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

Memories are such strong and important feelings. You can't forget them, you can't make them different, they're not going to change. Sometimes you want to keep all of your memories and feelings inside. But one day you'll have to get them out.

Memories

Bianca De Felice

October 29, 2007
Dementia in numbers

Canada

<table>
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<tr>
<th>Canadians living with dementia</th>
<th>TODAY</th>
<th>2031</th>
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<td>500,000+</td>
<td>937,000</td>
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<th>Costs of caring for Canadians with dementia</th>
<th>TODAY</th>
<th>2031</th>
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<td>$10.4 BILLION</td>
<td>$16.6 BILLION</td>
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- 50 million people currently live with dementia worldwide
- By 2050, 152 million people will be living with dementia
- The annual cost of dementia is over US$ 1 trillion – a figure set to double by 2030

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
Amyloid deposits in AD brain.
Brown: amyloid Aß, (senile plaques)
Black: Tau, (neurofibrillary tangles, NFT)

Alzheimer’s plaques and tangles
Why is it so hard to treat Alzheimer’s disease?

2,344 studies

~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

**THE BRAIN BENEFITS OF EXERCISE**

- Increases production of neurochemicals that promote brain cell repair
- Improves memory
- Lengthens attention span
- Boosts decision-making skills
- Prompts growth of new nerve cells and blood vessels
- Improves multi-tasking and planning
Physical exercise and brain health

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.

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

Staying physically active
Be active! Your physical fitness helps your brain fitness.
Irisin, an exercise-related hormone

Fibronectin type III domain containing 5

FNDC5

Irisin

Extracellular

Intracellular

Bruce Spiegelman - Harvard
An exercise-related hormone to fight dementia

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

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

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.

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.
Searching for a better way to transport irisin to the brain
Vesicles as an attractive approach

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 extracellular 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.

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

• **3)** Optimize physical exercise protocols in humans to improve cognition and increase brain irisin.
Thank you!

It Takes More Than an Apple a Day
The Global Impact of Dementia


Dementia
An “umbrella” term used to describe a range of symptoms associated with cognitive impairment.

- Alzheimer’s disease (60-70%)
- Vascular dementia (10-20%)
- Frontotemporal dementia (10%)
- Dementia with Lewy bodies (4%)
- Others (incl. prion diseases & Huntington’s) (<1%)

Alzheimer’s
50% - 75%

Vascular
20% - 30%

Lewy Body
10% - 25%

Frontotemporal
10% - 15%
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

Vehicle

Oligomers

De Felice et al., 2008
Neurobiol. Aging
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?

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.

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...
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