# FNDC5/irisin as a novel therapeutic approach in Alzheimer's disease

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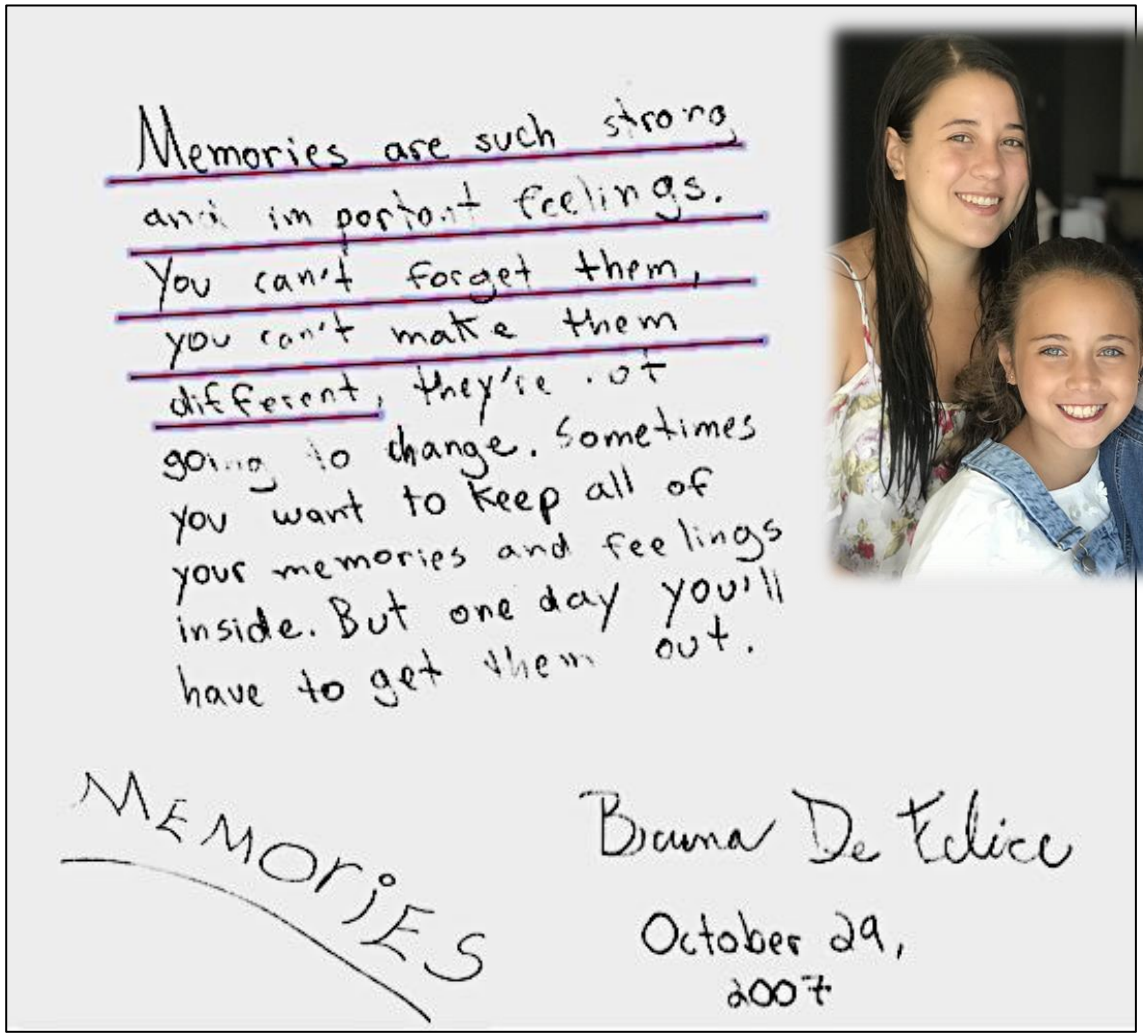
2001 PHD - Federal University of Rio de Janeiro

2008 Post-doctoral training - Northwestern University

# How everything started…

Jose Pelucio Ferreira

1928-2002



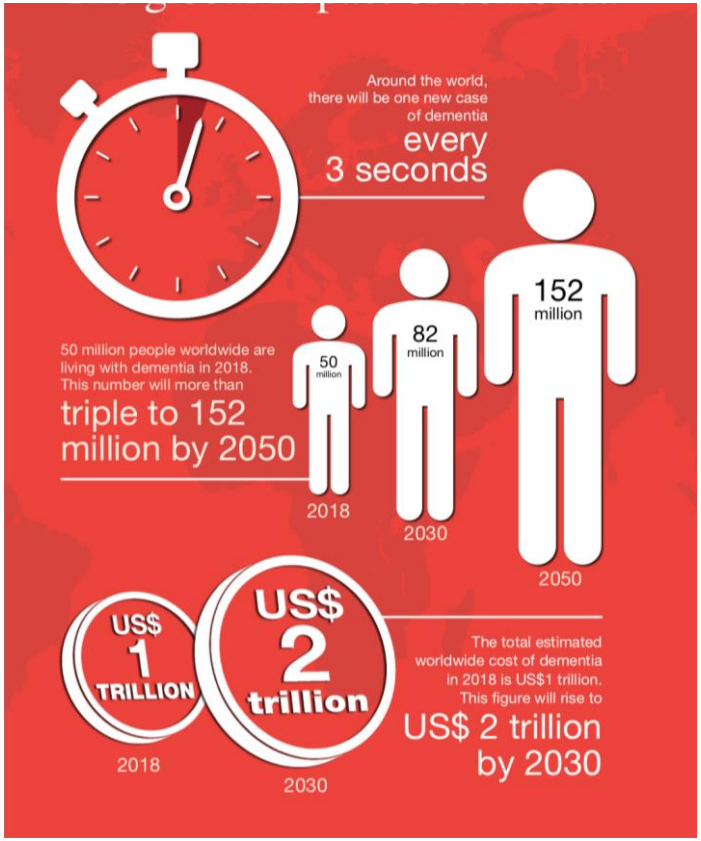
# Dementia in numbers

## Canada

| | TODAY | 2031 |
|---|---|---|
| Canadians living with dementia | **500,000+** | **937,000** |
| Costs of caring for Canadians with dementia | TODAY **$10.4** BILLION | 2031 **$16.6** BILLION |

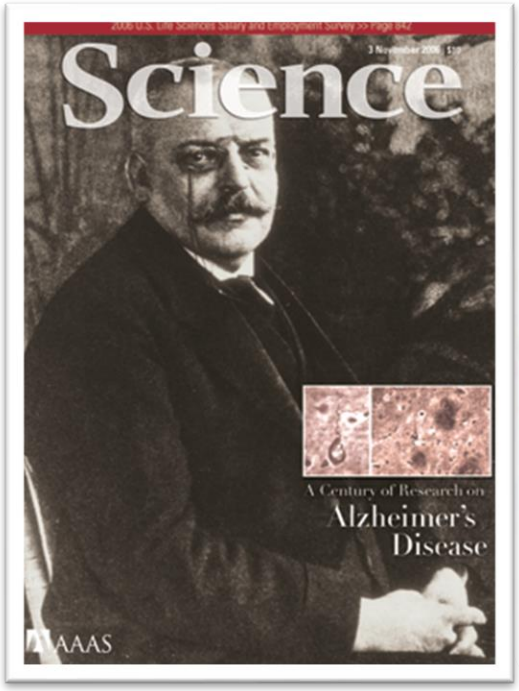
*Alzheimer Society of Canada (2017-2018) Impact report*

- 50 million people currently live with dementia worldwide
- By 2050, 152 million people will be living with dementia
- The annual cost of dementia is over US$ 1 trillion – a figure set to double by 2030



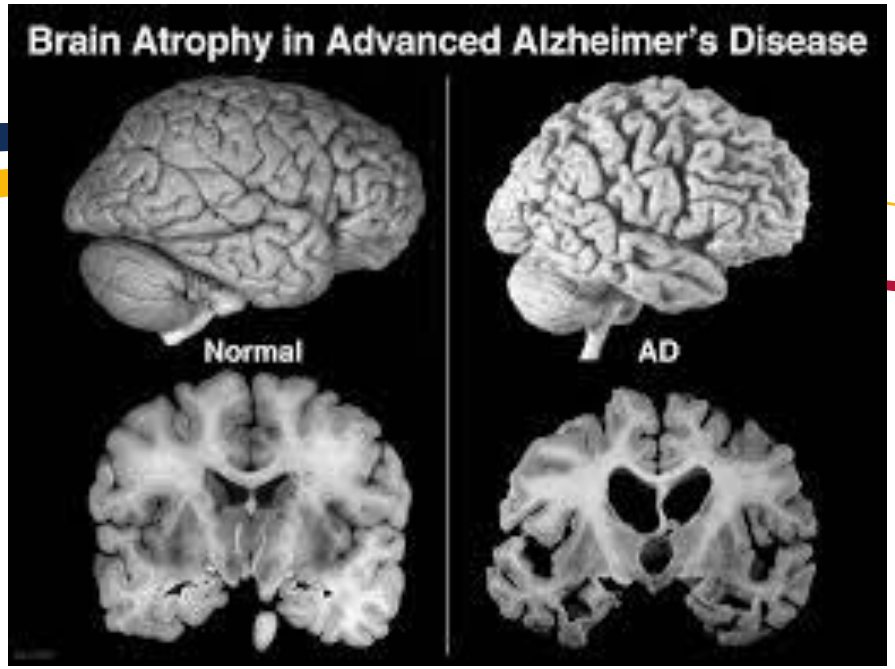

*World Alzheimer Report (2019)*

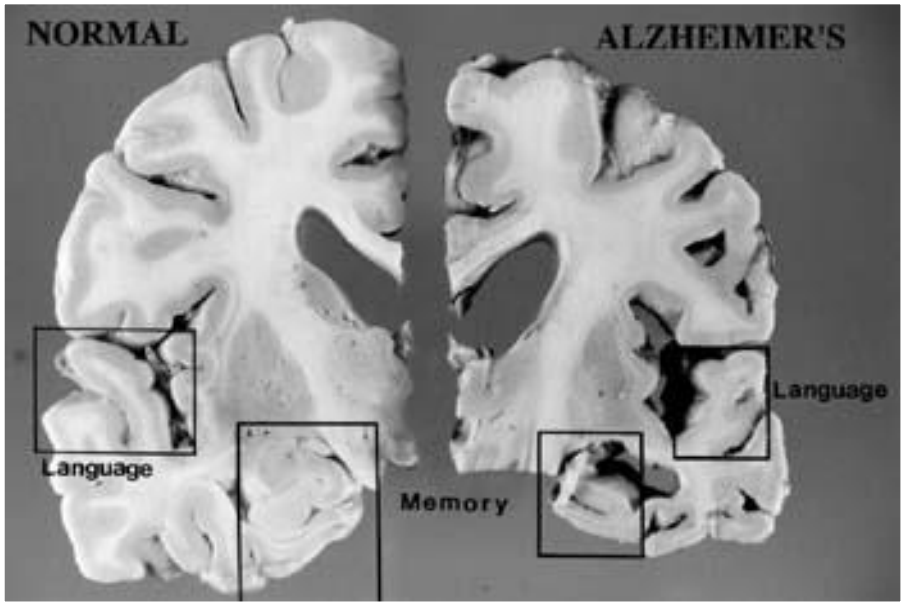
# First patient diagnosed with Alzheimer's disease - 1906



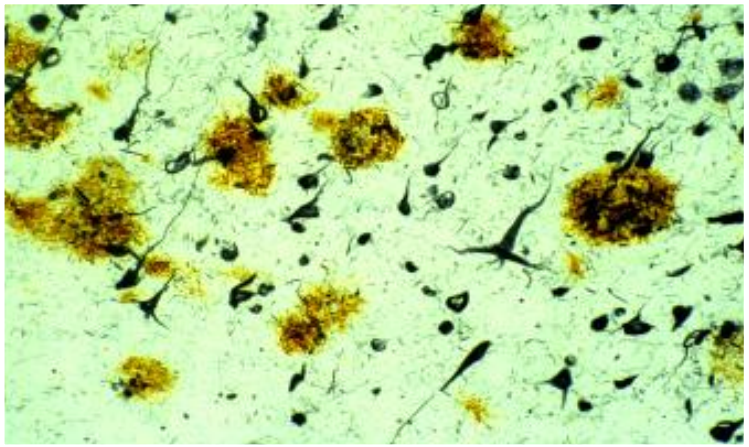

*"I have lost myself"*
Auguste D

- Memory loss
- Difficulties in communication, learning, thinking and reasoning
- Personality changes
- Behavioural symptoms: delusions, hallucinations




Alzheimer's plaques and tangles



# Why is it so hard to treat Alzheimer's disease?

Queen's UNIVERSITY

## 2,344 studies

NIH U.S. National Library of Medicine

ClinicalTrials.gov

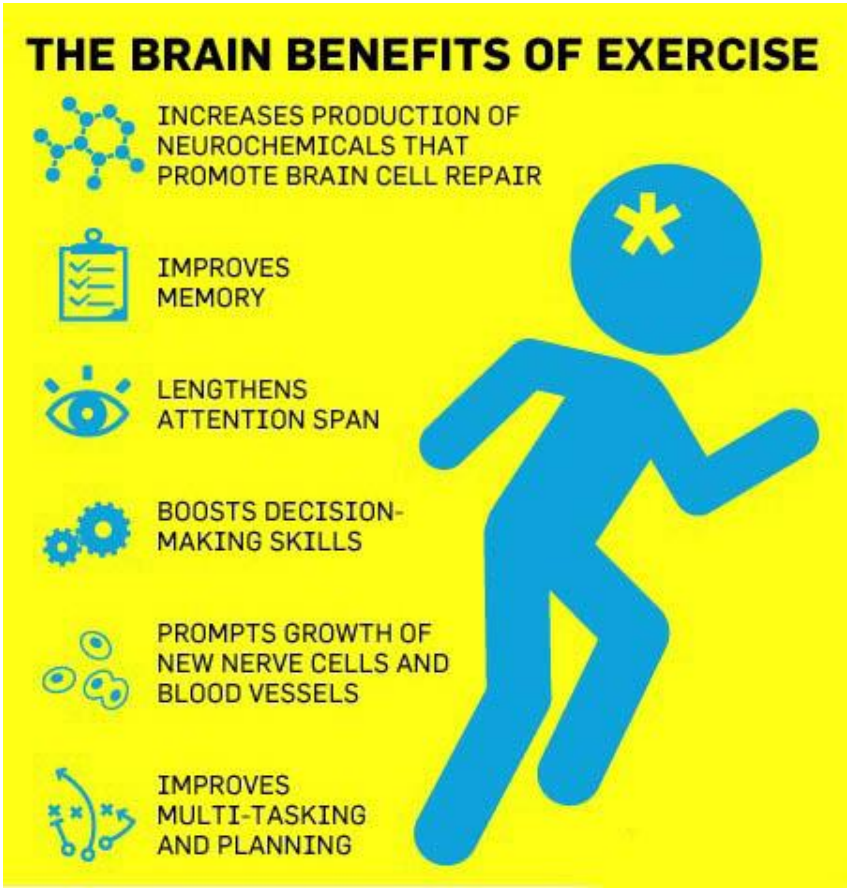
| General Name | Brand Name |
|---|---|
| Donepezil | Aricept |
| Rivastigmine | Exelon |
| Galantamine | Razadyne |
| Memantine | Namenda |

~350 compounds tested in humans since 2002

- only memantine, an NMDA receptor antagonist, has safely translated into AD clinical practice.

- modest effectiveness in promoting cognitive improvement

# The benefits of exercise for the brain



# Physical exercise and brain health

Alzheimer Society

## Staying physically active

Be active! Your physical fitness helps your brain fitness.

Alzheimer's Society United Against Dementia

### Physical exercise and dementia

Of all the lifestyle changes that have been studied, taking regular physical exercise appears to be one of the best things that you can do to reduce your risk of getting dementia.

alzheimer's association®

### Physical exercise

Regular physical exercise may be a beneficial strategy to lower the risk of Alzheimer's and vascular dementia.

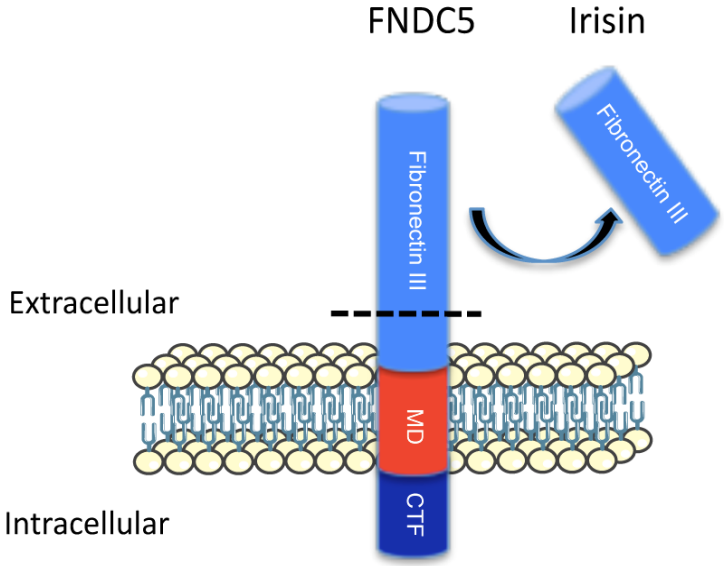
# Irisin, an exercise-related hormone

Queen's University

**Iris**

Goddess of the Rainbow

Fibronectin type III domain containing 5




Bruce Spiegelman - Harvard

Boström, P. et al. Nature 481, 463-468 (2012).

# An exercise-related hormone to fight dementia

Queen's University

Article Published: 07 January 2019

nature medicine

ARTICLES

https://doi.org/10.1038/s41591-018-0275-4

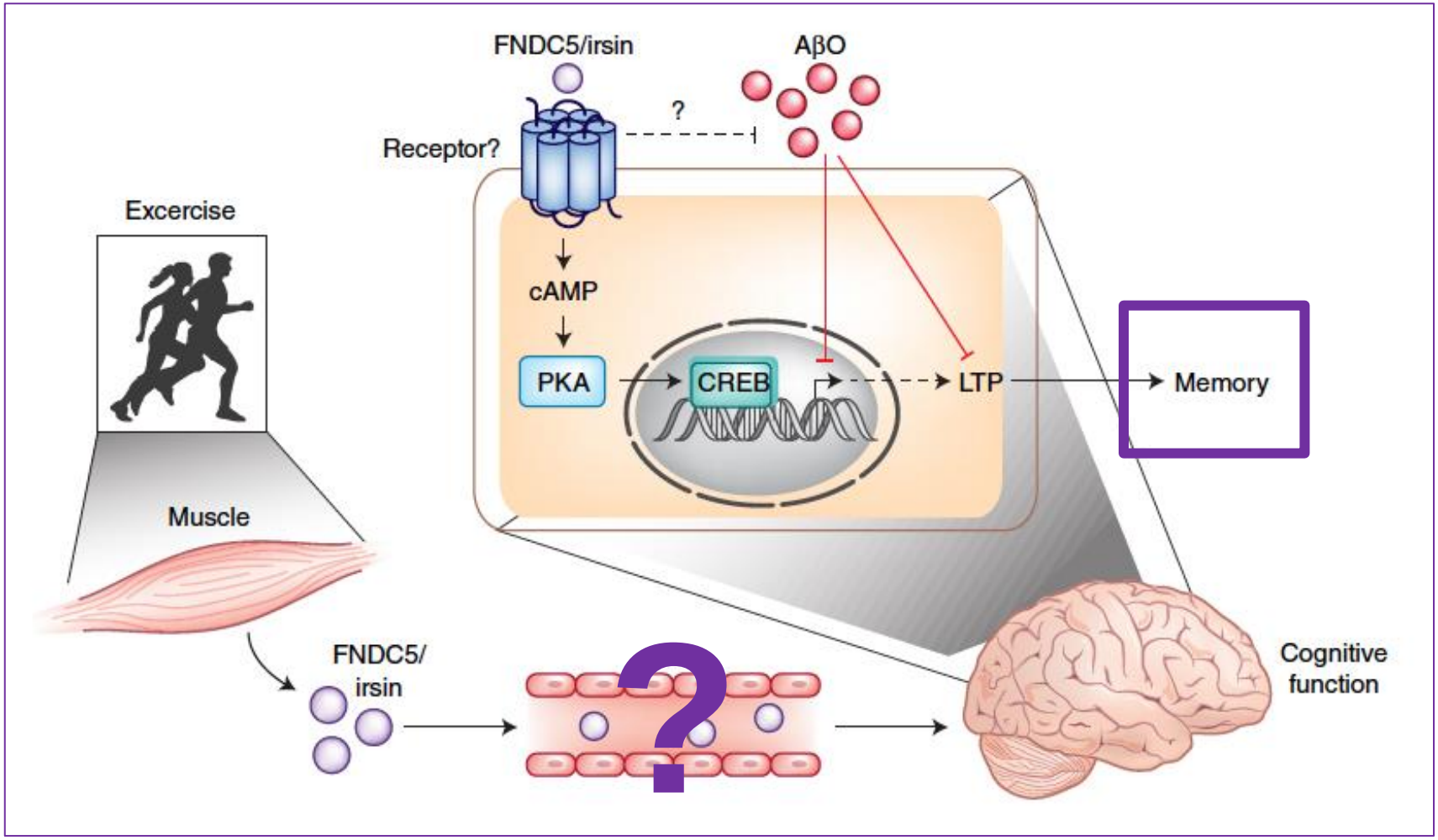
## Exercise-linked FNDC5/irisin rescues synaptic plasticity and memory defects in Alzheimer's models

Mychael V. Lourenco[1,2,3], Rudimar L. Frozza[1,4,19], Guilherme B. de Freitas[1,5,19], Hong Zhang[3], Grasielle C. Kincheski[1,2], Felipe C. Ribeiro[1,2], Rafaella A. Gonçalves[5], Julia R. Clarke[1,6], Danielle Beckman[1], Agnieszka Staniszewski[3], Hanna Berman[3], Lorena A. Guerra[1,2], Letícia Forny-Germano[1], Shelby Meier[7], Donna M. Wilcock[7], Jorge M. de Souza[8,9], Soniza Alves-Leon[8,9], Vania F. Prado[10,11,12], Marco A. M. Prado[10,11,12], Jose F. Abisambra[7], Fernanda Tovar-Moll[13,14], Paulo Mattos[13,15], Ottavio Arancio[3,16,17*], Sergio T. Ferreira[1,2*] and Fernanda G. De Felice[1,5,18*]

Alzheimer Society Canada

Weston Brain Institute

# Towards a medication that reproduces the beneficial effects of exercise



# The next big steps

- ***1)*** **Use gene-therapy to increase irisin in the brains of animal models of Alzheimer's disease and evaluate cognition.**

- *2)* Use vesicles and cell therapy to increase irisin in the brains of NHPs and evaluate cognition.

- *3)* Optimize physical exercise protocols in healthy humans to improve cognition and increase irisin.

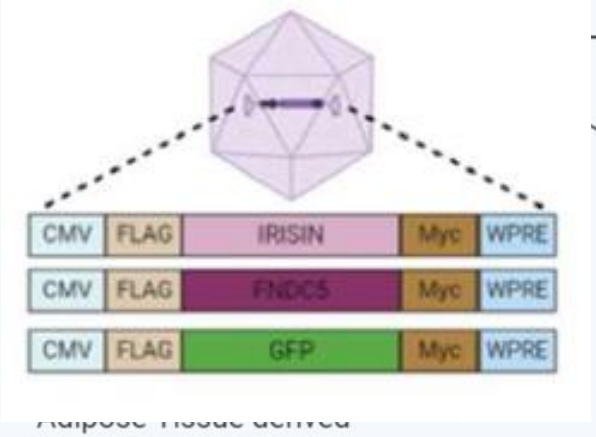
# Gene therapy using irisin

## Therapeutic strategy to deliver irisin to the brain

1

**AAVs to increase irisin**

**vesicles (EVs) enriched in irisin**




Mesenchymal Stem Cells (AdMSC) in culture

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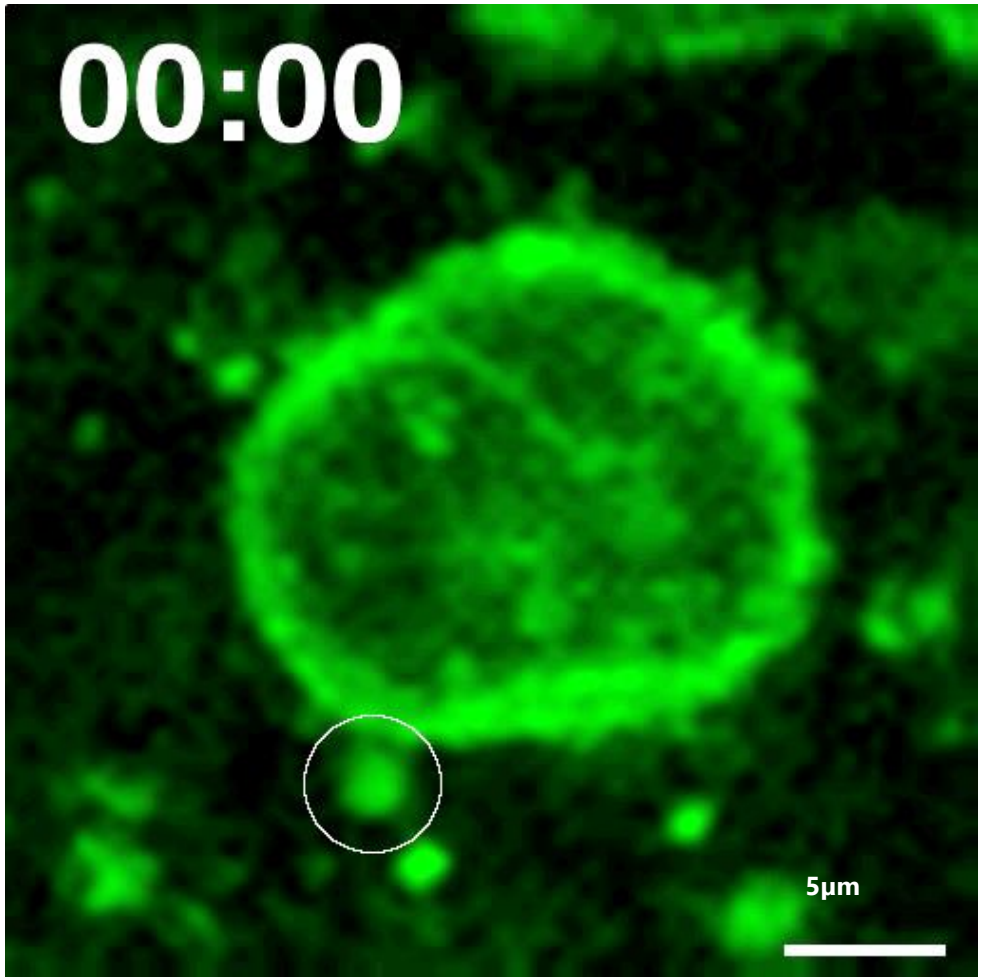
# Searching for a better way to transport irisin to the brain


Package

Transport

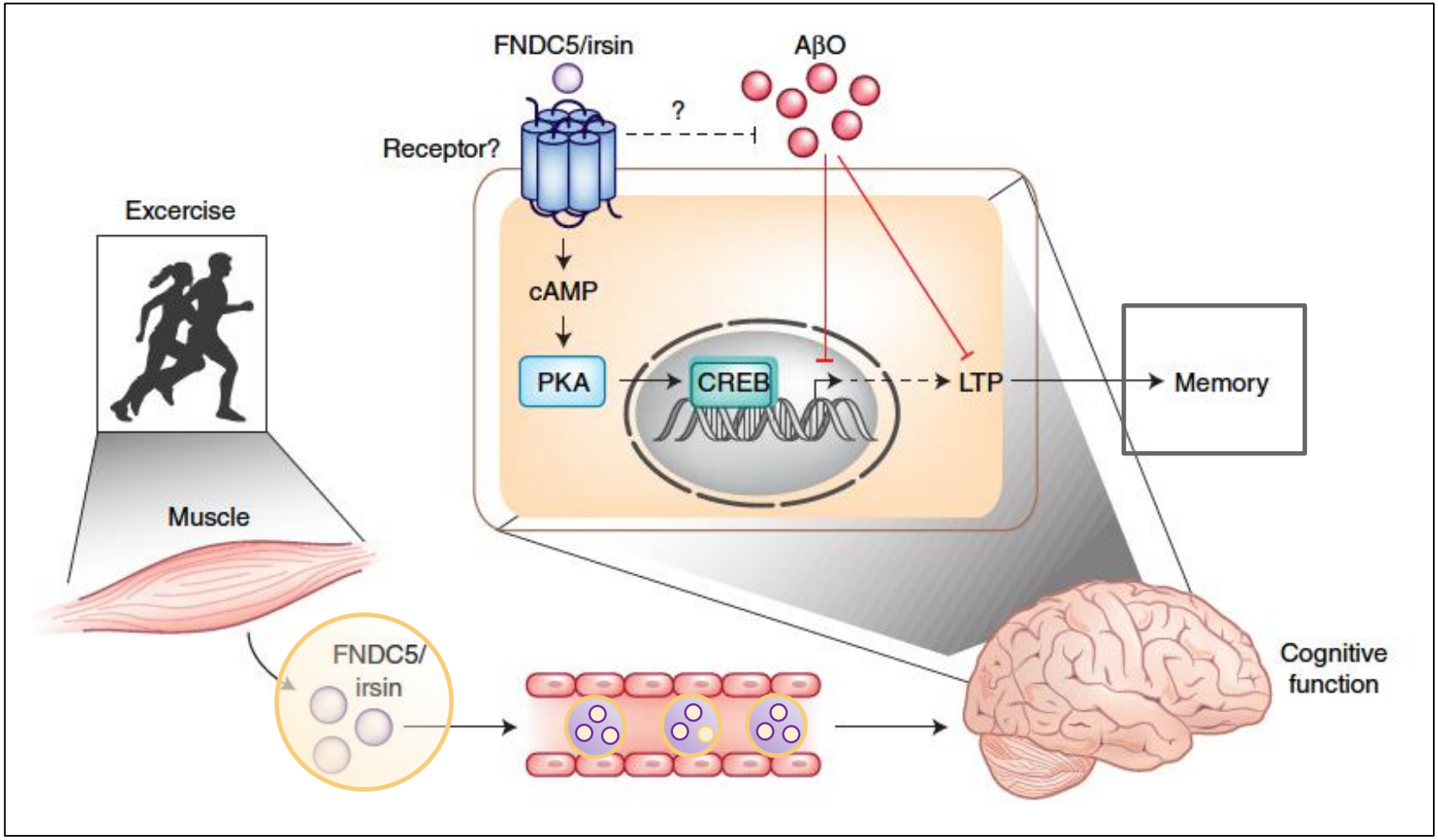
Delivery

# Vesicles as an attractive approach




*Lai C P. et al. Nature Communications (2015)*

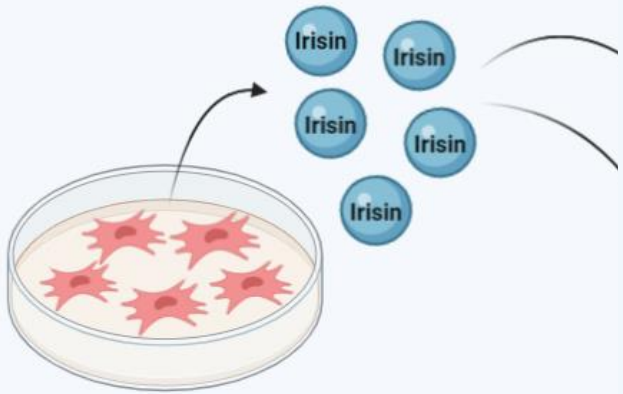
# Towards a medication that reproduces the beneficial effects of exercise



# Vesicles and cell therapy using irisin

## Therapeutic strategy to deliver irisin to the brain

1 *In vitro* production of extracellula vesicles (EVs) enriched in irisin




Adipose Tissue derived Mesenchymal Stem Cells (AdMSC) in culture

# The next big steps

- *1)* Use gene-therapy to increase irisin in the brains of animal models of Alzheimer's disease and evaluate cognition.

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- ***3)* Optimize physical exercise protocols in humans to improve cognition and increase brain irisin.**

# Thank you!

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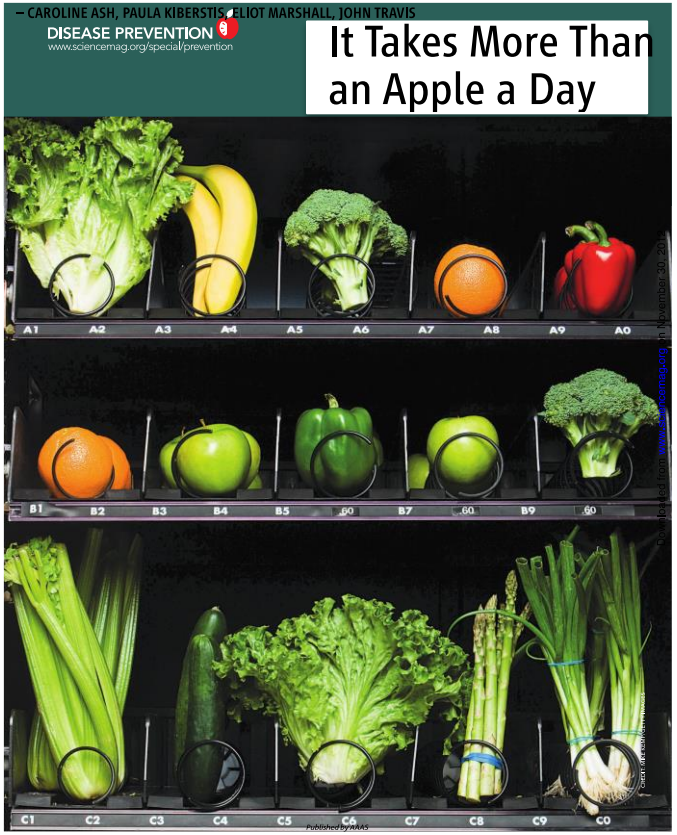
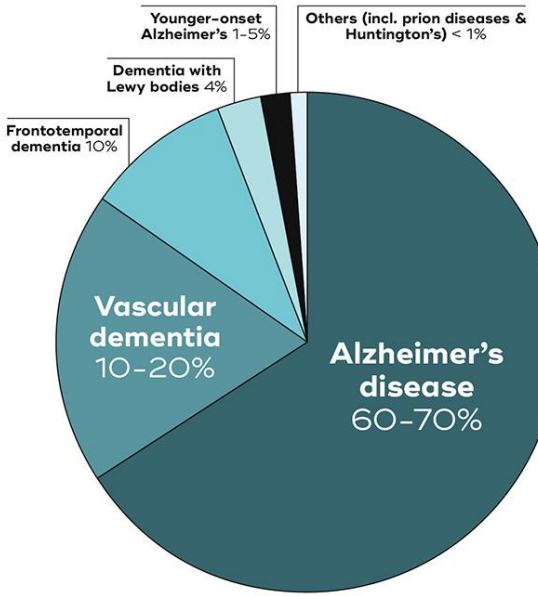
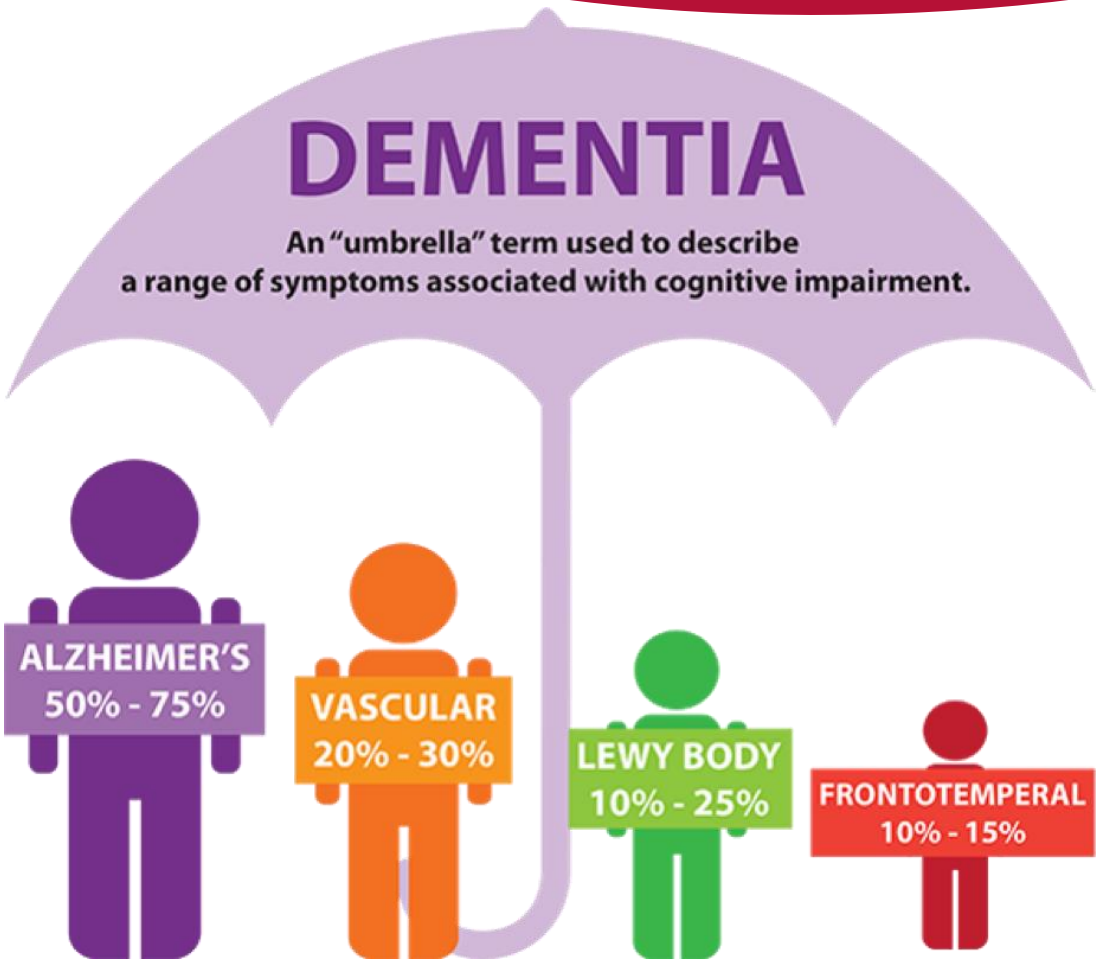



# The Global Impact of Dementia




World Alzheimer's Report, **2015**

# Why is it so hard to treat Alzheimer's disease?

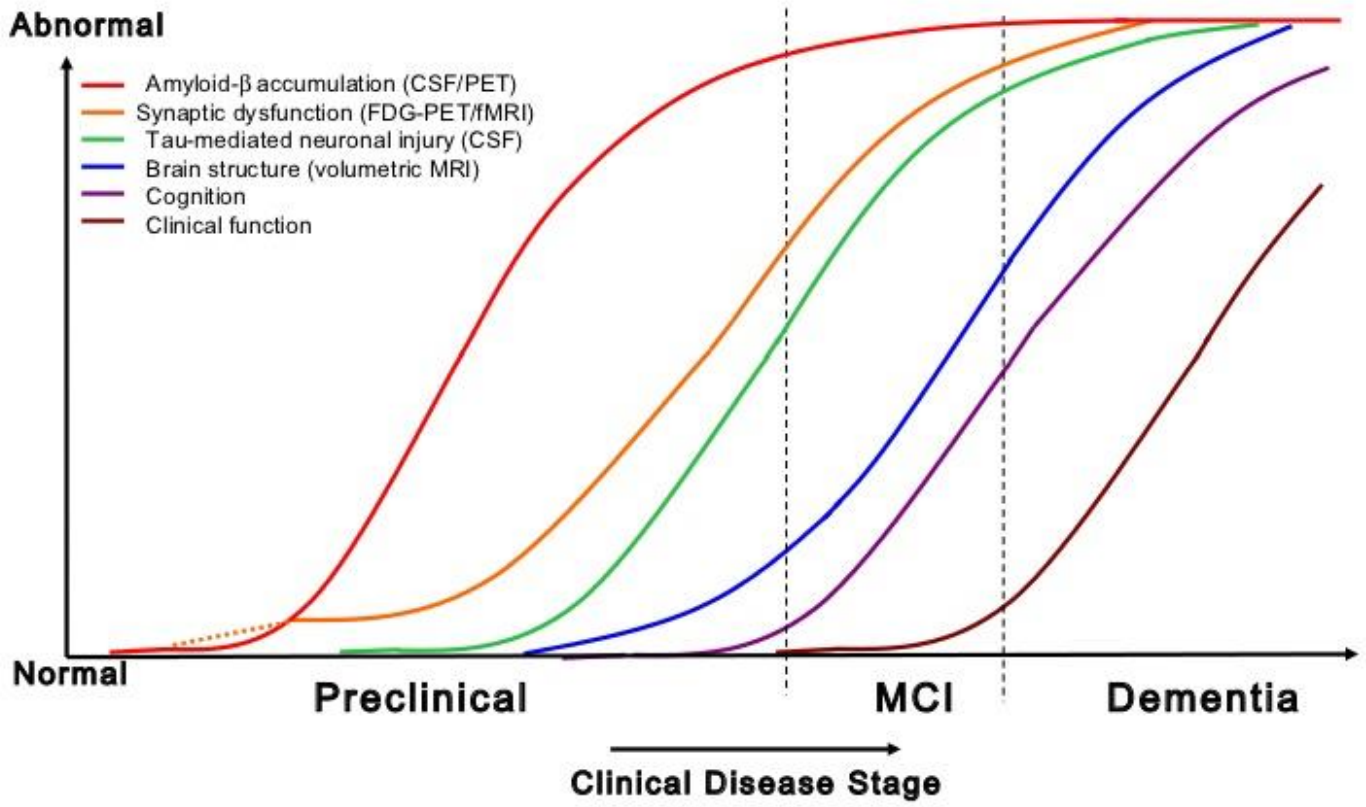
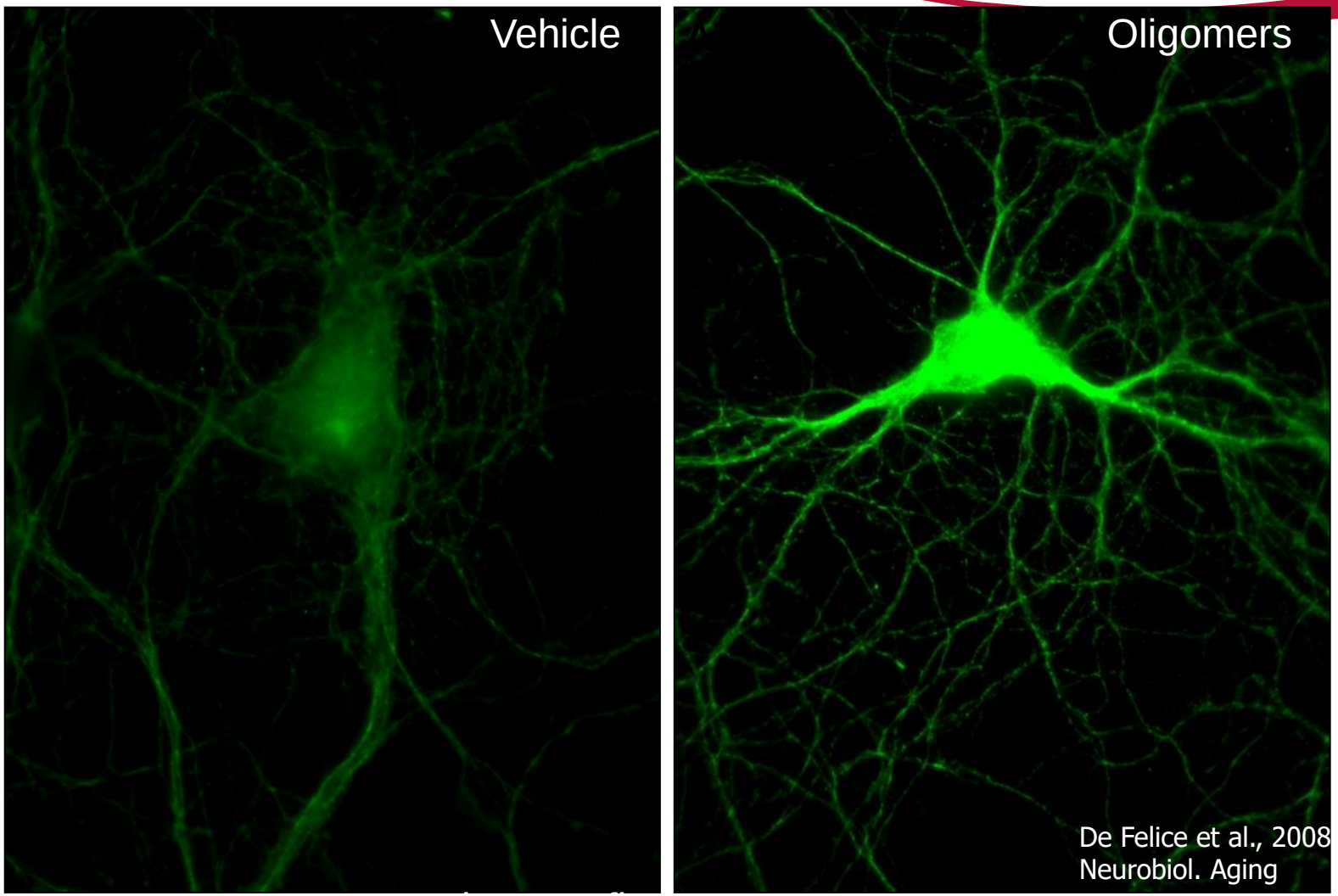
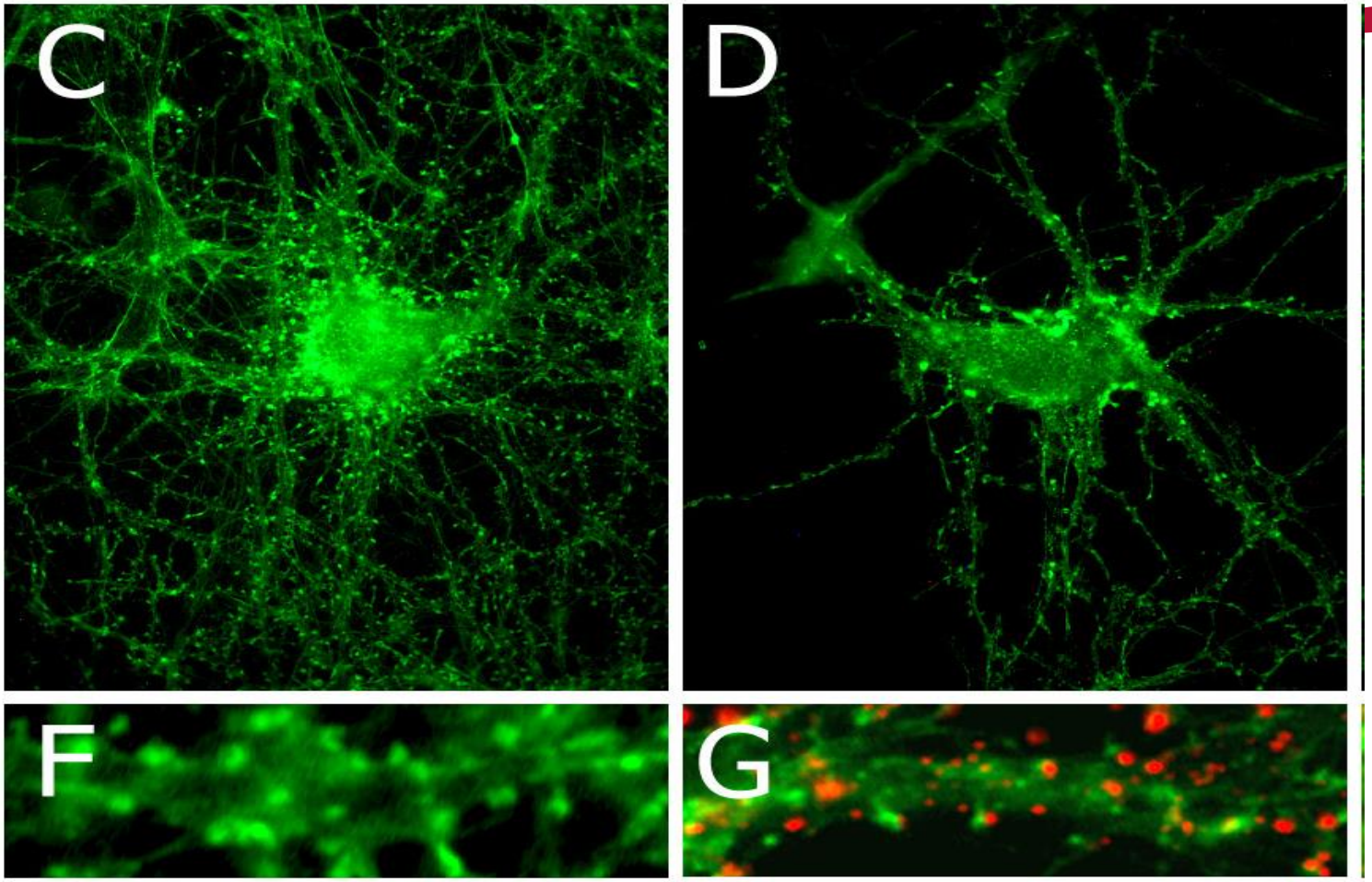



**Figure adapted from Jack *et al.* 2010**
Sperling et al *Alzheimer & Dementia 2011*

# Aβ oligomers induce tau pathology



# Aβ oligomers are toxic to synapses




Spines labeled with phalloidin

**De Felice, et al.**
**PNAS 2009**

# Why is it so hard to treat Alzheimer's disease?

27 MARCH 2014 | VOL 507 | NATURE

# Make mouse studies work

More investment to characterize animal models can boost the ability of preclinical work to predict drug effects in humans, says **Steve Perrin**.

Mice take the blame for one of the most uncomfortable truths in translational research. Even after animal studies suggest that a treatment will be safe and effective, more than 80% of potential therapeutics fail when tested in people. Animal models of disease are frequently condemned as poor predictors of whether an experimental drug can become an effective treatment. Often, though, the real reason is that the preclinical experiments were not rigorously designed[1,2].

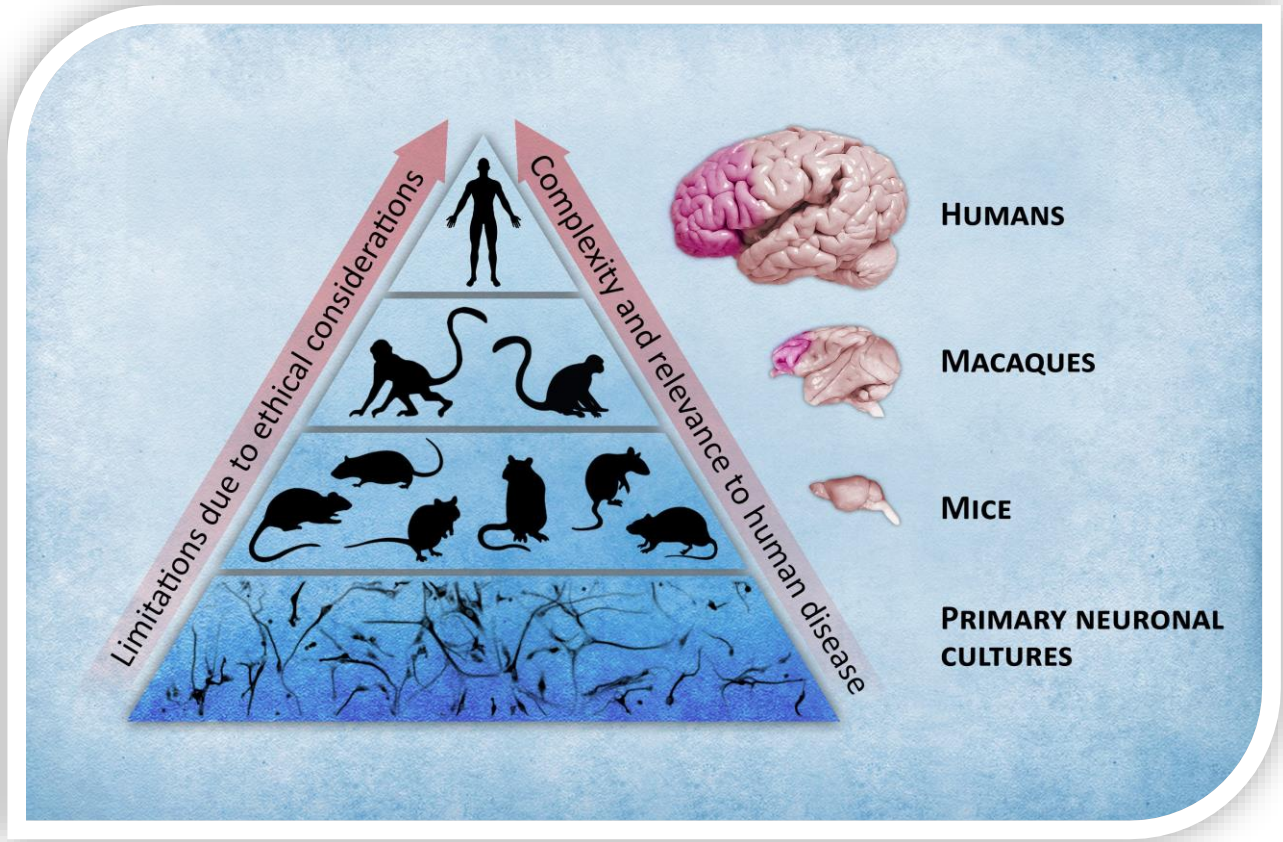
The series of clinical trials for a potential therapy can cost hundreds of millions of dollars. The human costs are even greater: patients with progressive terminal illnesses may have just one shot at an unproven but promising treatment. Clinical trials typically require patients to commit to year or more of treatment, during which they are precluded from pursuing other experimental options. Launching a clinical trial without the backing of robust animal data keeps patients out of tests for therapies that may have a better chance of success.

One such group of patients is those with amyotrophic lateral sclerosis (ALS), the fatal neurodegenerative condition also known as Lou Gehrig's or motor neuron disease. Over the past decade, about a dozen experimental treatments have made their way into human trials for ALS. All had been shown to ameliorate disease in an established animal model. All but one failed in the clinic, ▶

ILLUSTRATIONS BY CLAIRE WELSH/*NATURE*

# Alzheimer's therapies that work in rodents often do not translate to humans

**Douglas Munoz,**
Centre for Neuroscience Studies




De Felice & Munoz,, Aging Res Reviews 2016