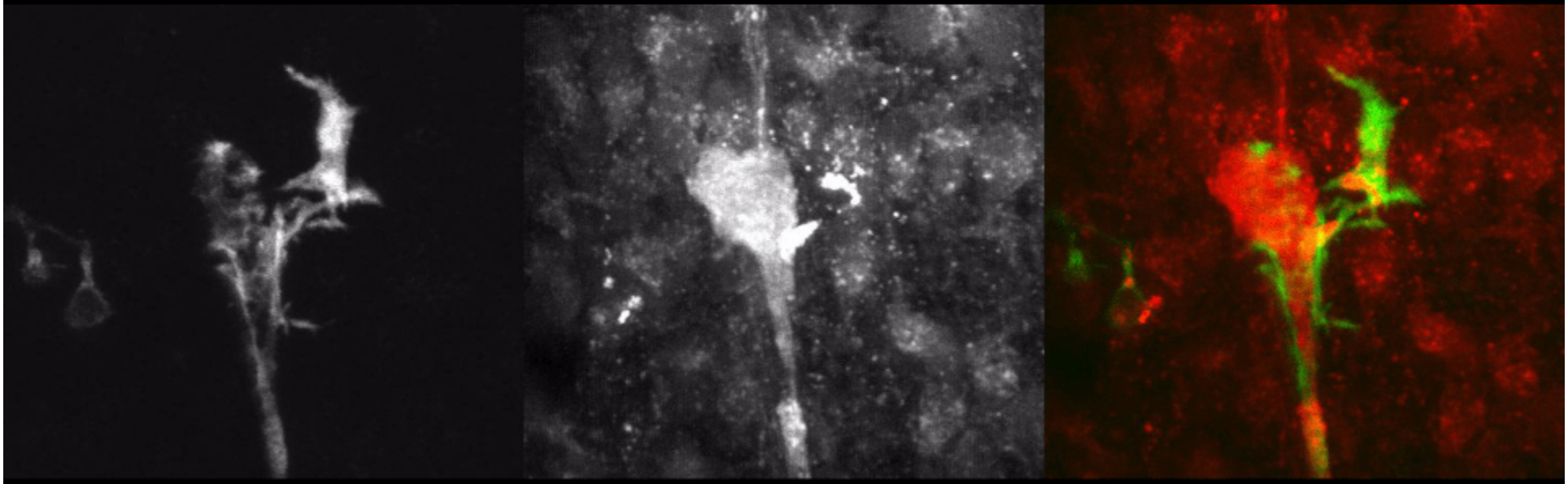




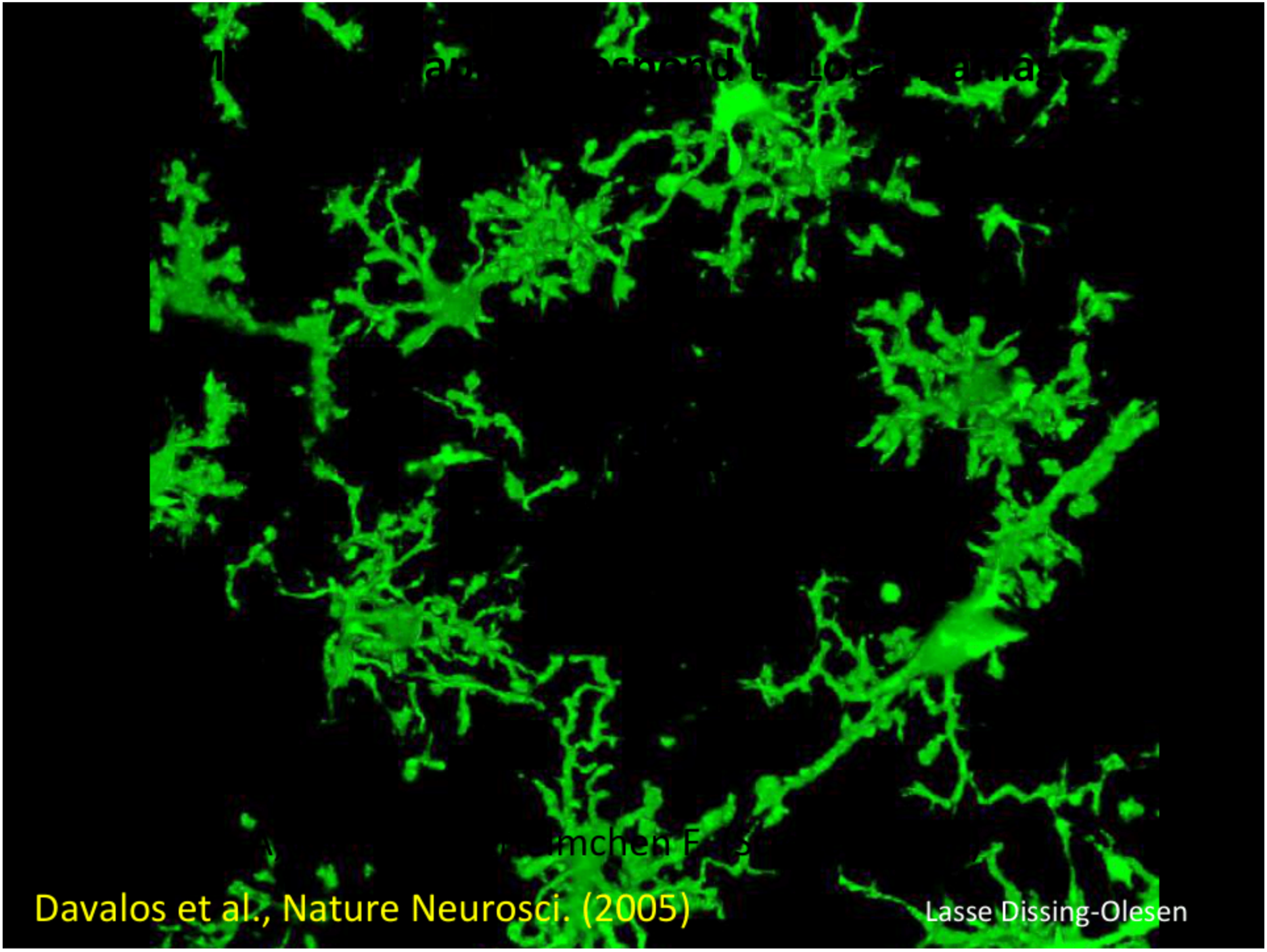


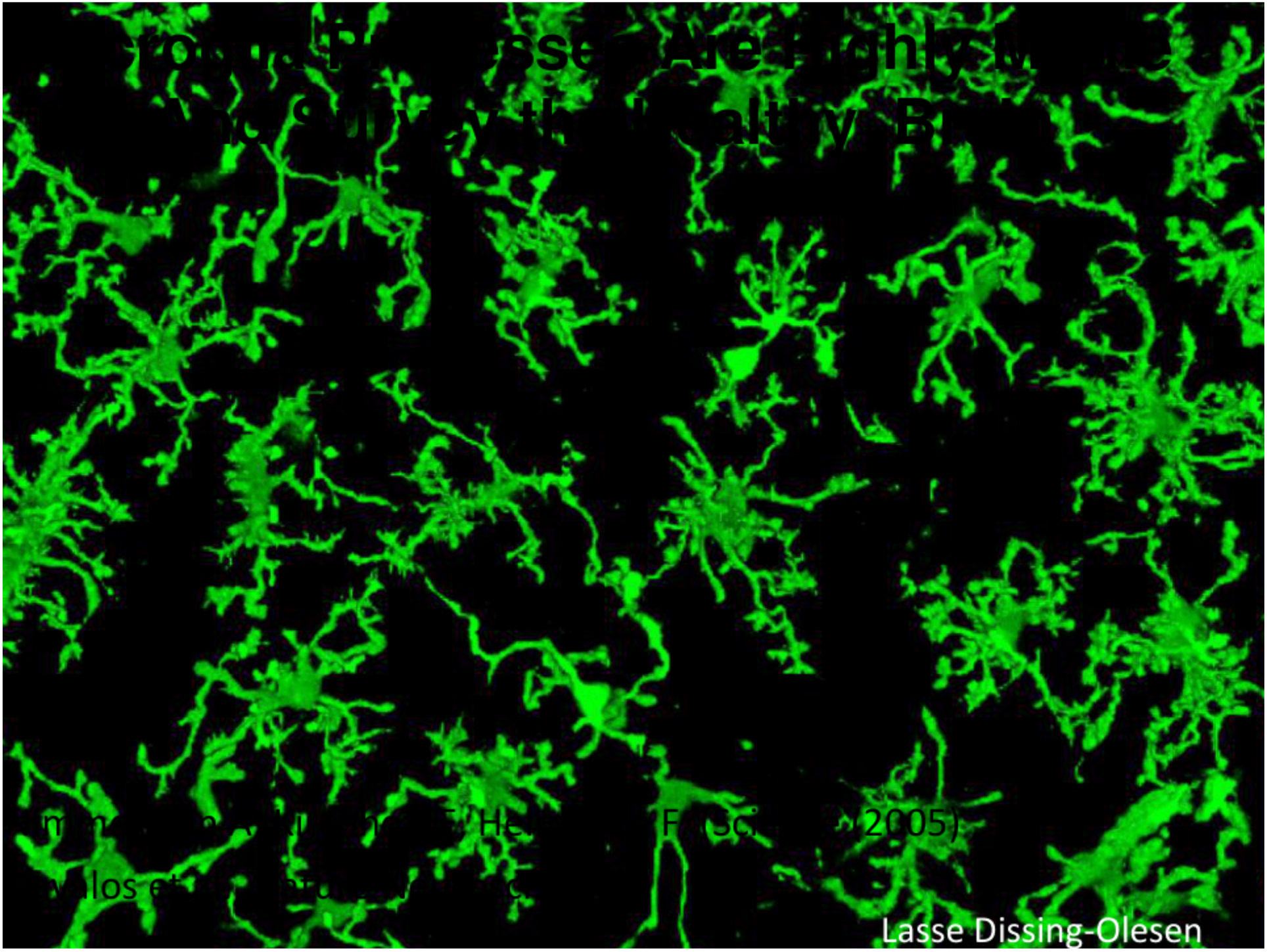
Microglia: CX3CR1-EGFP Mouse

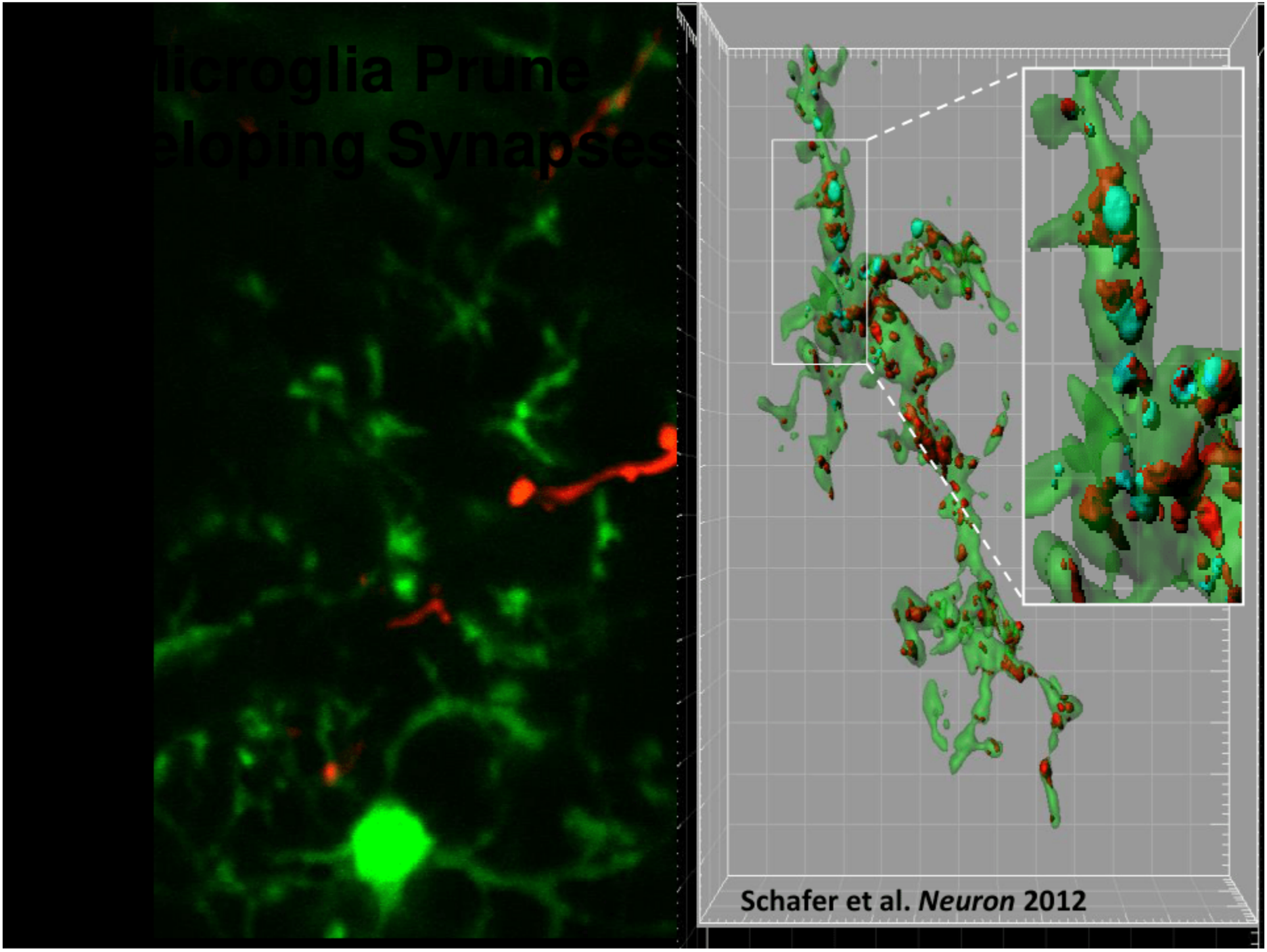
In Vivo Imaging: Mouse Cerebellum



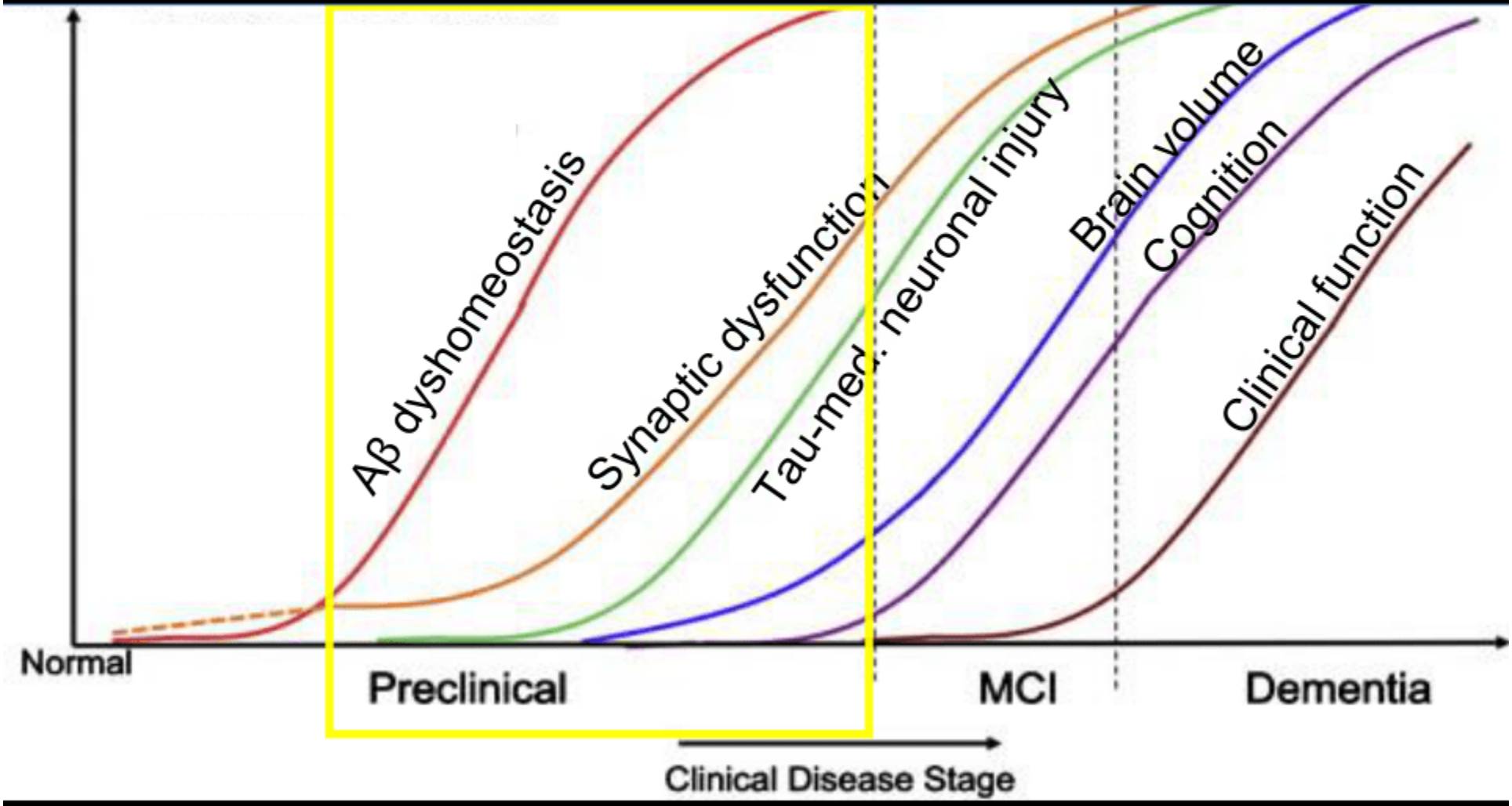
Microglia: CX3CR1-EGFP
Neuron Thy1 YFP


Davalos et al., Nature Neurosci. (2005)
Lasse Dissing-Olesen


Lasse Dissing-Olesen

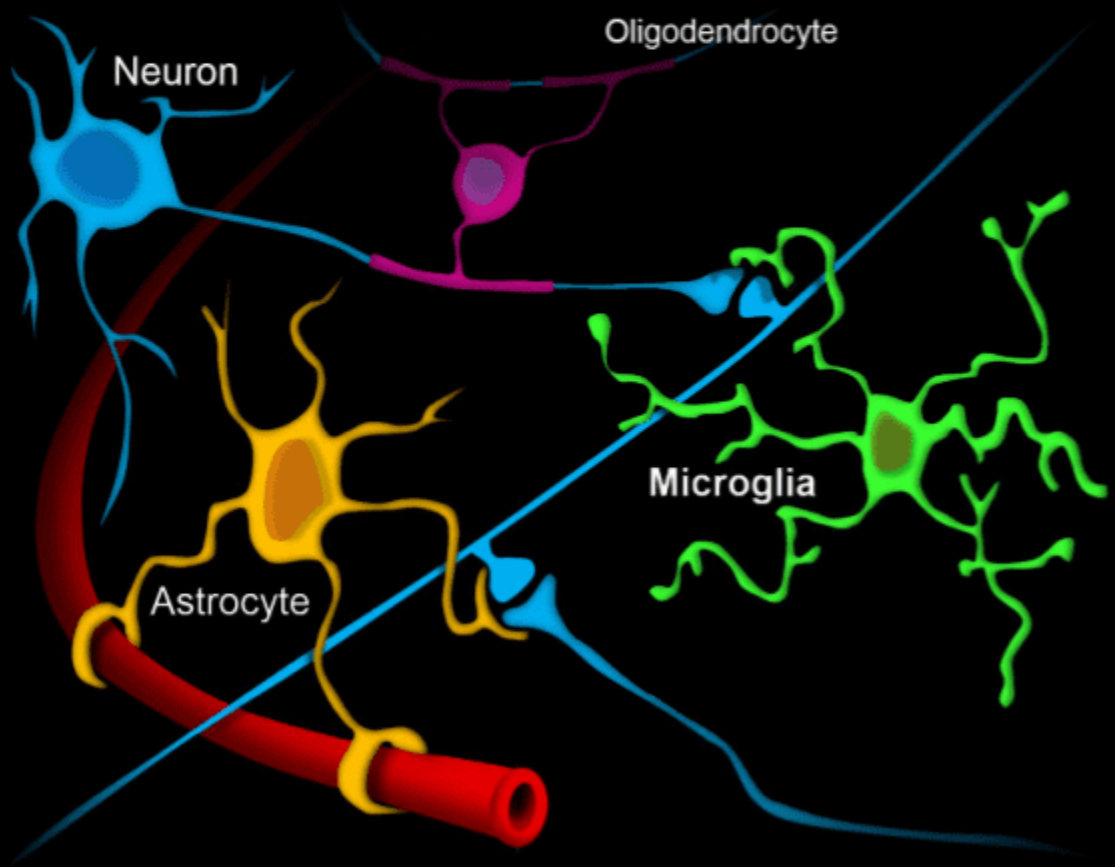

Schafer et al. *Neuron* 2012

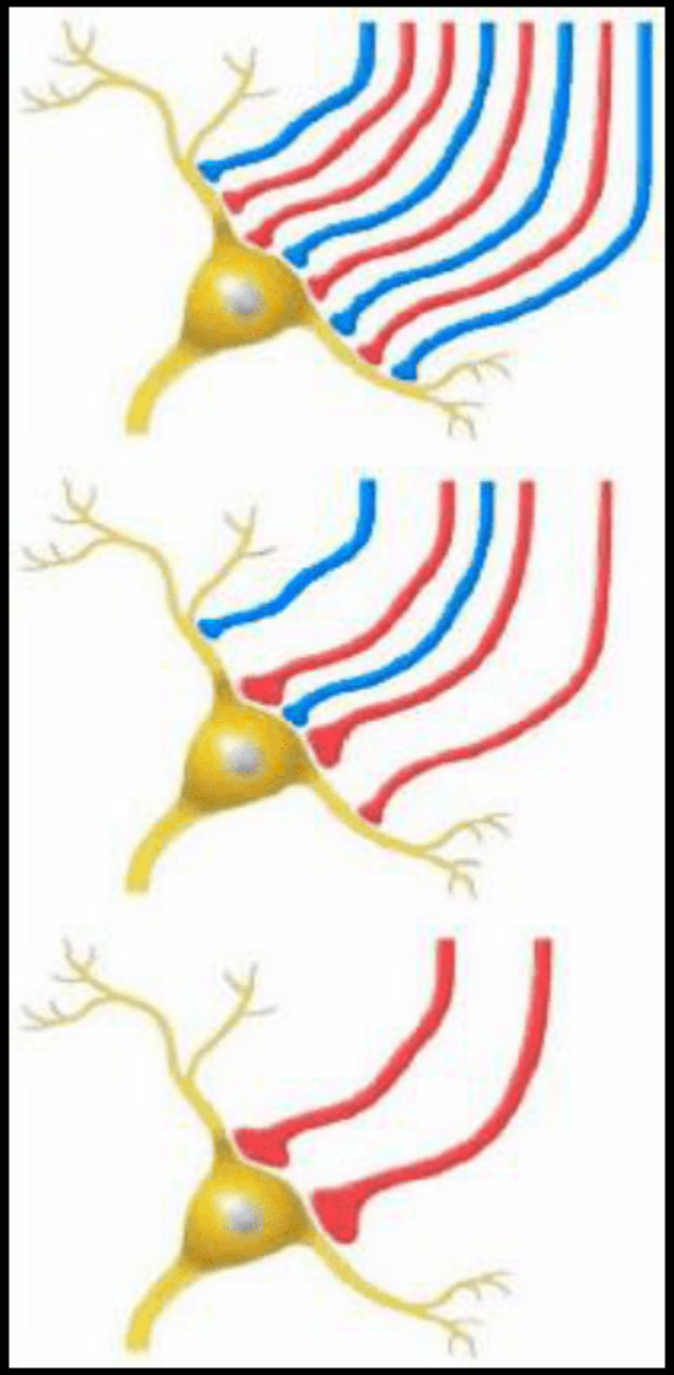
Synapse Loss: The Strongest Correlate of Cognitive Decline



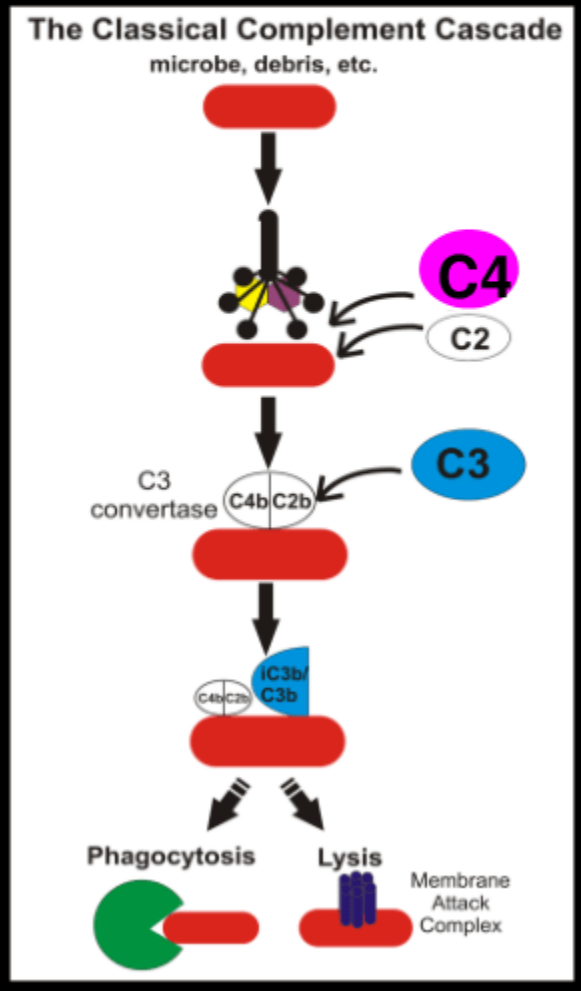
Sperling et al., 2011

How are CNS Synapses Eliminated ?



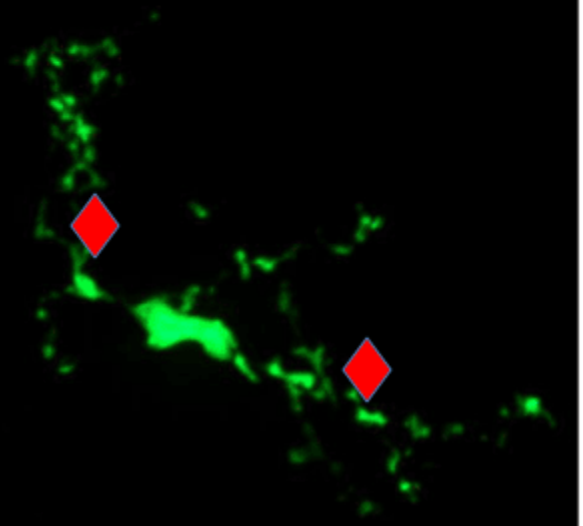


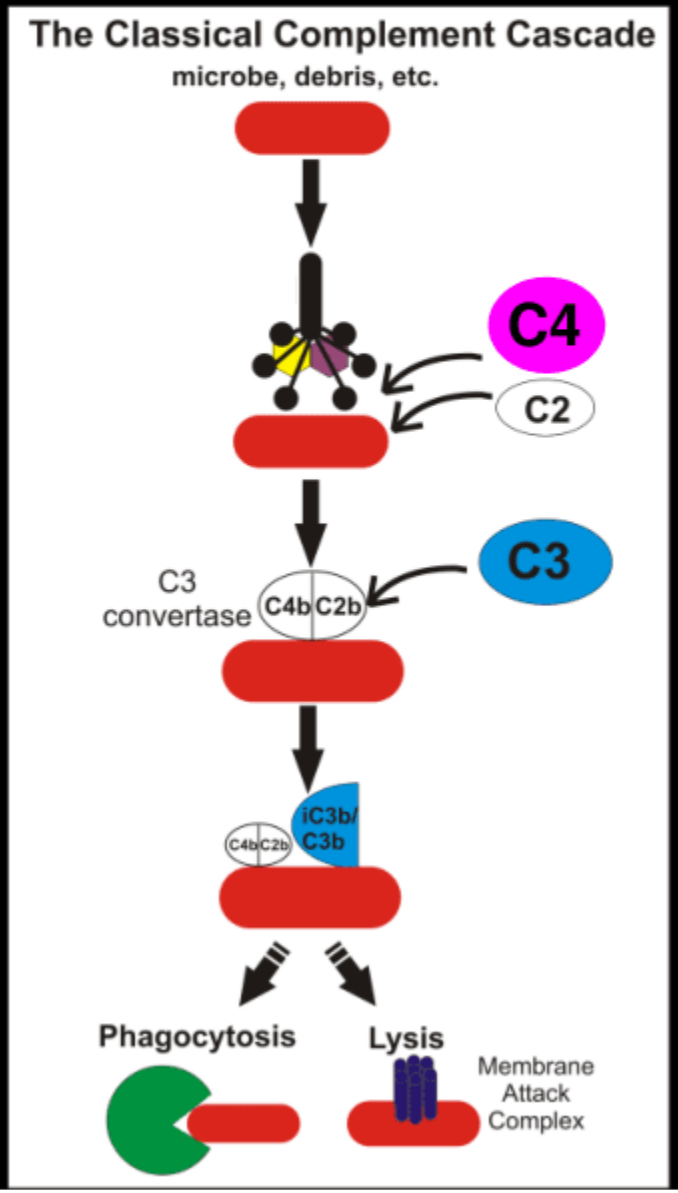
Immune System: Complement Proteins are 'Eat me' signals that Tag Apoptotic cells and Bacteria for Rapid Elimination

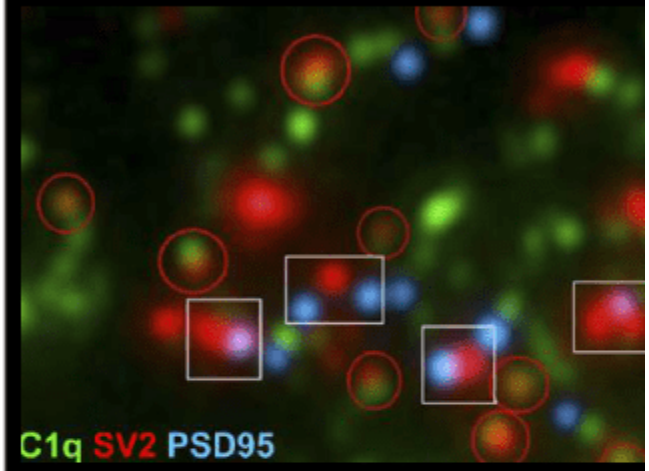


Brain: Complement Proteins Tag Synapses for Elimination by Microglia

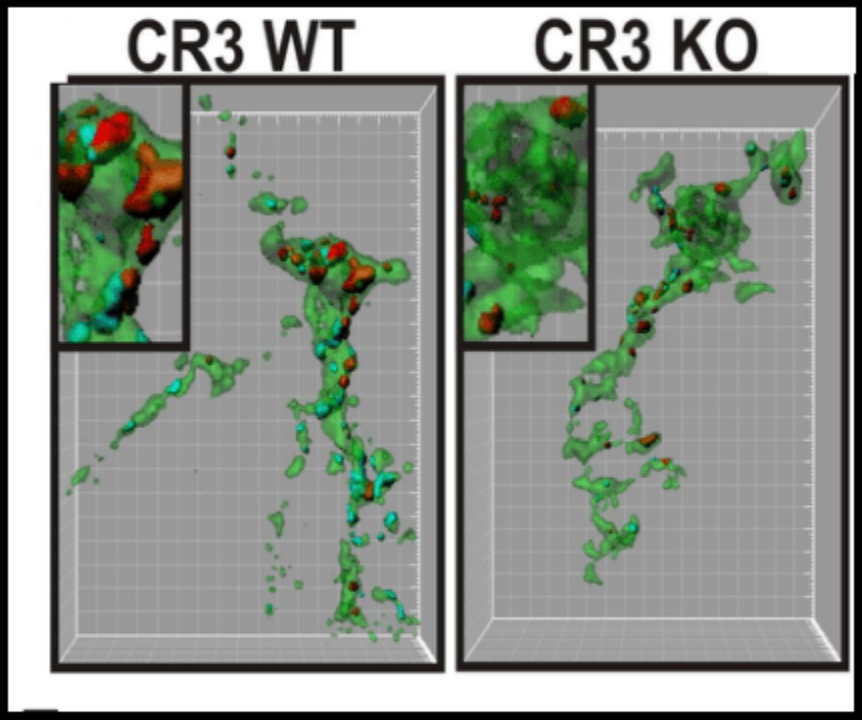
CR3



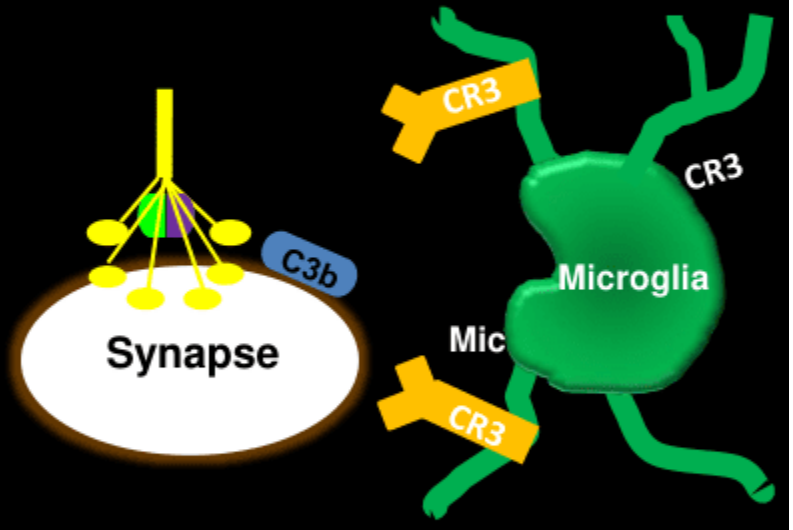


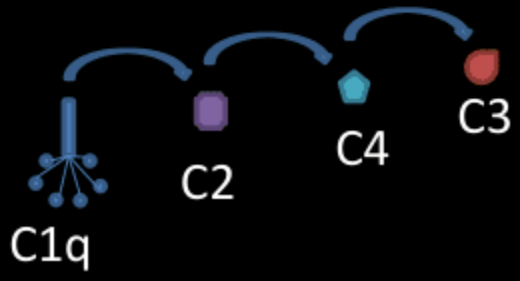


Microglial-Mediated Pruning Dependent on Complement Signaling

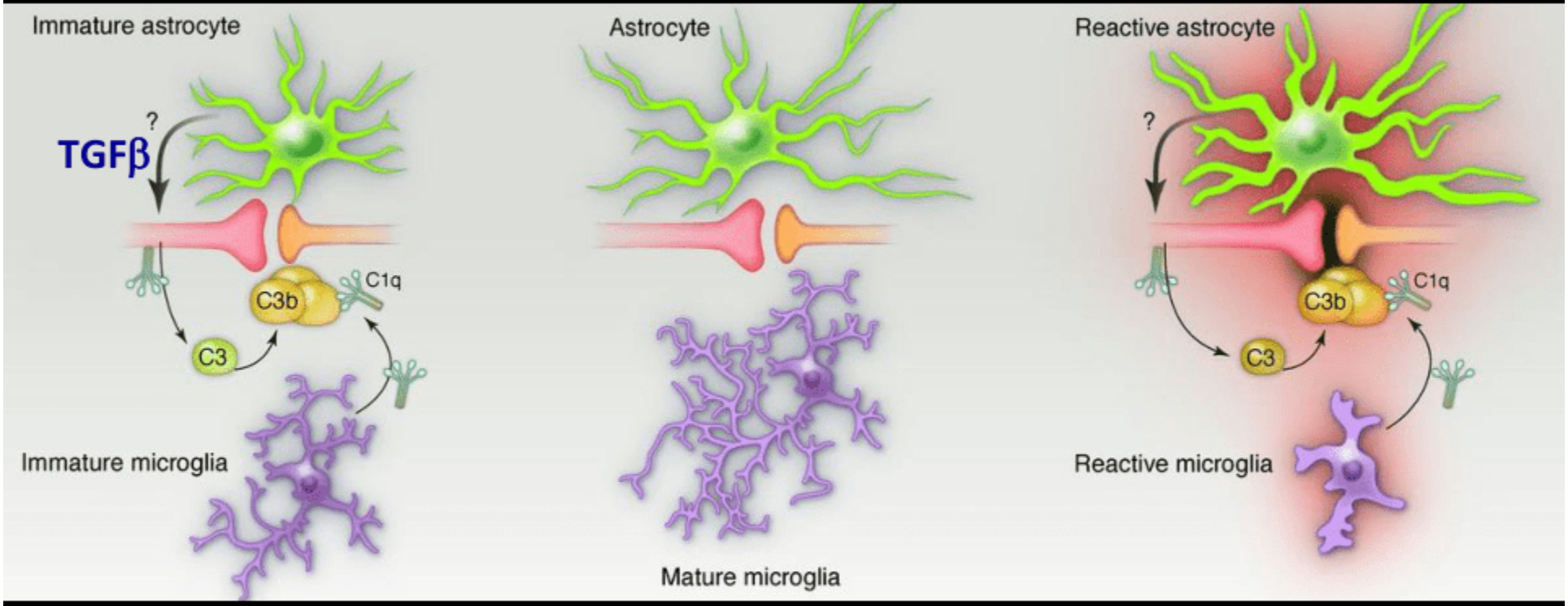


Schafer et al., Neuron 2012
Stevens et al., Cell 2007





Are Developmental Mechanisms of Synapse Pruning Aberrantly Reactivated in AD?

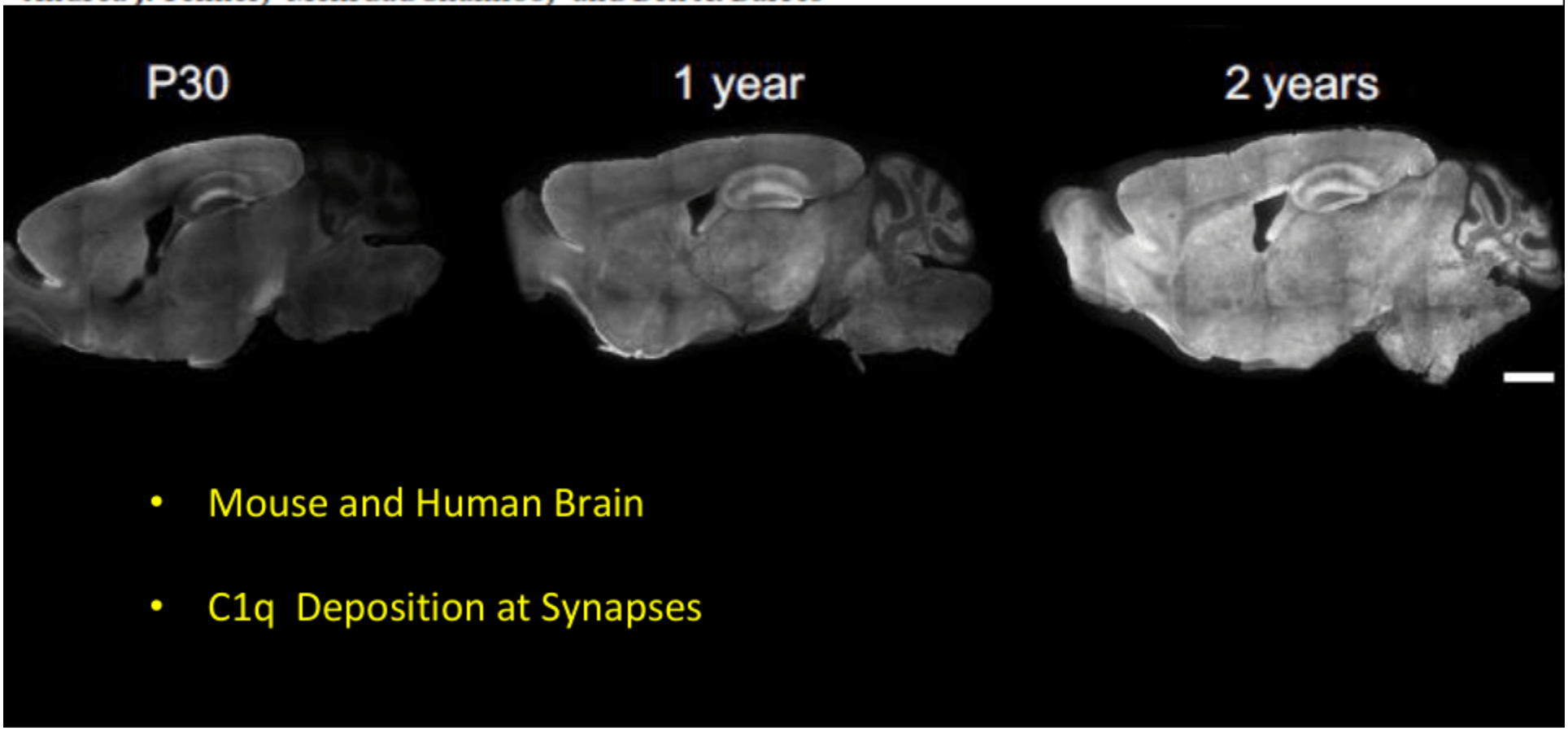


Development/Plasticity/Repair

J J Neuroscience (2013)

A Dramatic Increase of C1q Protein in the CNS during Normal Aging

Alexander H. Stephan,[1] Daniel V. Madison,[2] José María Mateos,[3] Deborah A. Fraser,[4] Emilie A. Lovelett,[1] Laurence Coutellier,[5] Leo Kim,[5] Hui-Hsin Tsai,[6,7,8] Eric J. Huang,[9] David H. Rowitch,[6,7,8] Dominic S. Berns,[1] Andrea J. Tenner,[4] Mehrdad Shamloo,[5] and Ben A. Barres[1]



- Mouse and Human Brain
- C1q Deposition at Synapses

Do Microglia Contribute to Synapse Loss and Cognitive Dysfunction in AD ?

1. AD Models:

- J20 APP
  - APP/PS1
- Acute oAβ Model

Dennis Selkoe
Cynthia Lemere

Soyon Hong

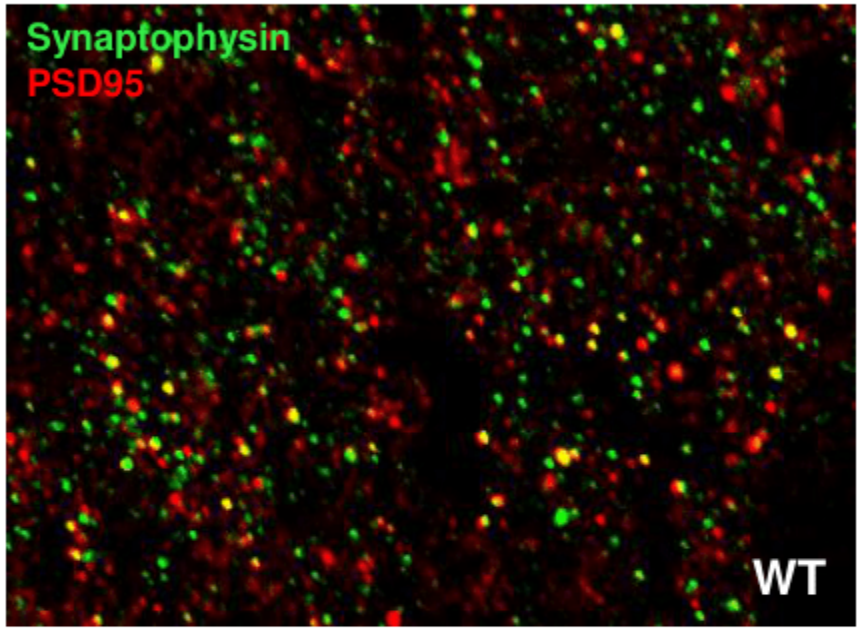
2. Human AD Brain

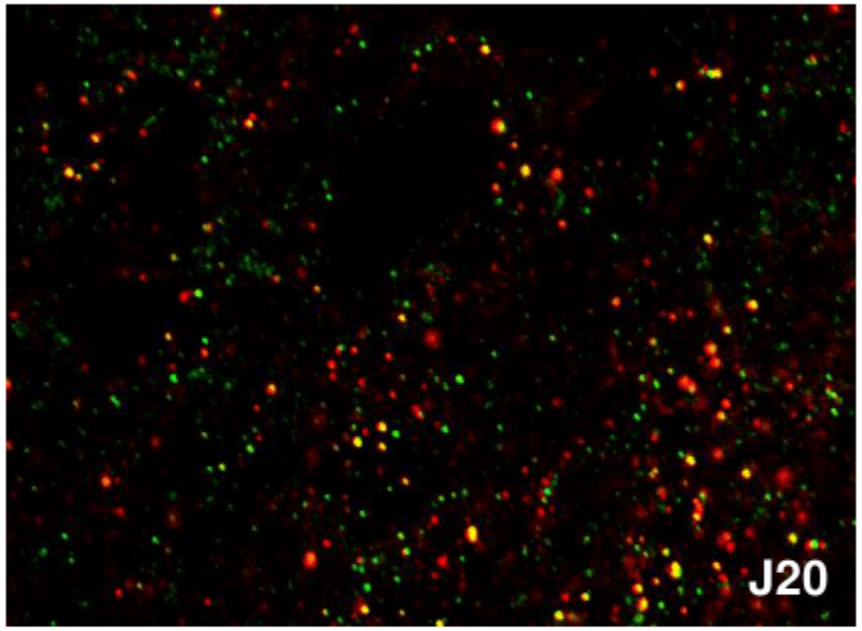
- AD Brain
- CSF

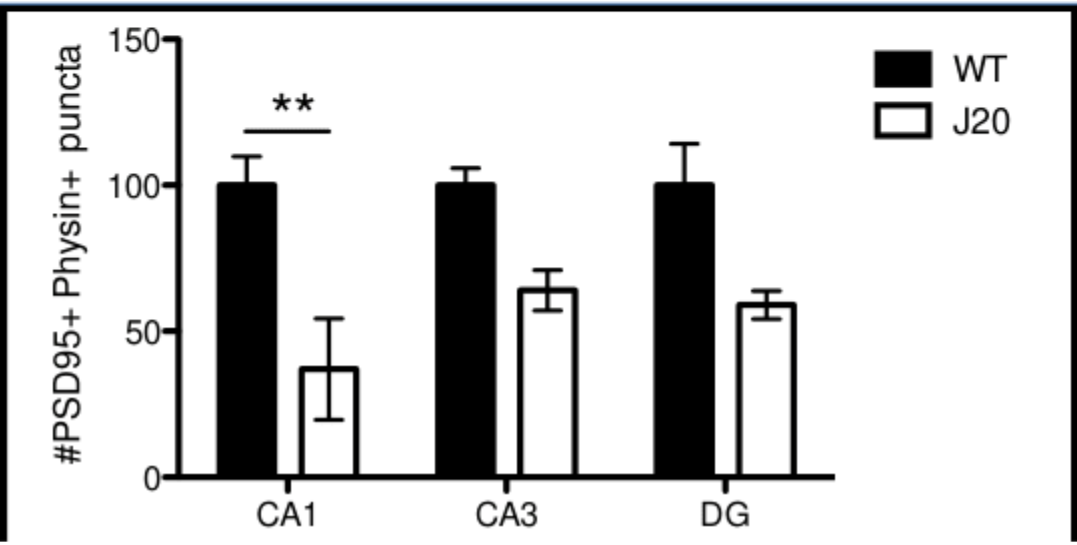
Brad Hyman, Tara Spires
Lee; John Trojanowsky
C. Haass

Early, Region Specific Loss of Synapses in AD Models

Hippocampus of 3 month J20 Mice





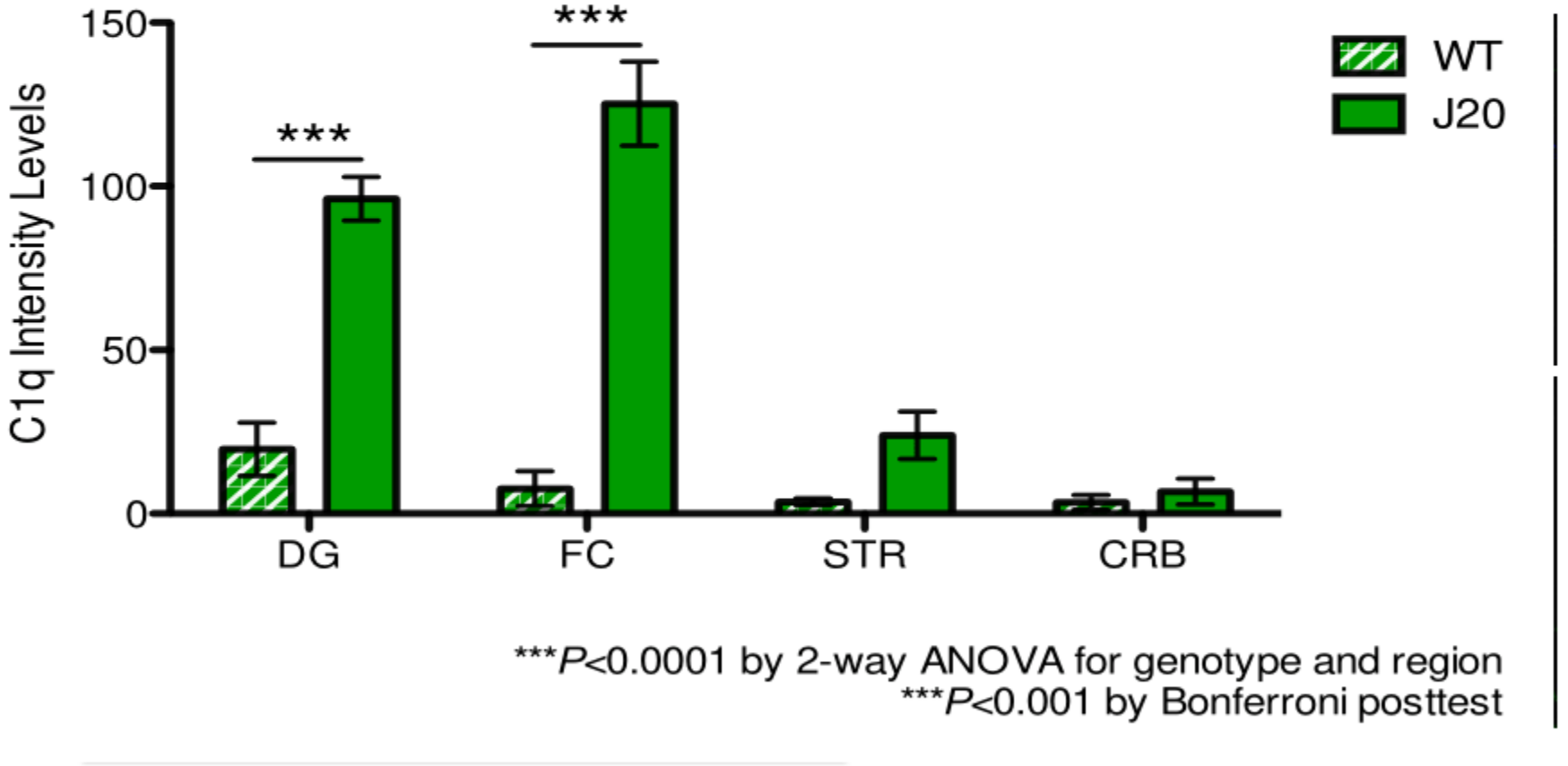


Dentate Gyrus

N=3 per genotype
**P <0.01 for CA1 by Bonferroni post-test

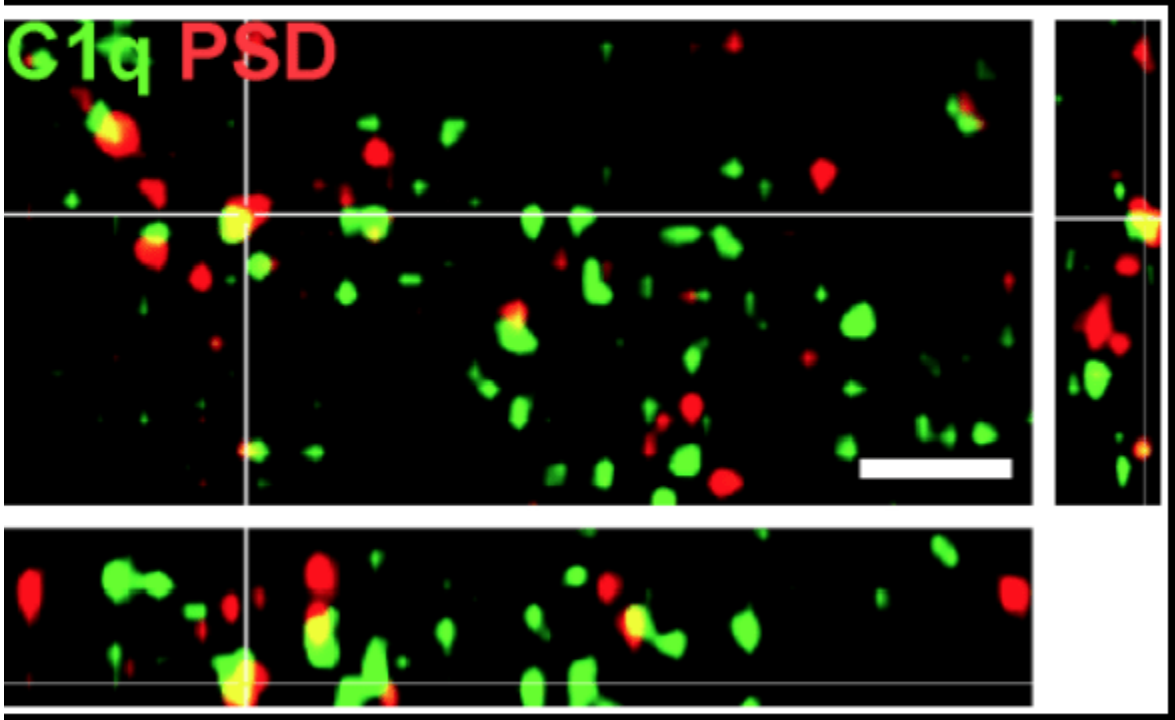
Early, Region-Specific Upregulation of Complement C1q

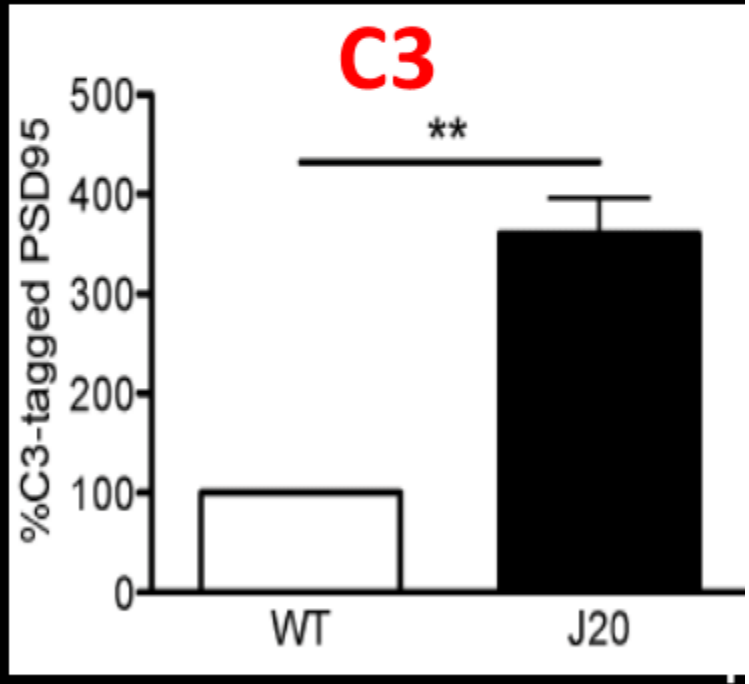
As early as 1 month in Regions Vulnerable to Aβ Deposition



***P<0.0001 by 2-way ANOVA for genotype and region
***P<0.001 by Bonferroni posttest

Early Increased C1q Deposition to PSD95+ Synapses in Hippocampus of AD Mice



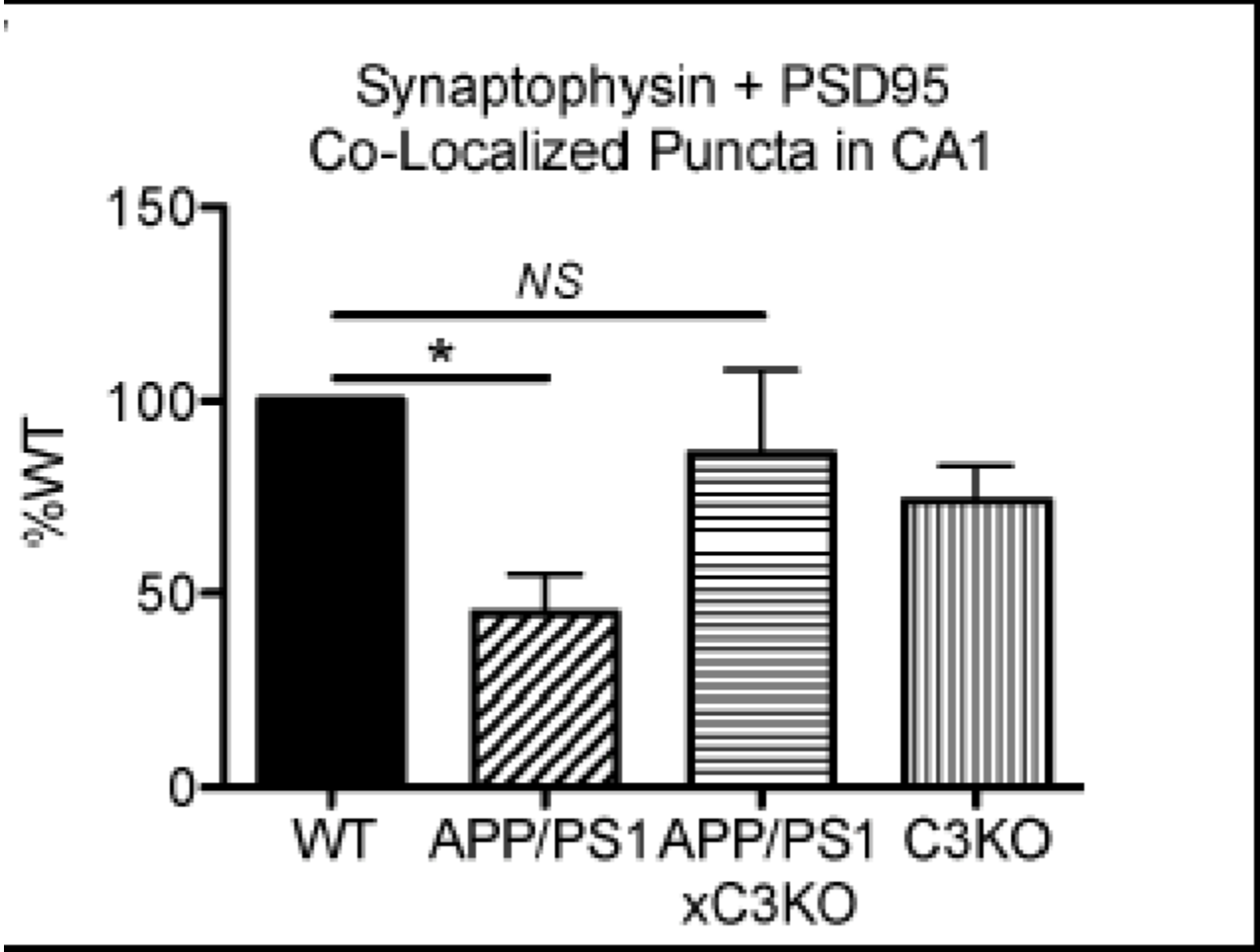


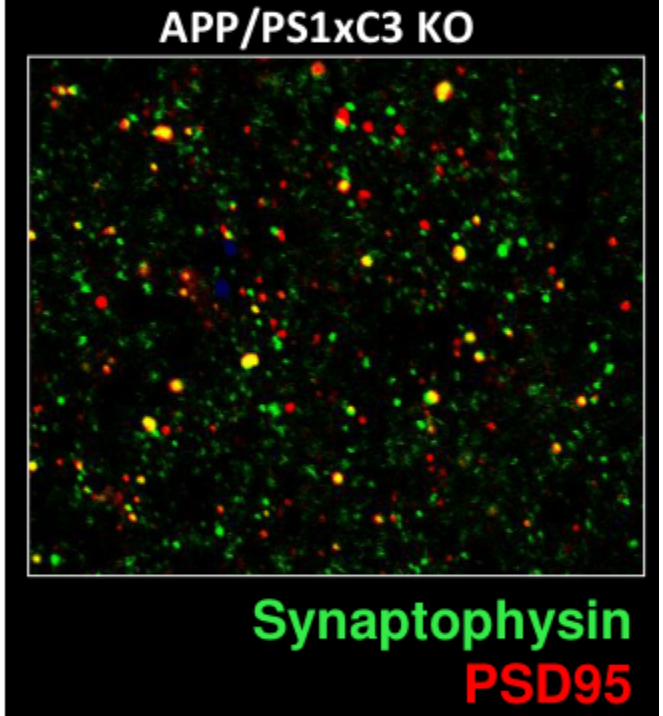
Does Inhibition of Microglia- Synaptic Pruning Rescue Synapse Loss and Cognitive Decline?

Measure:

1) Synapse Loss
2) Microglia Activation and Synaptic Eating
3) Memory and Cognitive tests

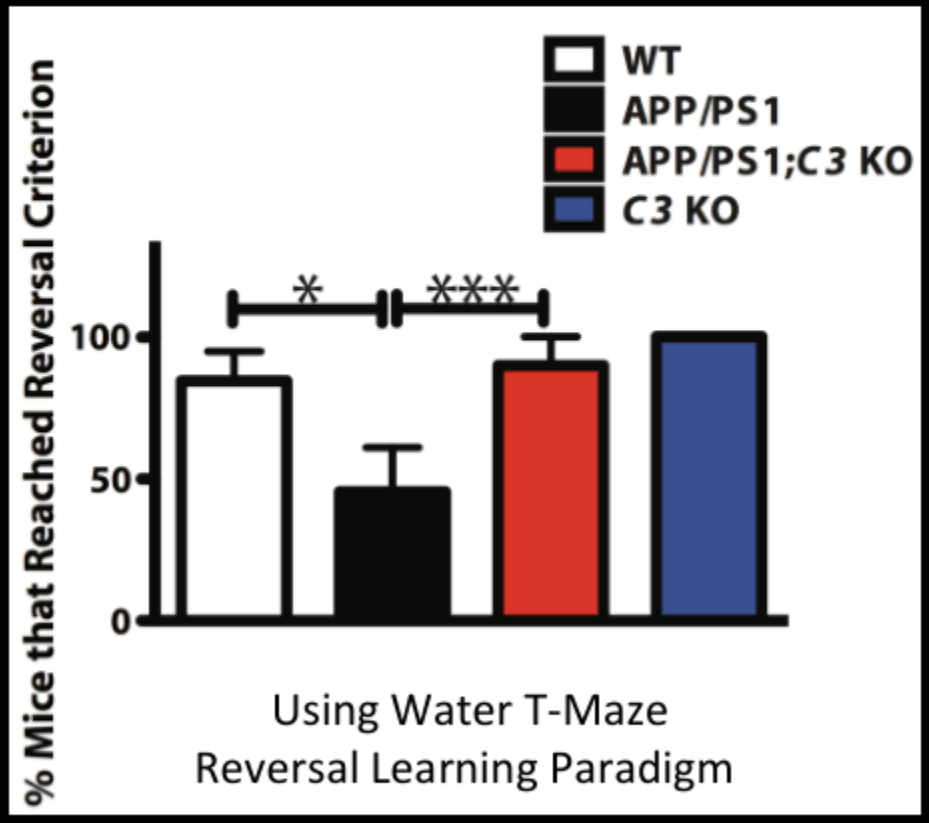
C3 Deficiency Protects Against Synapse Loss in APP/PS1 Mice (4 m and 16 m)

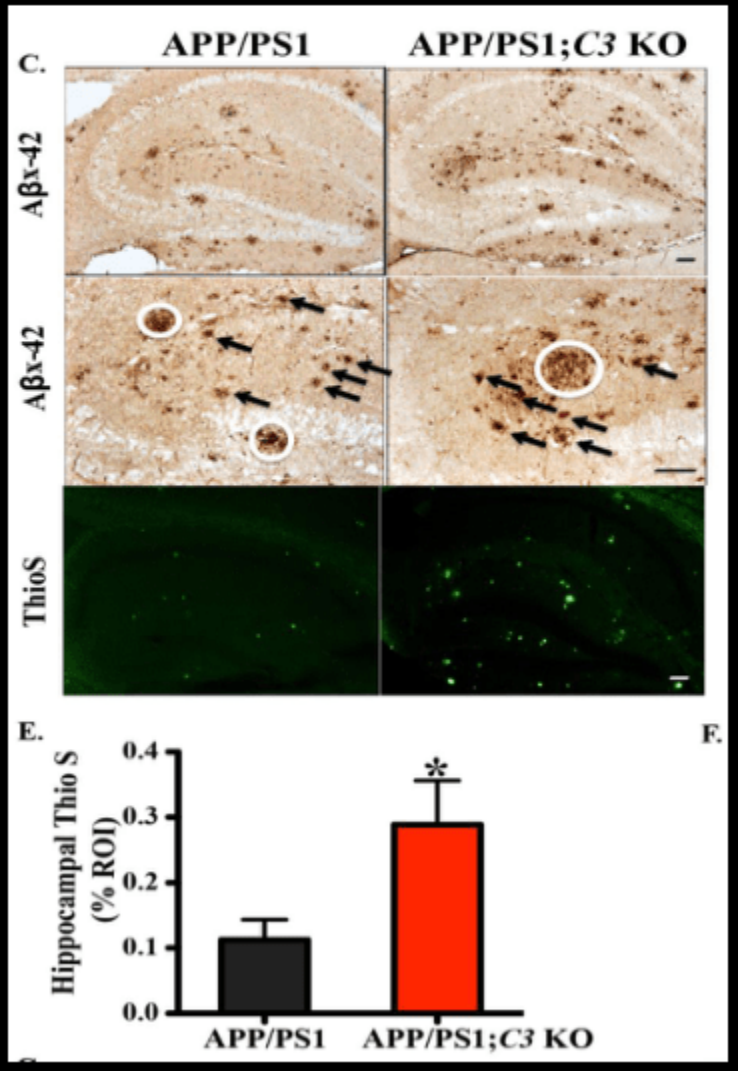




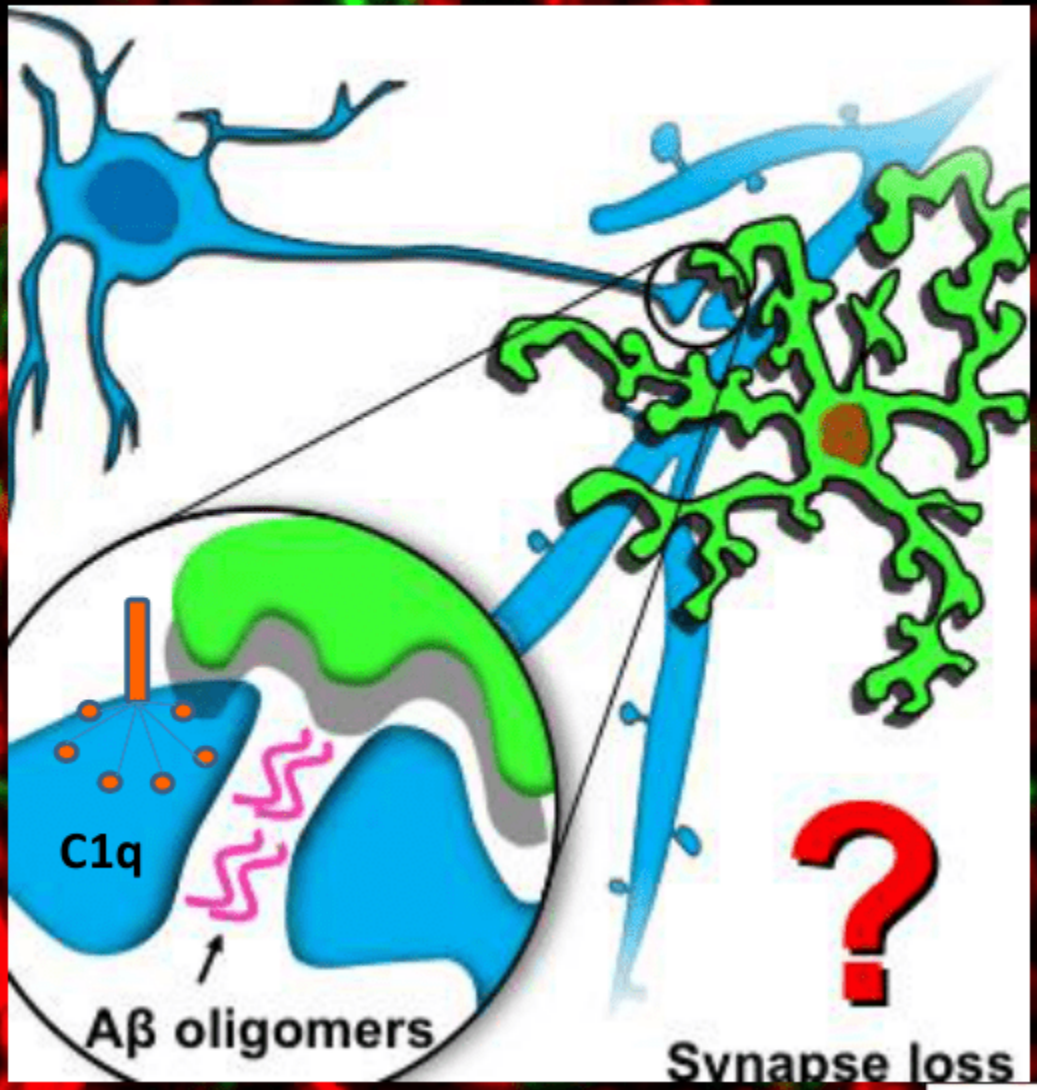
C3-deficiency resulted in improved spatial and contextual memory performance in AD mice

Despite Enhanced Plaque Load

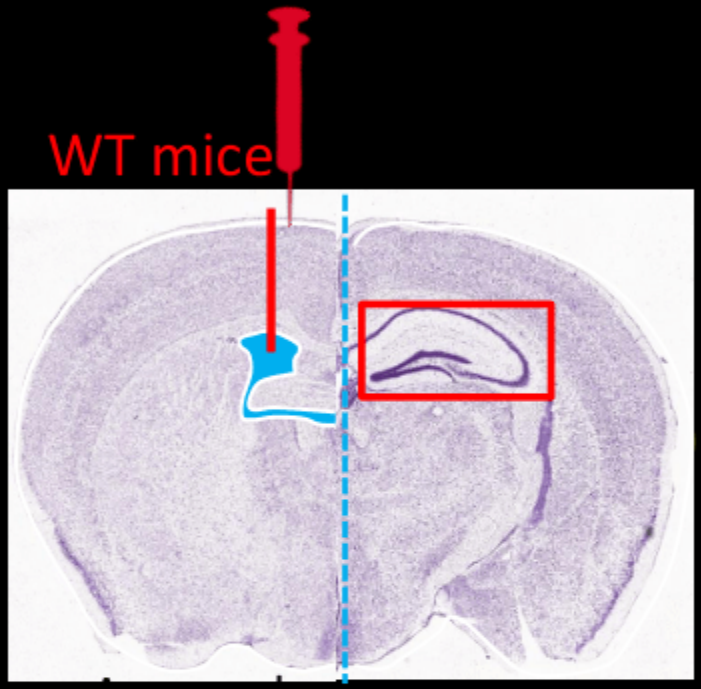




Do Microglia Aberrantly Prune Synapses in AD Models ?



In Vivo Model of Acute Synapse Loss

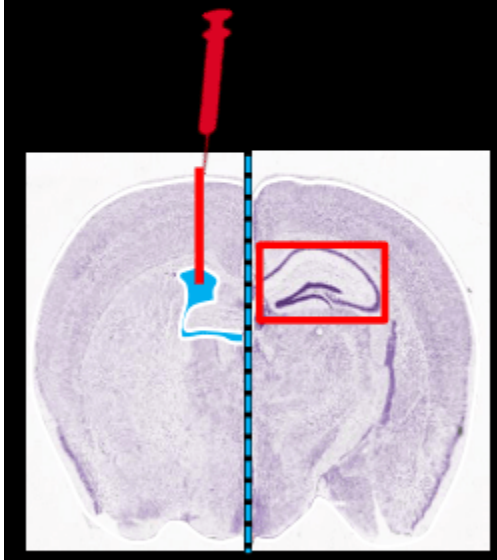


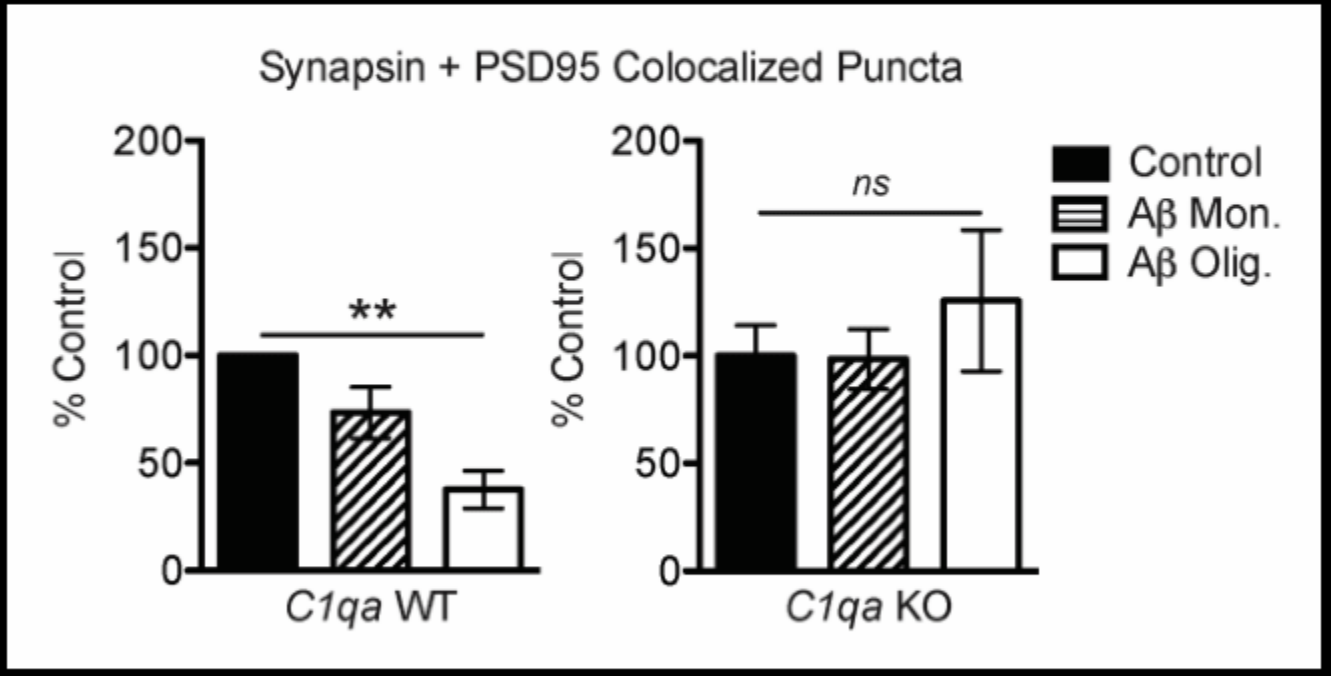
Is Synapse Loss Rescued in the Absence of Complement?

C1q : Necessary for Aβ-Induced Synapse Loss

In Vivo Model of Acute Synapse Loss

WT mice

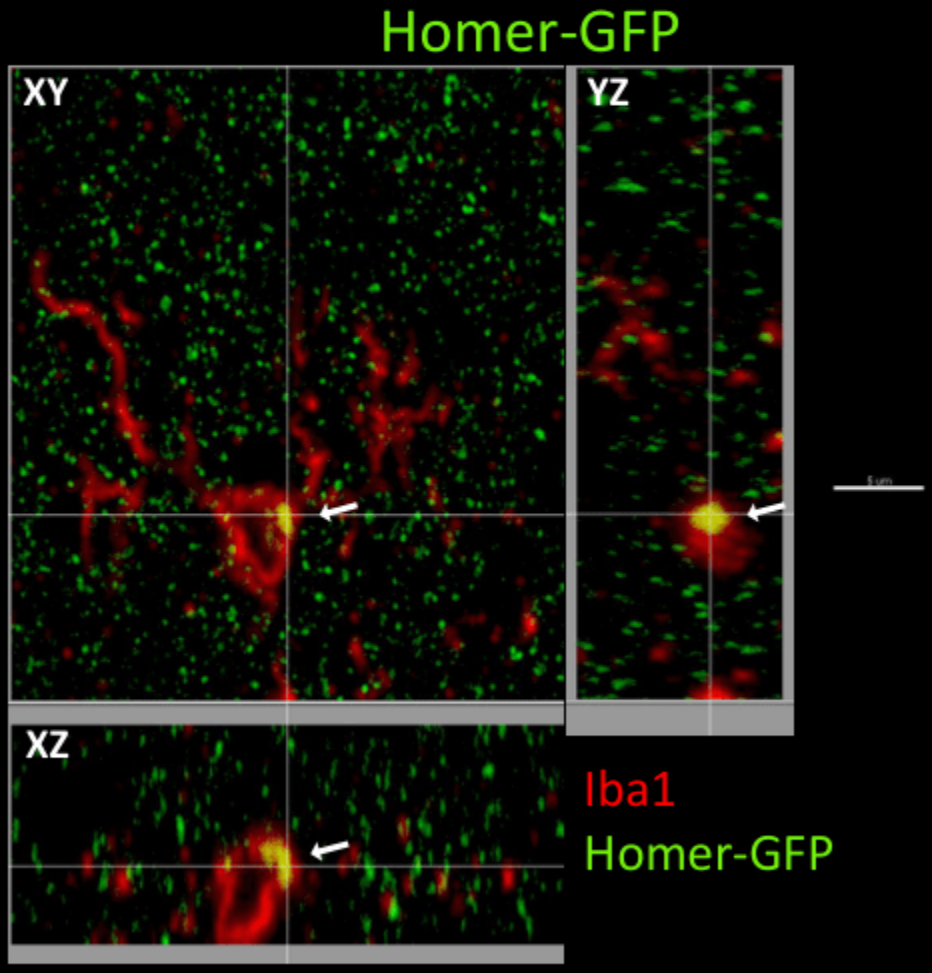


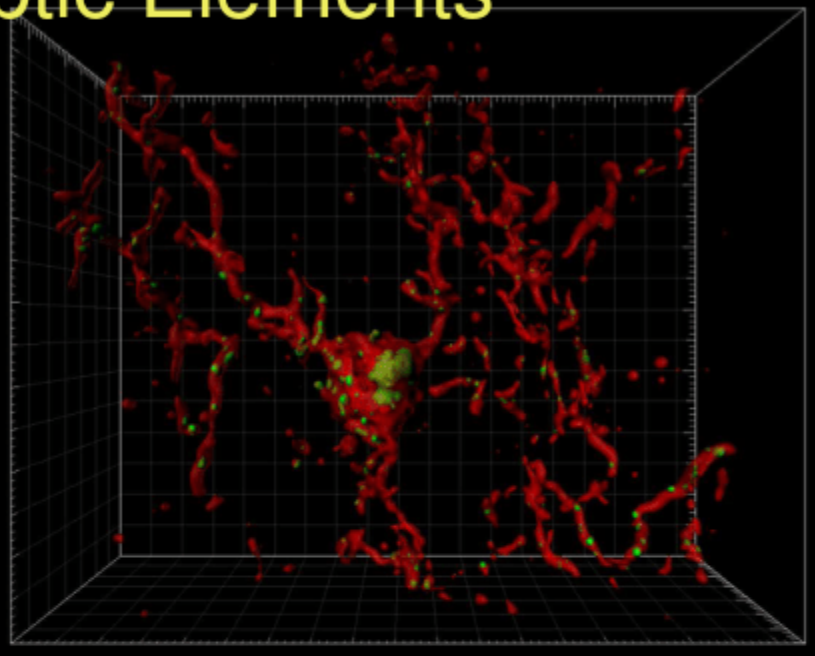


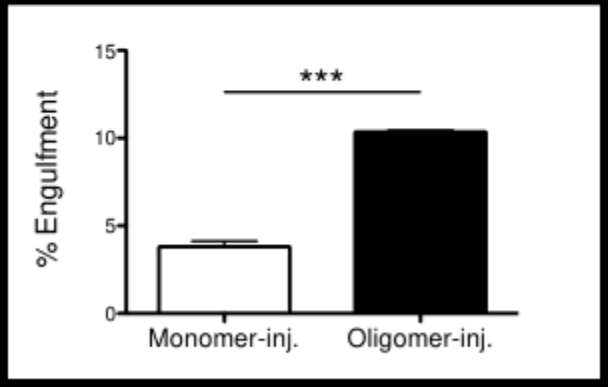
Also see similar protection using C1 blocking antibody

annexon biosciences

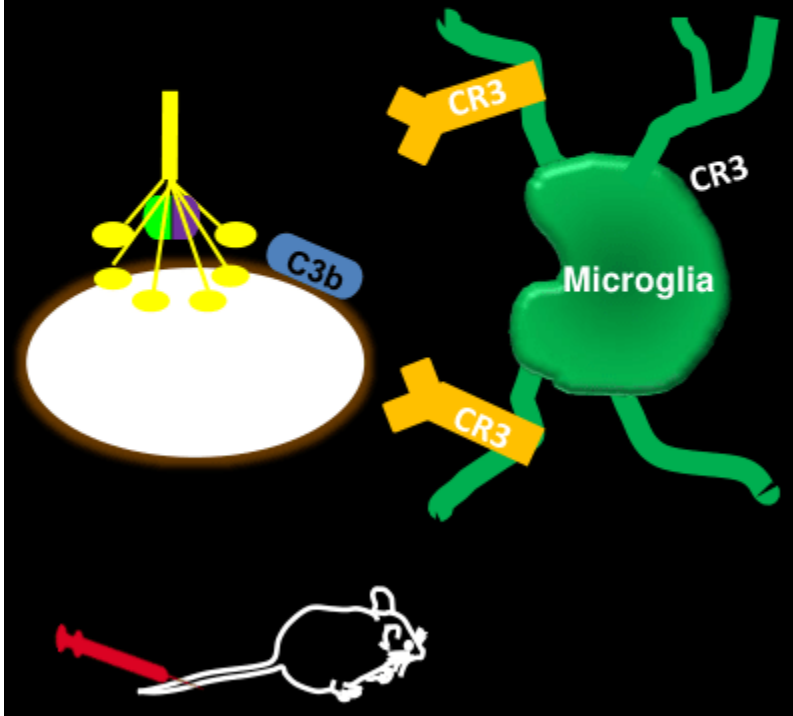
Aβ Oligomers Induce Microglia to Engulf Synaptic Elements

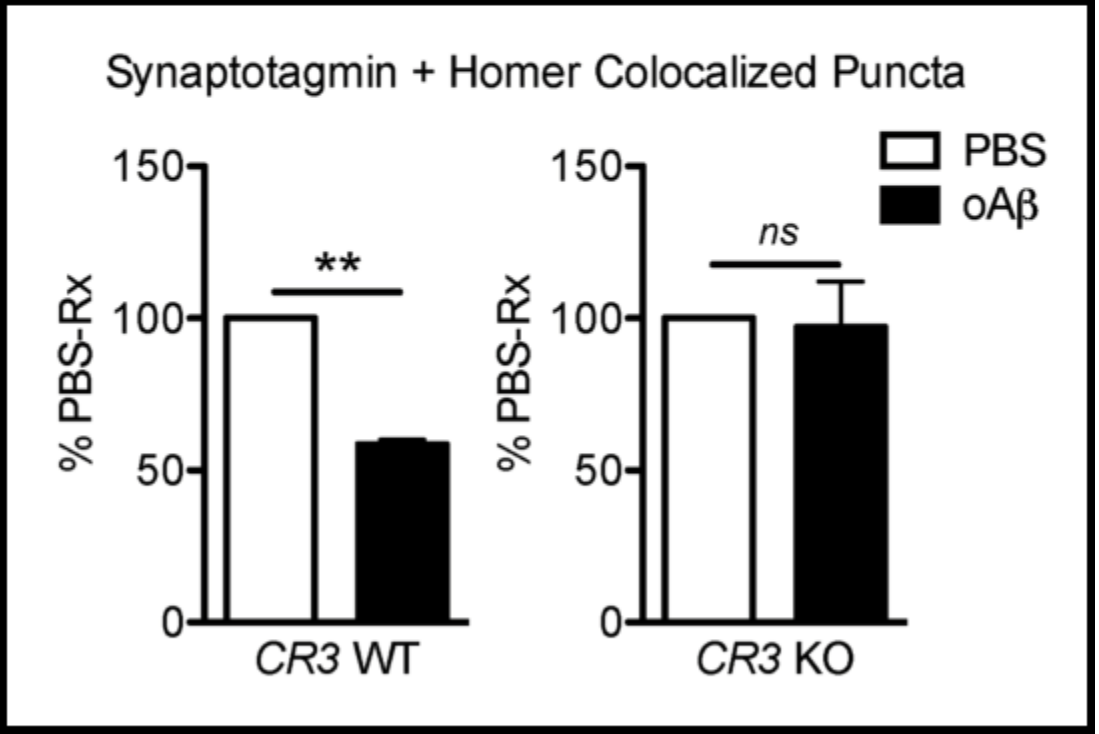




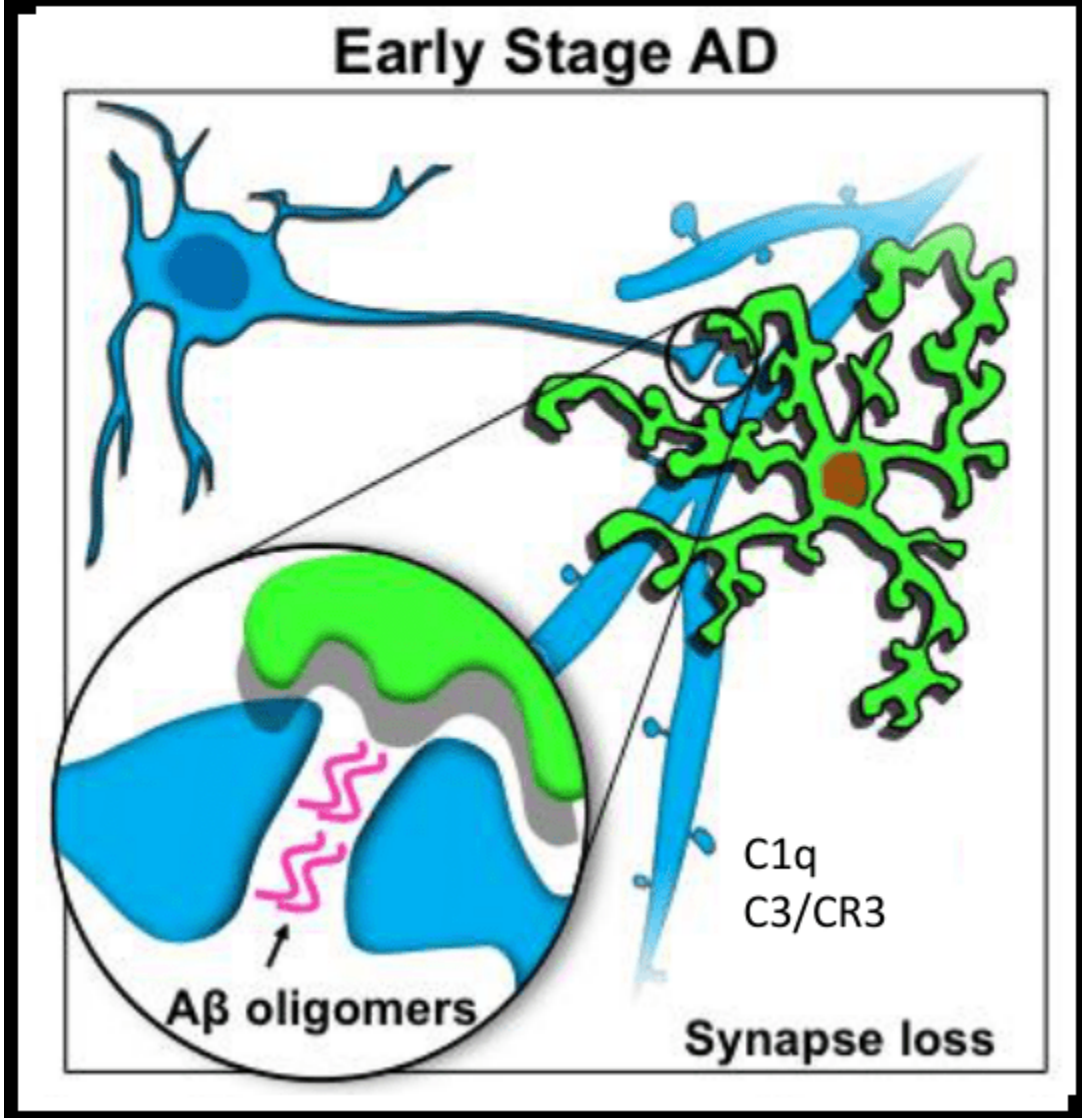


Blocking Microglial Engulfment Protects Synapses





New Role of Microglia in Synaptic Pathology

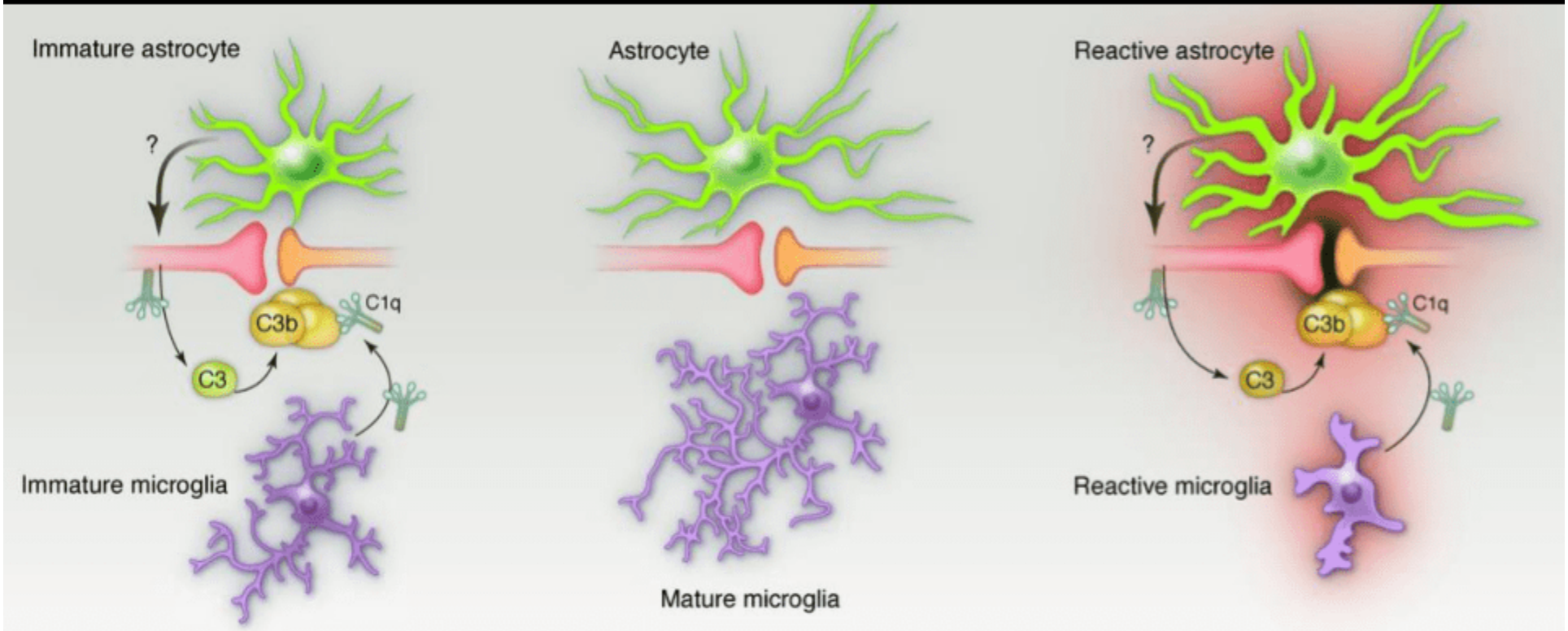


Complement- Synapse Elimination Pathways as Novel Therapeutics ?

- Complement inhibitors and blocking antibodies
- Microglial phagocytic receptors
- Early Biomarkers?

Broader Relevance for Other CNS Disorders?

A Common Mechanism of Synapse Loss and Cognitive Dysfunction?



Alzheimer's Disease

Glaucoma Howell et al JCI 2011; Stevens et al.,2007)

FTD

West Nile Virus Models

Huntington's Disease (DAN WILTON; UNPUBLISHED)

How to Translate to Human Disease?

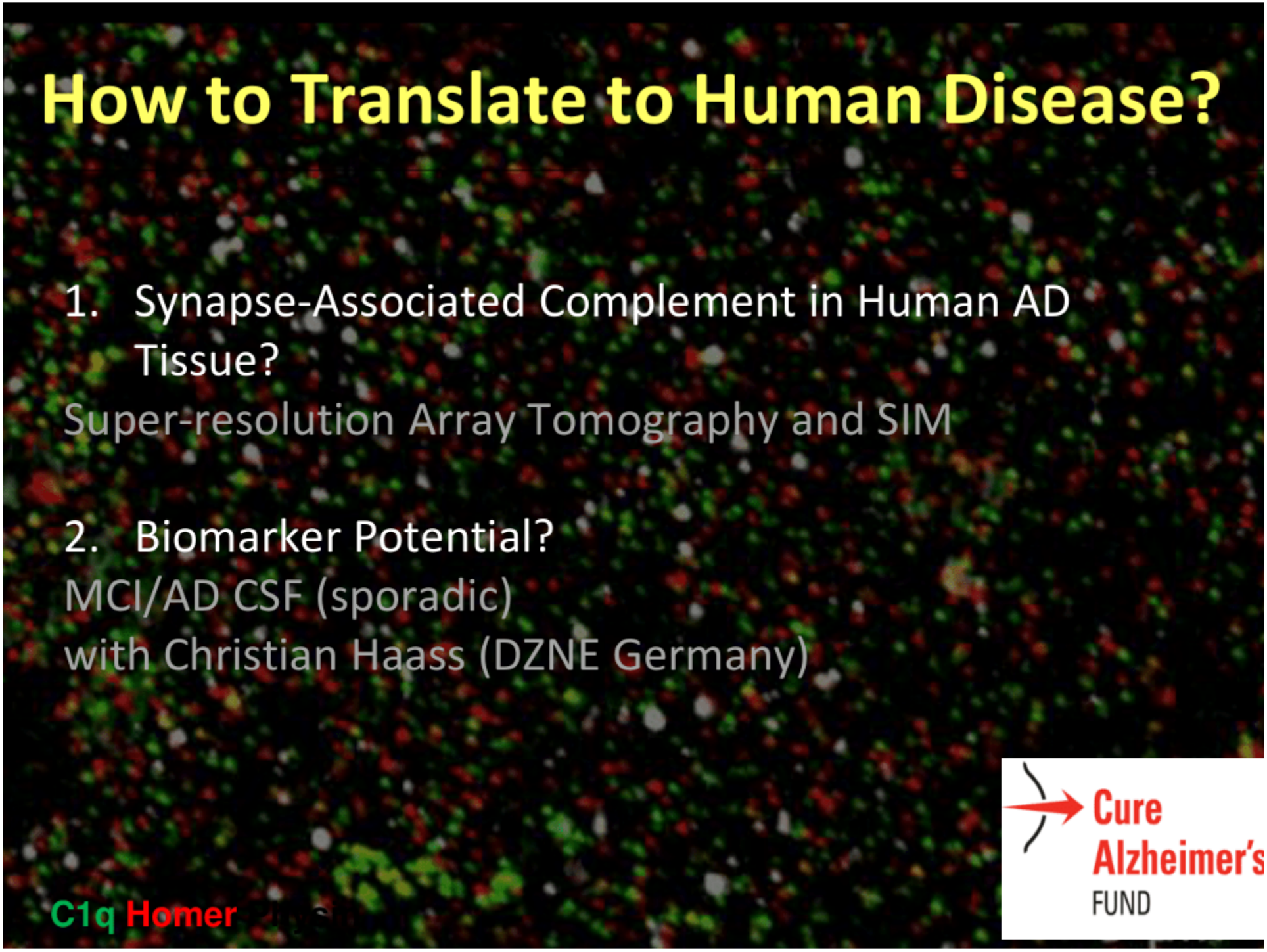
1. Synapse-Associated Complement in Human AD Tissue?

Super-resolution Array Tomography and SIM

2. Biomarker Potential?

MCI/AD CSF (sporadic)

with Christian Haass (DZNE Germany)

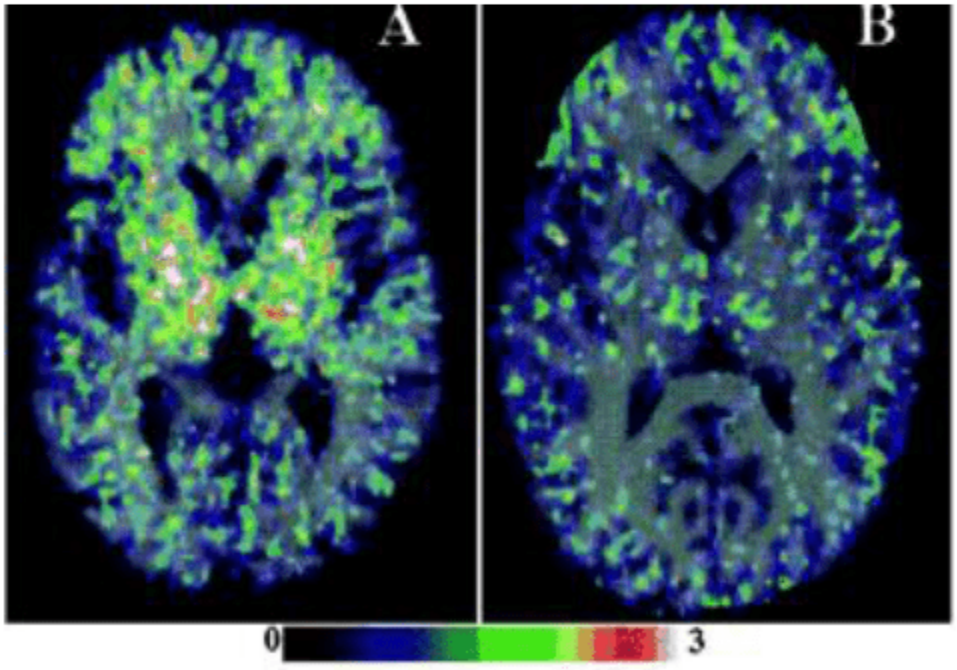


Cure Alzheimer's FUND

Microglia as Potential Biomarkers of Neuroinflammation and Dementia

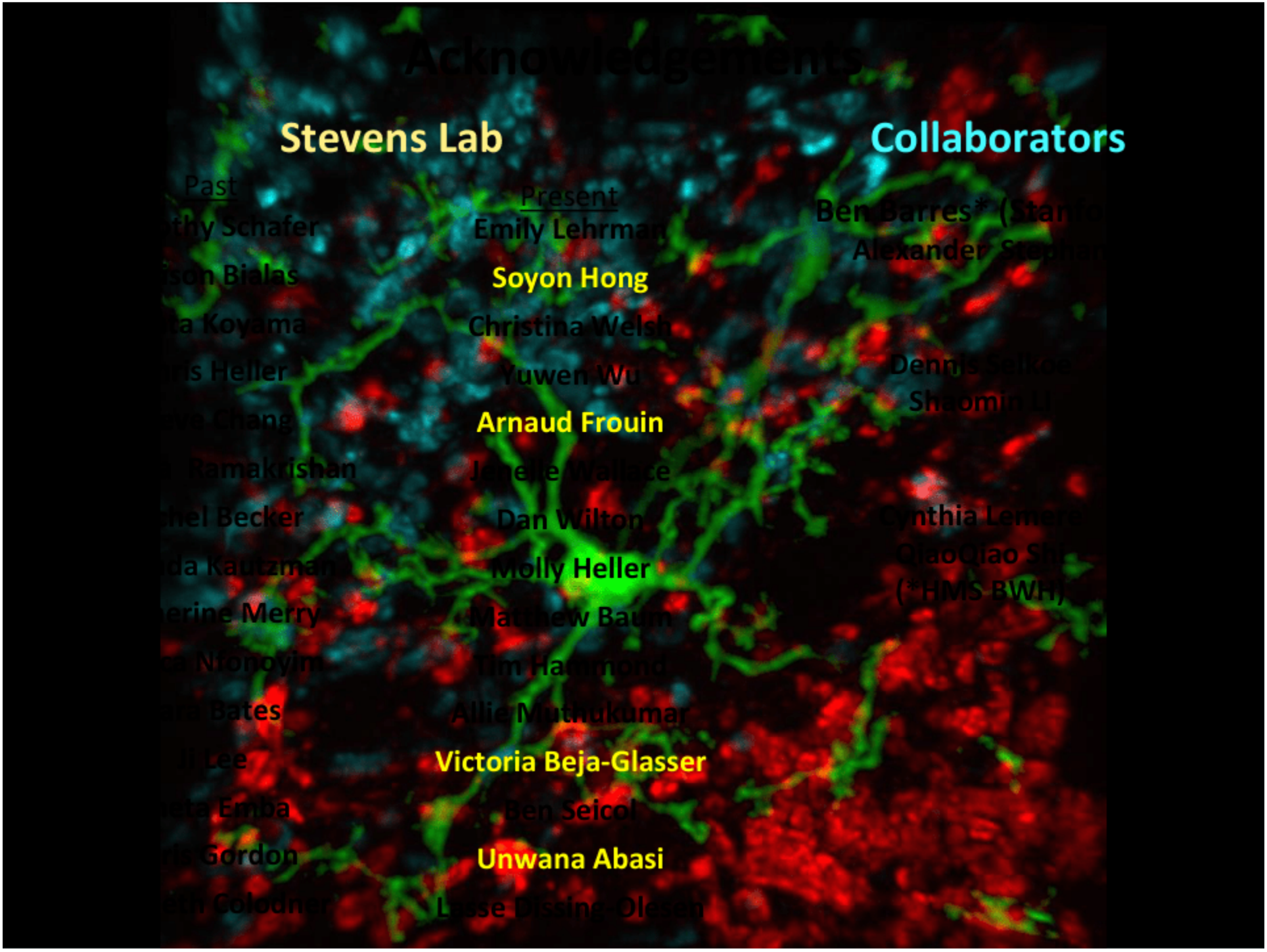
TSPO Ligands (PK- 11195)

Huntington's Disease **Healthy adult**

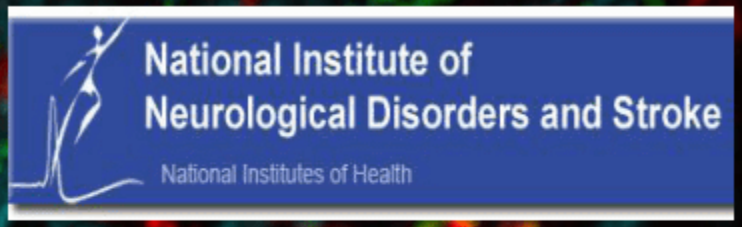


Development of Novel Microglia PET ligands

- Specific for Microglia
- Increased Early in Disease
- Biomarker of Synaptic and Cognitive Dysfunction


Acknowledgements
Stevens Lab
Past
Present
Emily Lehrman
Soyon Hong
Christina Welsh
Yuwen Wu
Arnaud Frouin
Dan Wilton
Molly Heller
Victoria Beja-Glasser
Unwana Abasi
Collaborators
Ben Barres* (Stan
Alexander
Dennis
Shaomin
Cynthia
QiaoQiao
(*HMS BWH)

THANK YOU!



Cure AD Fund

Merck Scholars Program

Ellison Foundation

Dana Foundation

Smith Family Foundation

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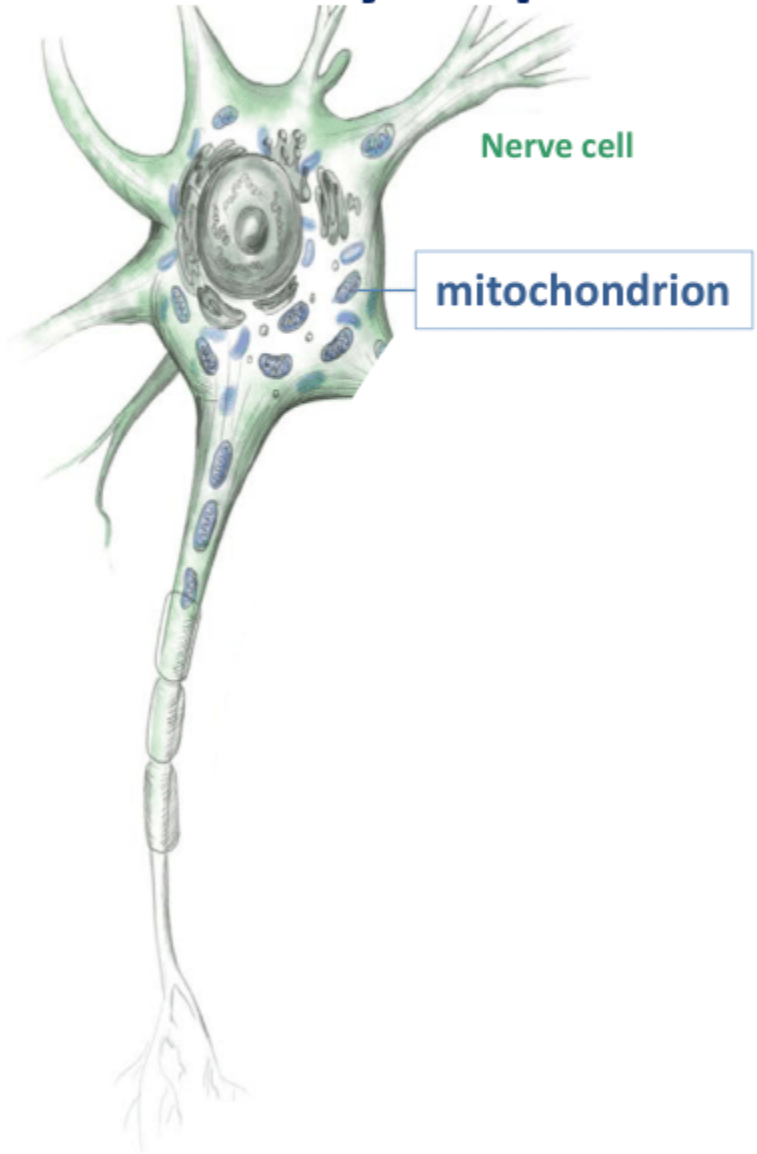
Agenda

- DDF update
- Portfolio overview
- **Scientific deep dive into current prioritised areas of scientific focus for DDF**
  1) Microglia, the role of glia in synaptic health, lead by Professor Beth Stevens
  2) **Mitochondrial dynamics and their role in dementia, lead by Professor Daria Mochly-Rosen**
- DDF summary

Treating Neurodegeneration and Dementia by Improving Mitochondrial Health



Daria Mochly-Rosen

Professor, Chemical and Systems Biology
Stanford University, School of Medicine
Founder and Director of SPARK at Stanford
President of SPARK Global
mochly@Stanford.edu
SPARKmed.Stanford.edu

Conflict of interest:
Inventor of patents related to the talk
Founder of Mitoconix, September 2016

STANFORD UNIVERSITY

Treating Neurodegeneration and Dementia by Improving Mitochondrial Health

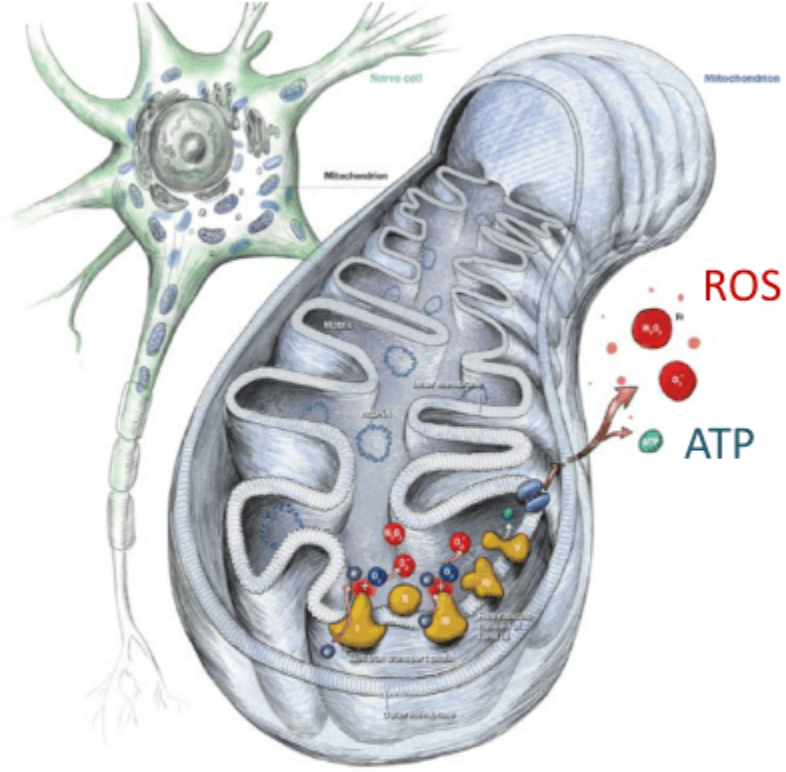
More functional mitochondria = more ATP = more repair = more neurons = **better behavior**

Observer was blinded to the experimental conditions

http://info.noldus.com/topic/rats

Guo *et al.*, J Clin Invest. 2013; 123:5371–5388

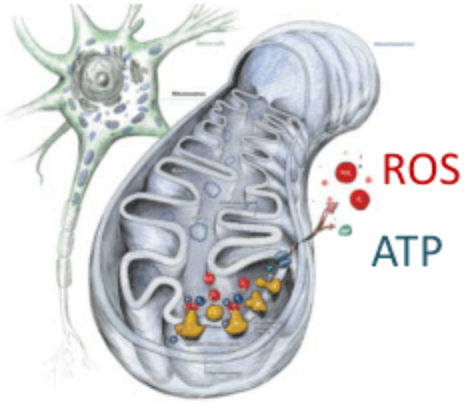
What are mitochondria? What do they do?



http://www.immortalhumans.com/wp-content/uploads/feat_mitochondria_diag_zoom.jpg

- Power producers, **ATP**
- Polluters; **free radicals** (ROS)
- **Detoxifiers** (aldehydes)
- Building blocks producers (**neurotransmitters**)
- Coordinators of apoptosis (**program cell death**)

Why focus on mitochondria health for dementia treatment?

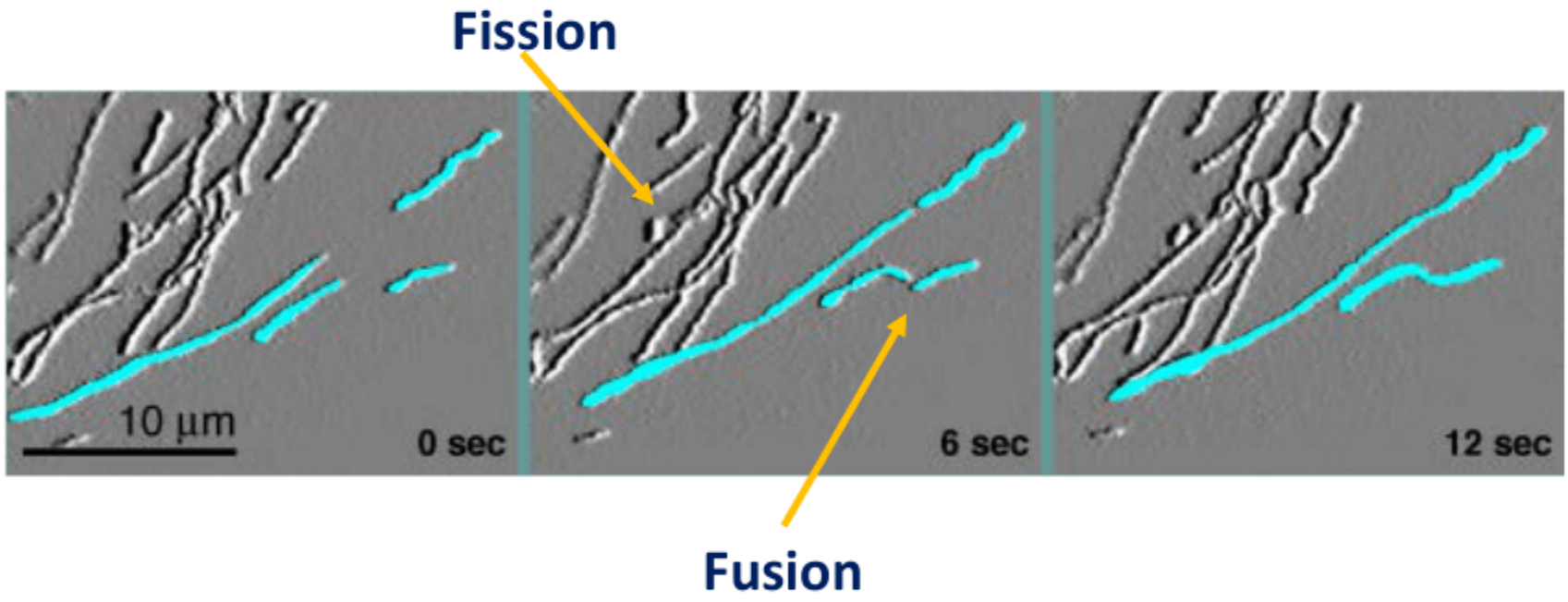


The brain:

- 2% of the body mass (1.5kG)
- Consumes of ~20% of the oxygen
- Uses 25% of the body's glucose to generate **ATP**
- Uses ~4.7 billion ATP molecules per second
- Richest in mitochondria — highest **ROS** producer..

Healthy mitochondria = healthier neurons

Mitochondria are dynamic organelles

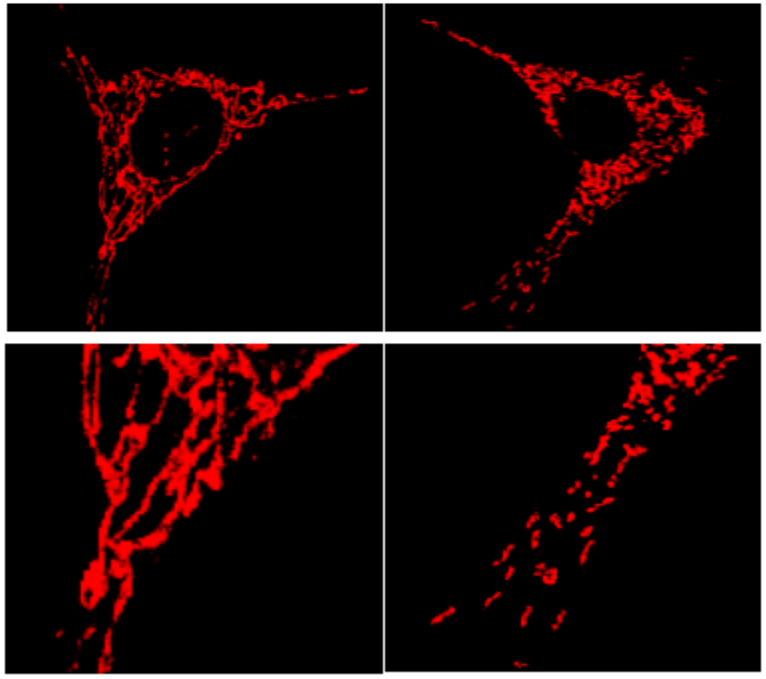


Chen et al (2003) J Cell Biol *160*, 189-200.

Excessive mitochondrial fragmentation is observed in several neurodegenerative diseases

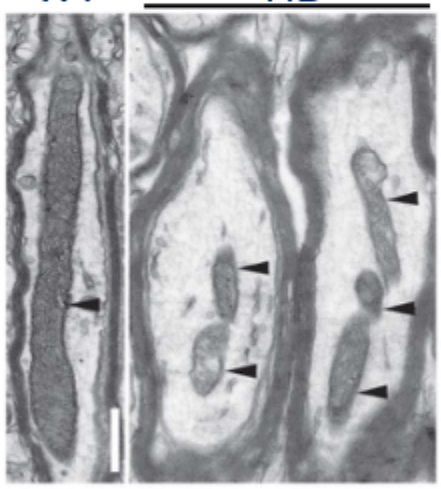
e.g., Huntington's disease (HD) models and in patients derived cells:

mouse neurons



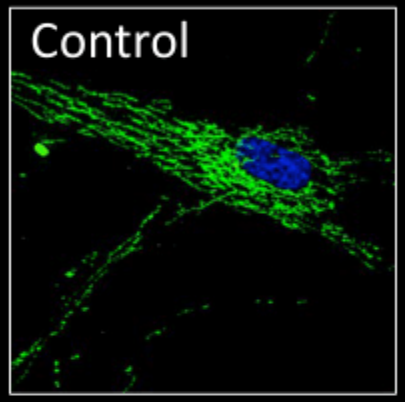
Qi X., JCI, 2013

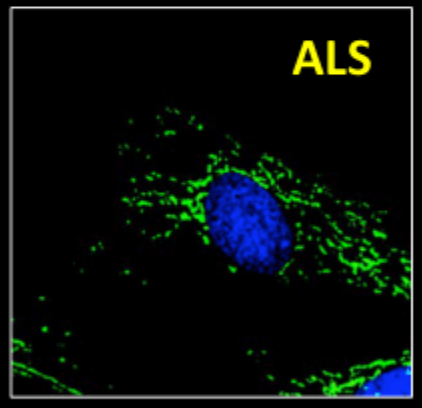
HD mouse brain

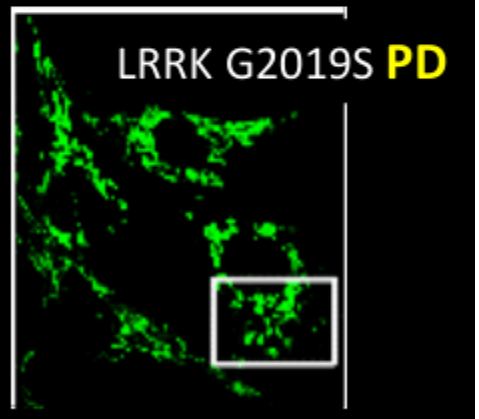


Song W., et al., Nature Medicine 2011

Excessive mitochondrial fragmentation also in fibroblasts from patients with AD, ALS and PD



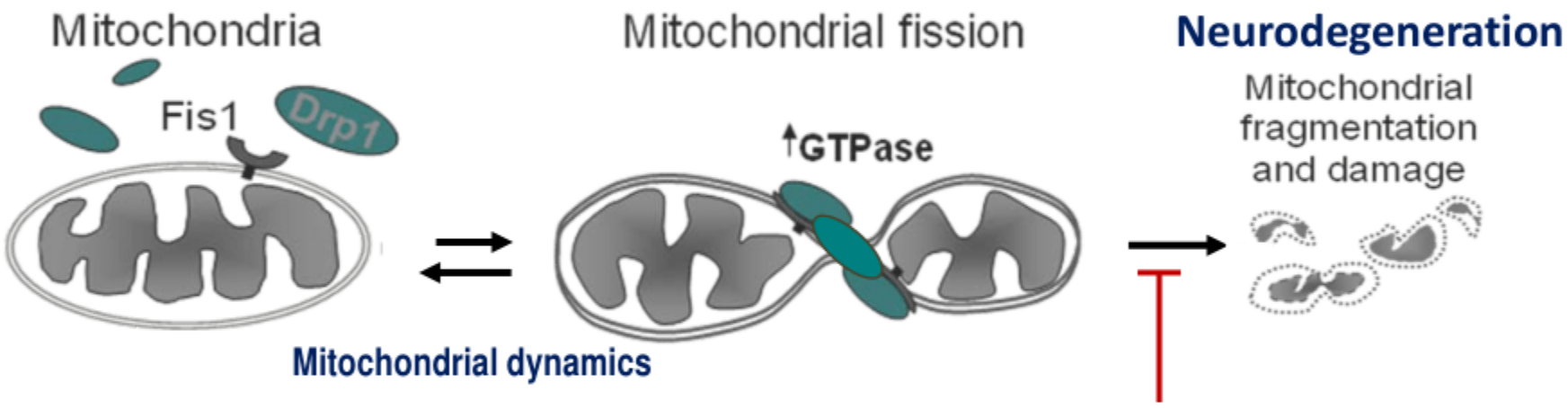




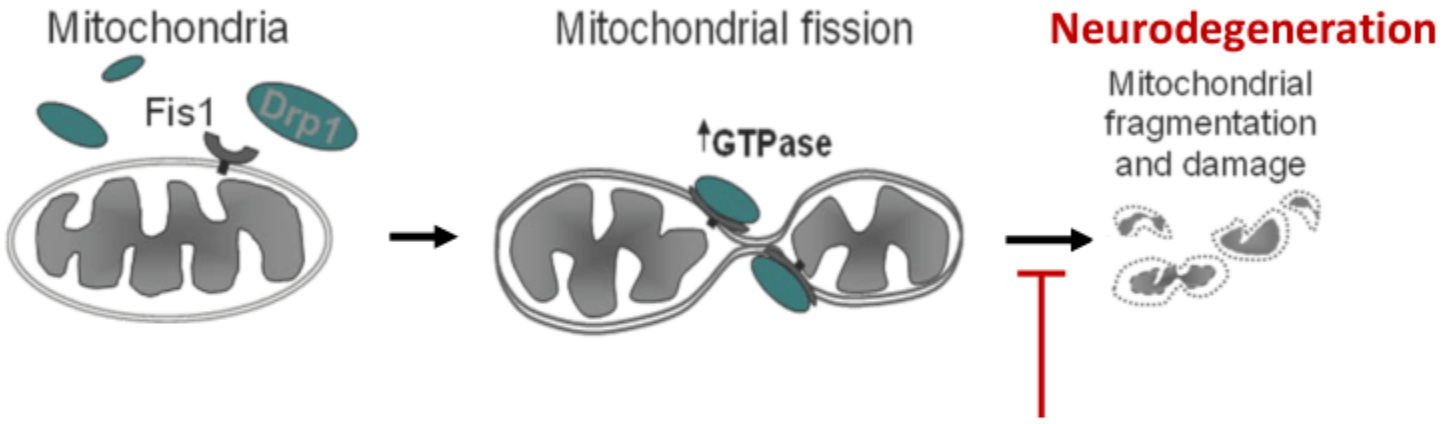
Joshi, *in preparation*

What regulates mitochondrial fragmentation?

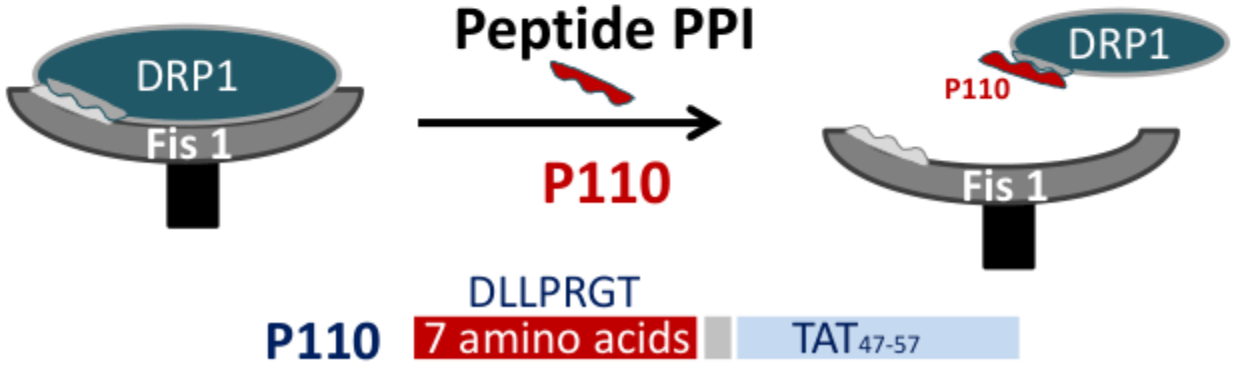
Dynamin-related protein 1 (Drp1) and its partner, Fis1



Can excessive mitochondrial fission be inhibited?

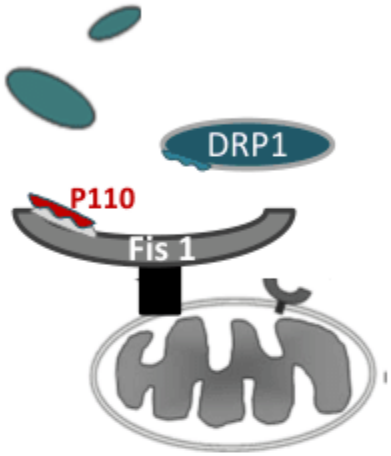


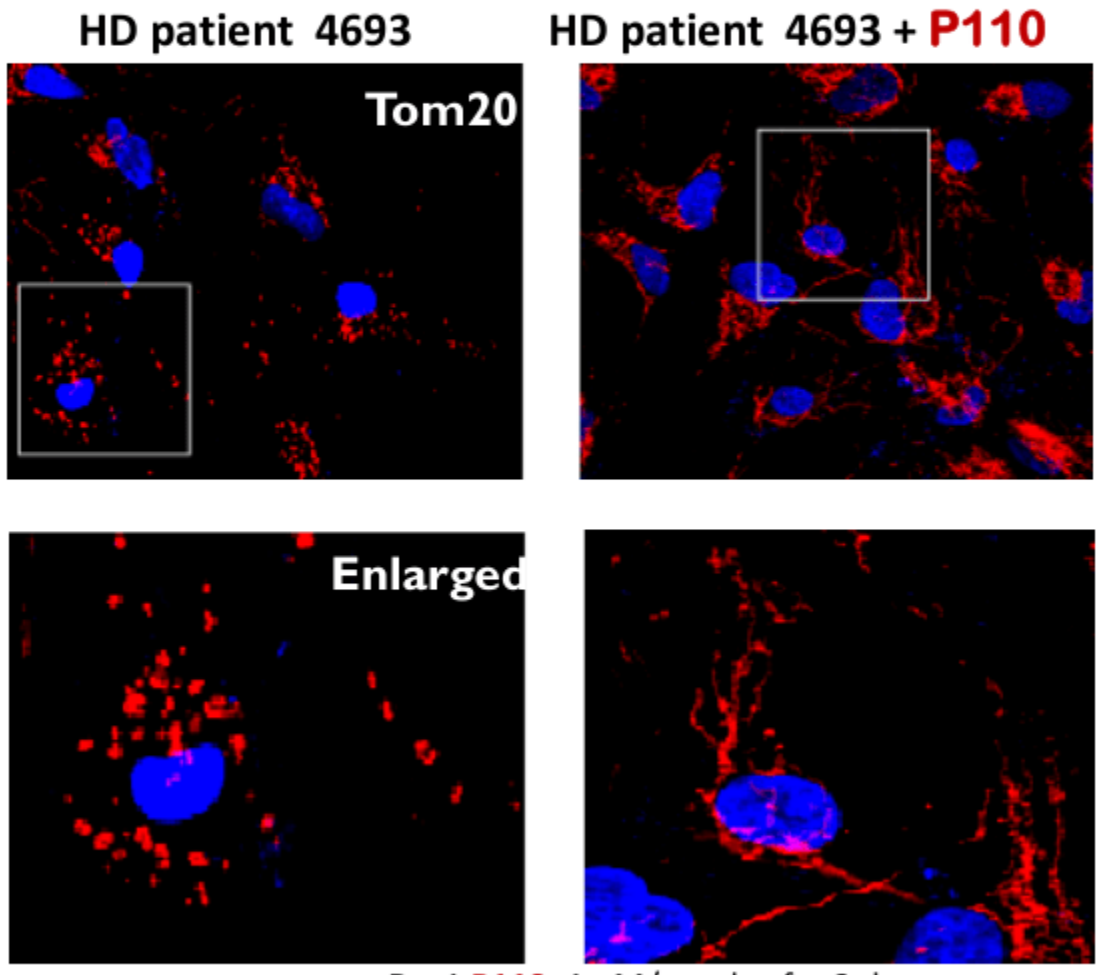
Rational design identifies a specific protein-protein (PPI) interaction inhibitor of Fis1/Drp1 interaction



Qi *et al.*, JCS, 126, 789–802, 2013

P110 reduces mitochondrial fragmentation in neurons derived from HD patients

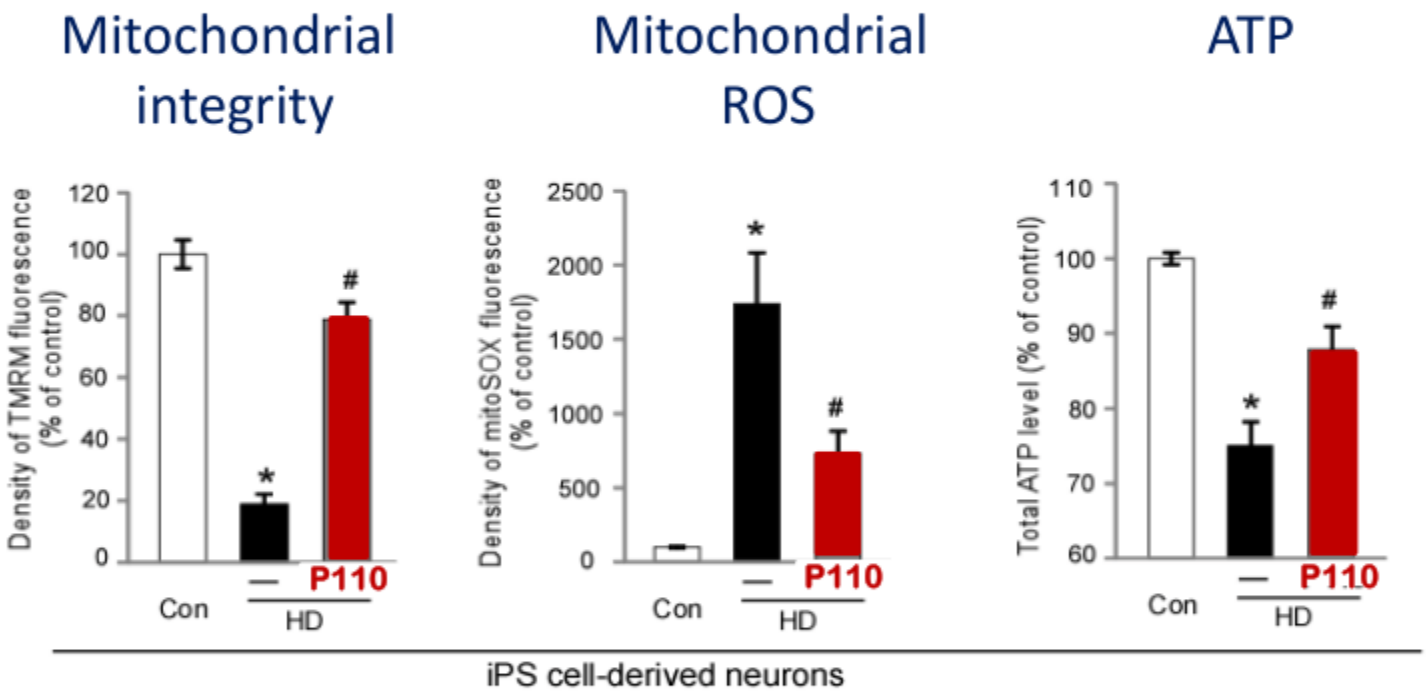




Drp1 P110: 1 uM/per day for 3 days treatment

Guo *et al., J Clin Invest*. 2013; 123:5371–5388

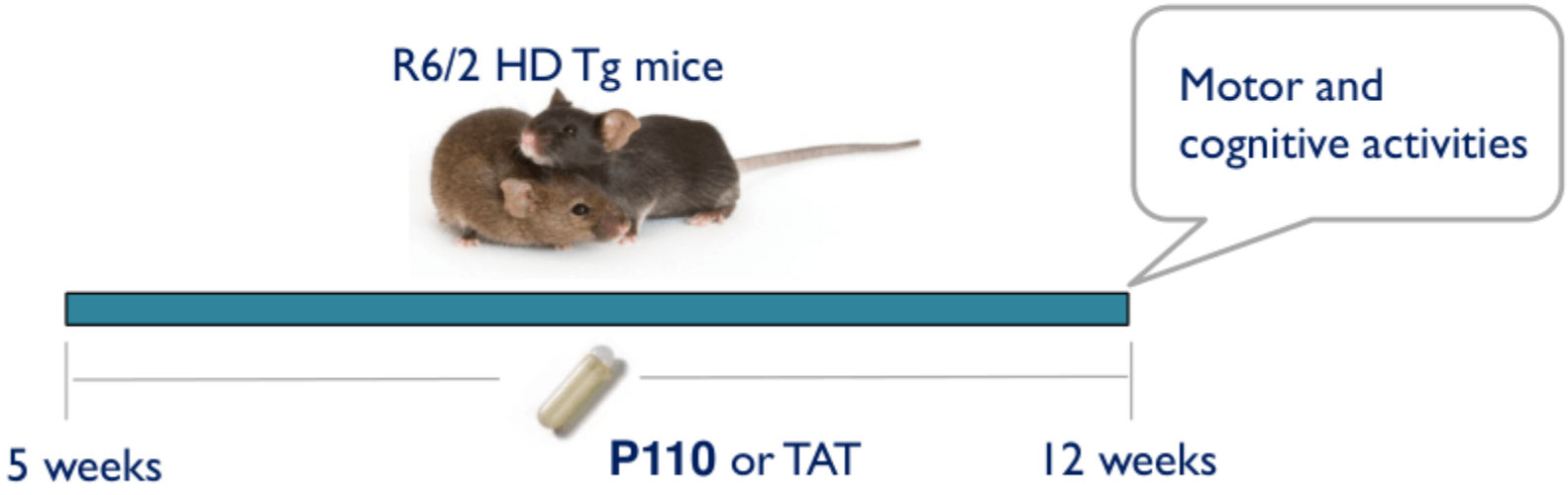
P110 treatment corrected mitochondrial dysfunction in neurons derived from HD patients



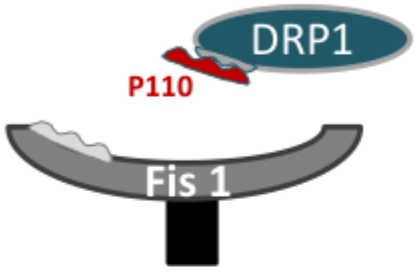
P110: 1μM/per day for 5 days

Guo *et al.*, J Clin Invest. 2013; 123:5371–5388

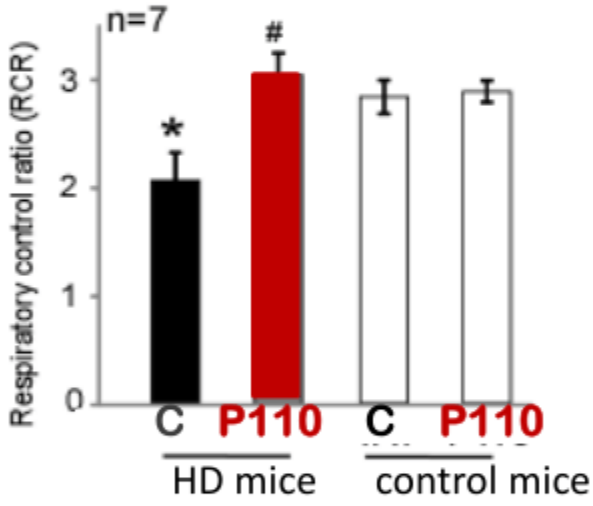
And *in vivo* – does **P110** treatment improve behavioral deficit in HD mouse model?



P110 treatment increases mitochondrial function in HD mice



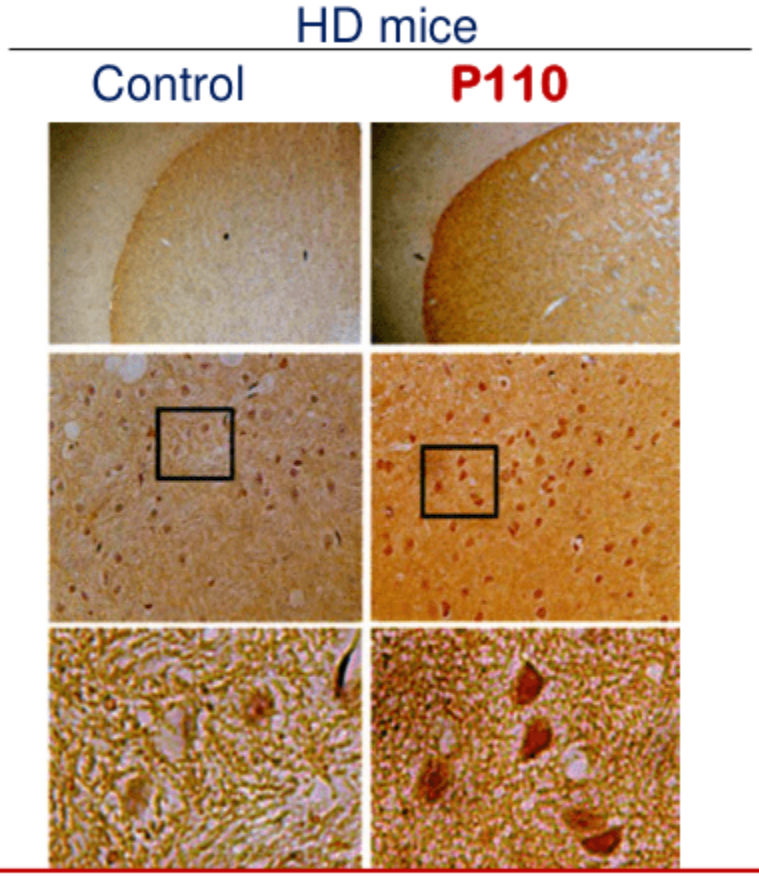
Oxygen consumption

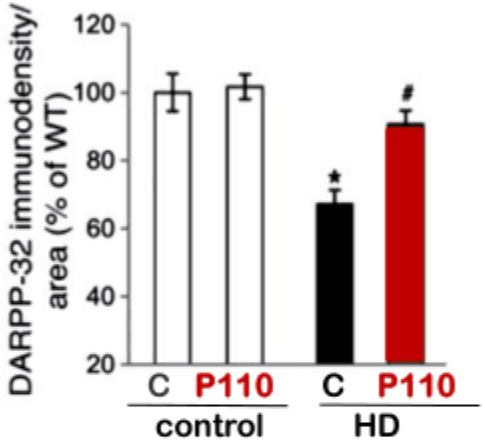


More functional mitochondria = more ATP

Guo et al, *J Clin Invest 2013*

Sustained treatment with **P110** increases number of dopaminergic neurons in HD mice



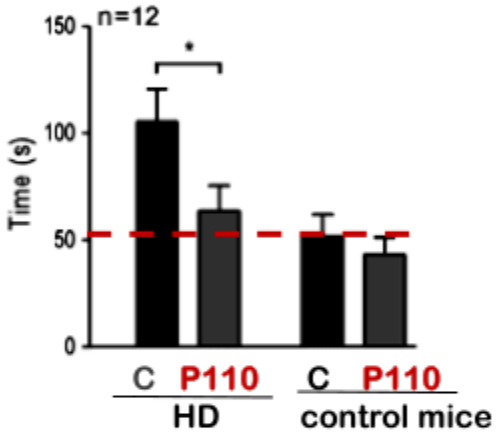


More functional mitochondria = more ATP = more repair = **more neurons**

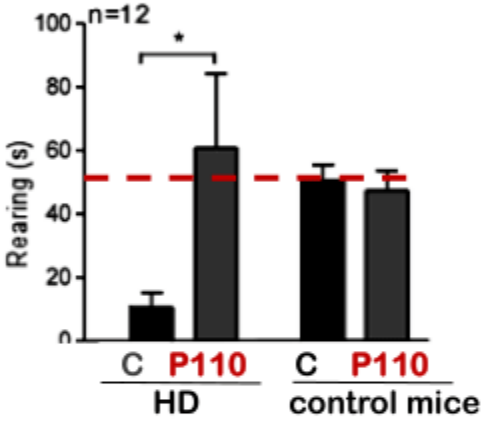
Guo. J Clin Invest 123:5371,2013

P110 improves motor activity of HD mice

Inactivity period



Rearing activity



More functional mitochondria = more ATP = more repair = more neurons = **better behavior**

Observer was blinded to the experimental conditions

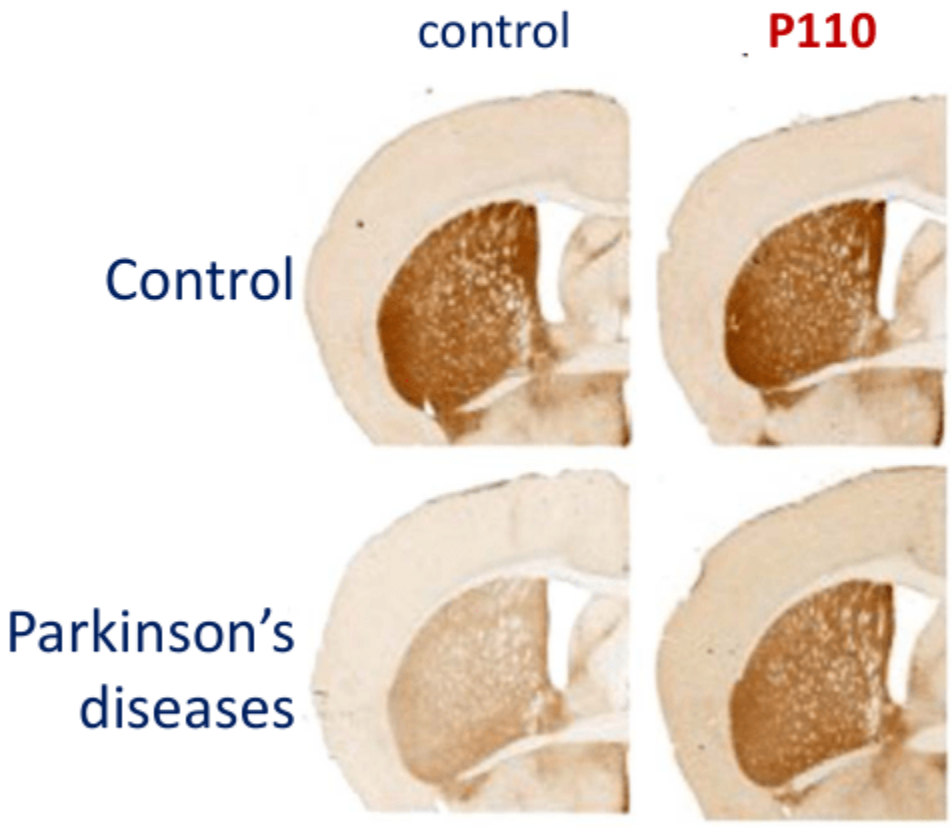
http://info.noldus.com/topic/rats

Guo *et al.*, J Clin Invest. 2013; 123:5371–5388

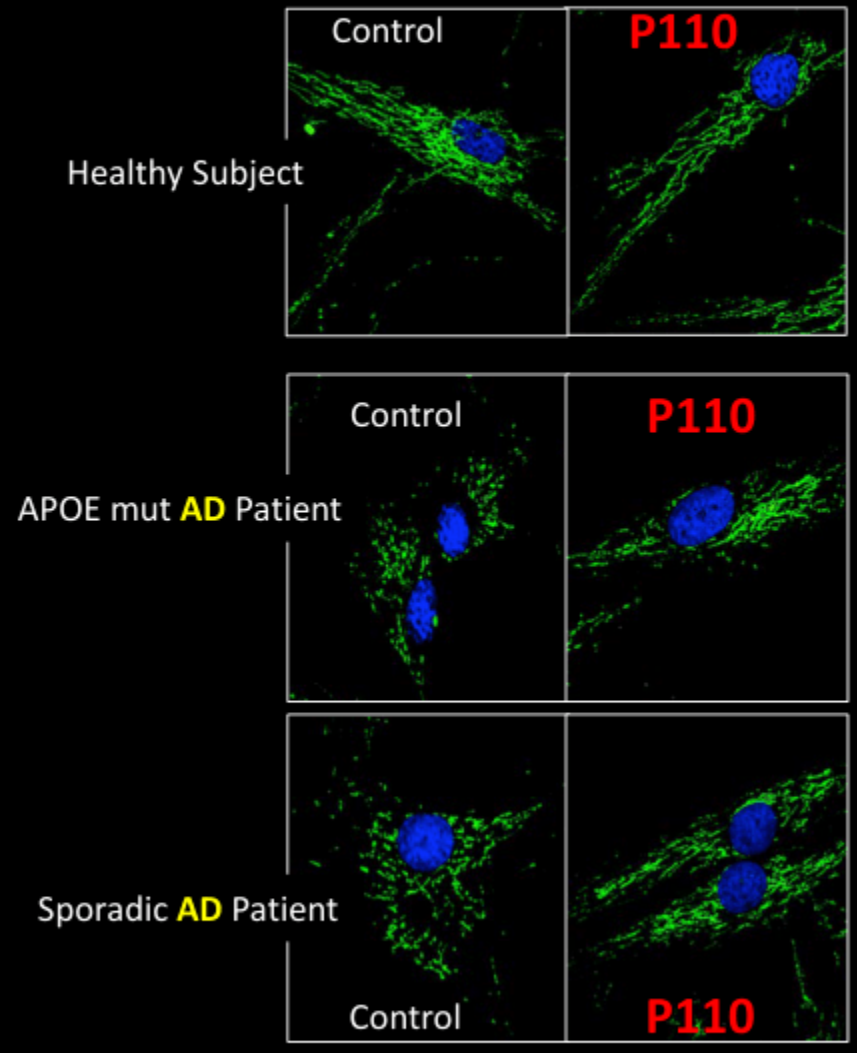
Sustained treatment with **P110** increases survival of HD mice (data from four independent studies)

More functional mitochondria = more ATP =
more repair = more neurons = better behavior **= longer life**

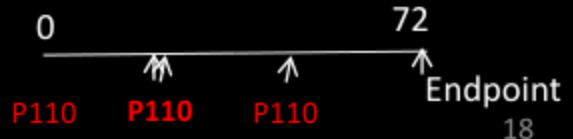
Benefit of **P110** in **other** neurodegenerative diseases
Parkinson's disease



And in sporadic & familial AD patient fibroblasts; P110 corrects excessive mitochondrial fission in



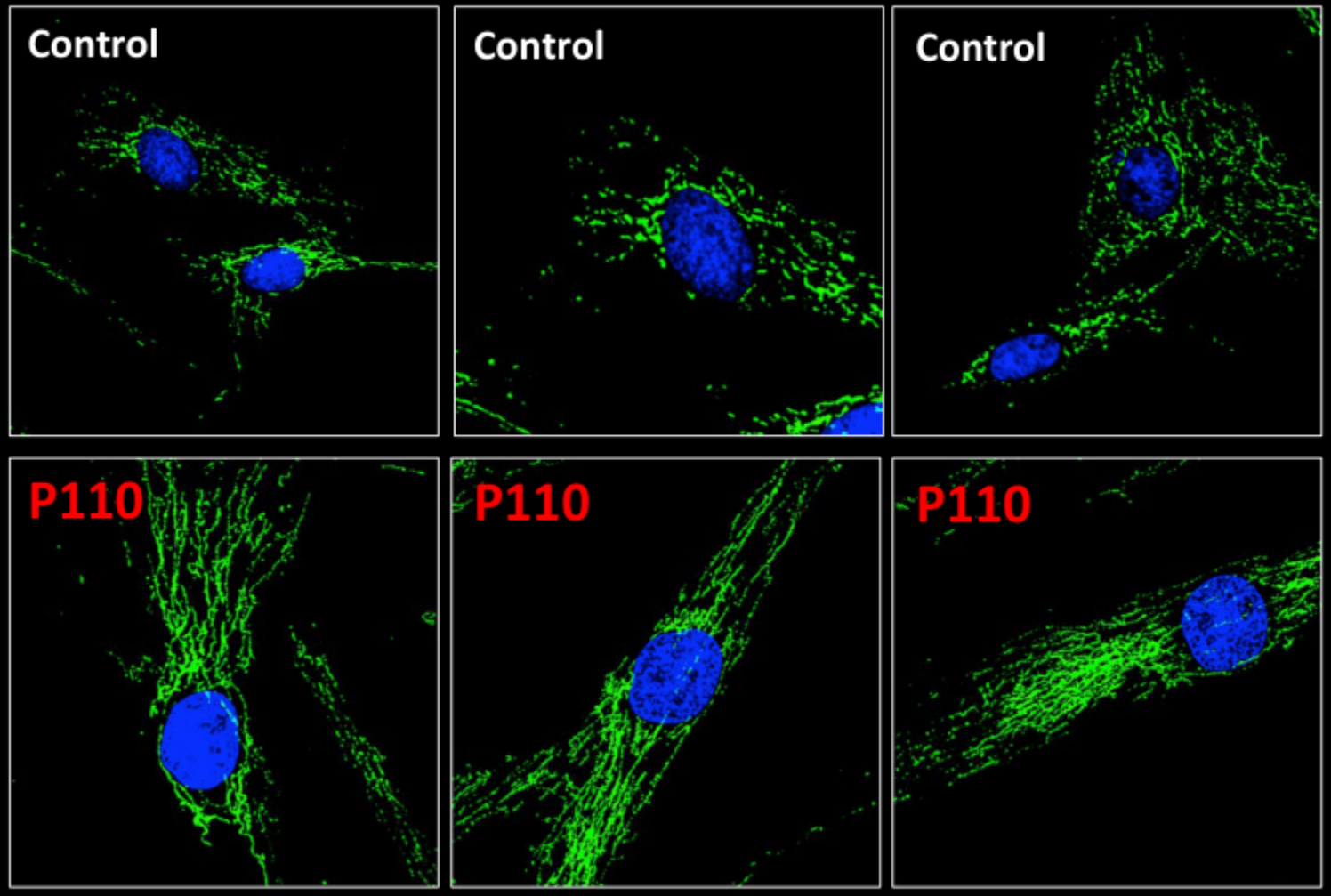
Amit Joshi, *in preparation*



18

n=3 in duplicate 120 cells per condition

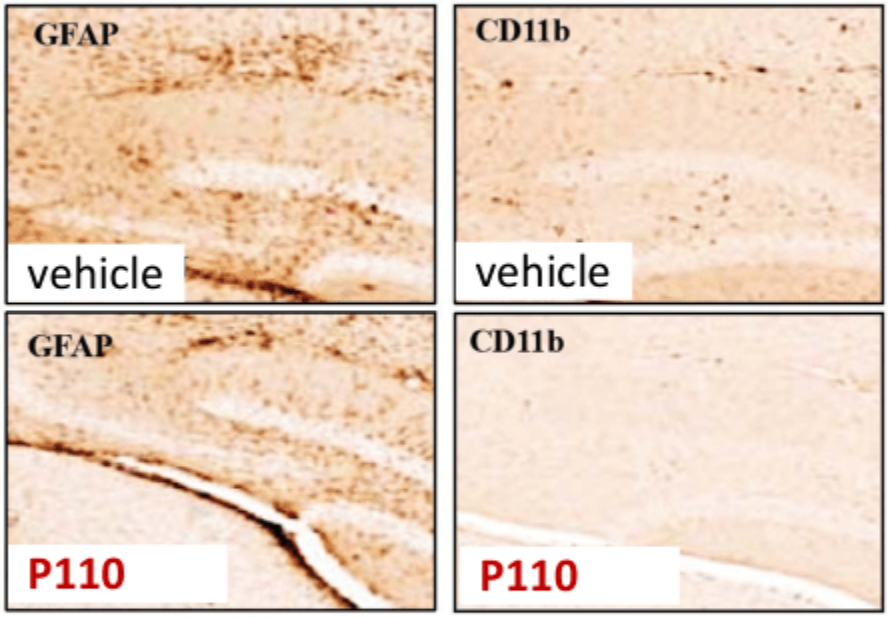
And in ALS patient fibroblasts
P110 corrects excessive mitochondrial fission

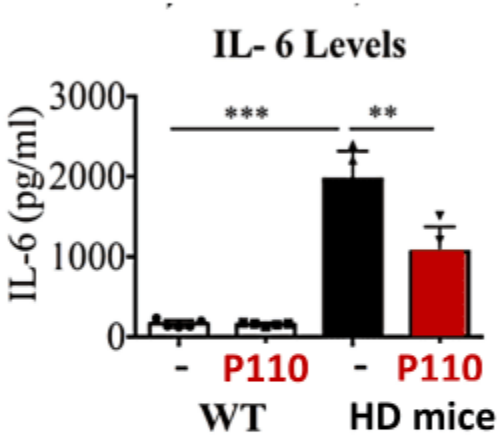


Amit Joshi, *in preparation*

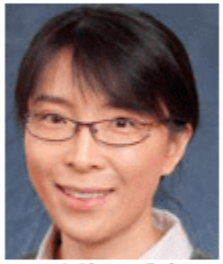
n=3 in duplicate 120 cells/ condition

P110 inhibits neuroinflammation, *in vivo*
e.g., Huntington's disease





P110 *may* benefit patients with a number of neurodegenerative and ischemic diseases including Parkinson's and Huntington's Disease



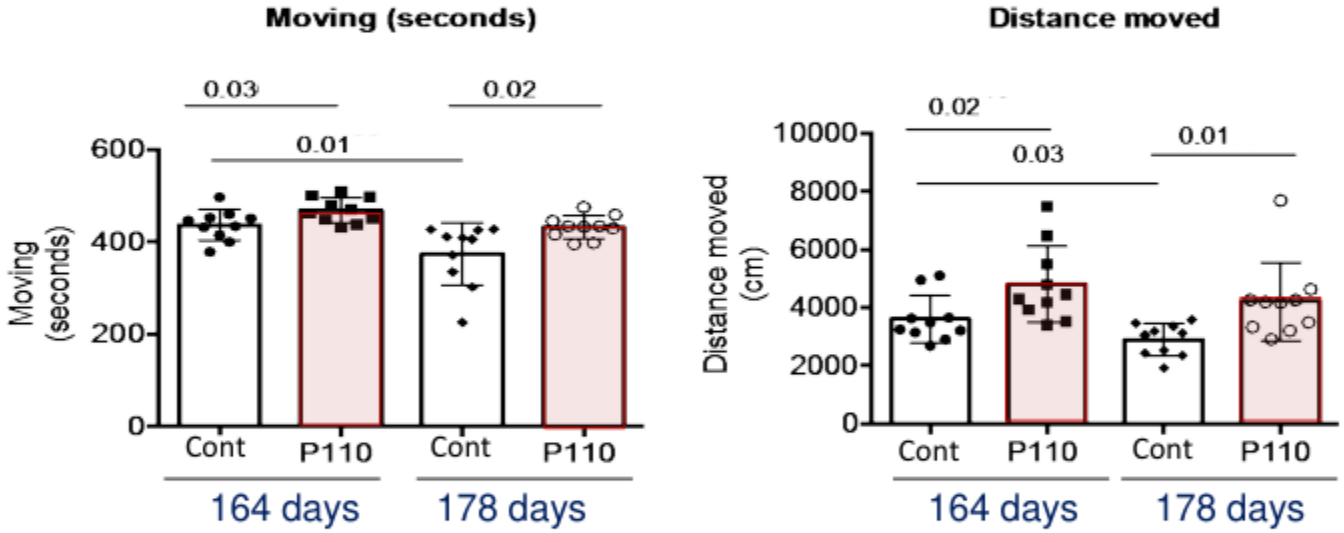
Xin Qi
(Case Western)

Marie-Helene Disatnik

Amit Joshi

Mitoconix

Sustained treatment with **P110** for 5 month is safe; it *may* reduce aging-induced dysfunctions in normal mice



Amit Joshi, *in preparation*

Agenda

- DDF update
- Portfolio overview
- Scientific deep dive into current prioritised areas of scientific focus for DDF
    1) Microglia, the role of glia in synaptic health, lead by Professor Beth Stevens
    2) Mitochondrial dynamics and their role in dementia, lead by Professor Daria Mochly-Rosen
- **DDF summary**

First year DDF performance

Investments

- 12 investments to date exploring novel mechanisms across all key themes
- 14% of current capital committed (invested, committed and reserved is £47m (48%)
- DDF investments leveraged with other investors' and grant funding

Deal flow

- Proactive translation of novel biology using targeted project-based funding in addition to investments in emerging companies
- Sourcing science and academic relationships in UK, US and Israel to date

DDF team

- Core DDF team supported by EIRs and world-class consultants in London and Boston
- Streamlined, rapid communication and decision making processes in place

Fundraising:

- ~40% of fund raised (£97.4m)
- Broadening investors beyond strategics to include financial investors, family offices, sovereign wealth, impact investors and pension funds

Scope to increase DDF's impact

Raising further capital will enable DDF to:

1. Expand the landscape of novel targets and mechanisms to develop into new dementia drugs (no shortage of opportunities)
    - Including mechanisms proven in oncology, inflammation, metabolism etc
    - Share learnings (successes and failures)
    - Broader geographic sourcing of science/academics
2. Build more robust preclinical and clinical translational data packages to increase the success of new drug development
    - Human tissue preclinical models
    - Biomarker development
    - Broader clinical evaluation in stratified patient groups
3. Leverage DDF's investments in novel translational biology to build momentum and confidence in the field, bringing more R&D funding into dementia drug discovery
4. Invest further in catalytic infrastructure to support dementia drug discovery beyond ChemCo, e.g. blood-brain-barrier technologies, iPSC banks, diagnostic technologies, novel clinical end points

→ **Larger DDF fund will enable discovery and development of *many more* than 2-3 novel drugs for dementia patients (both through the DDF and beyond)**