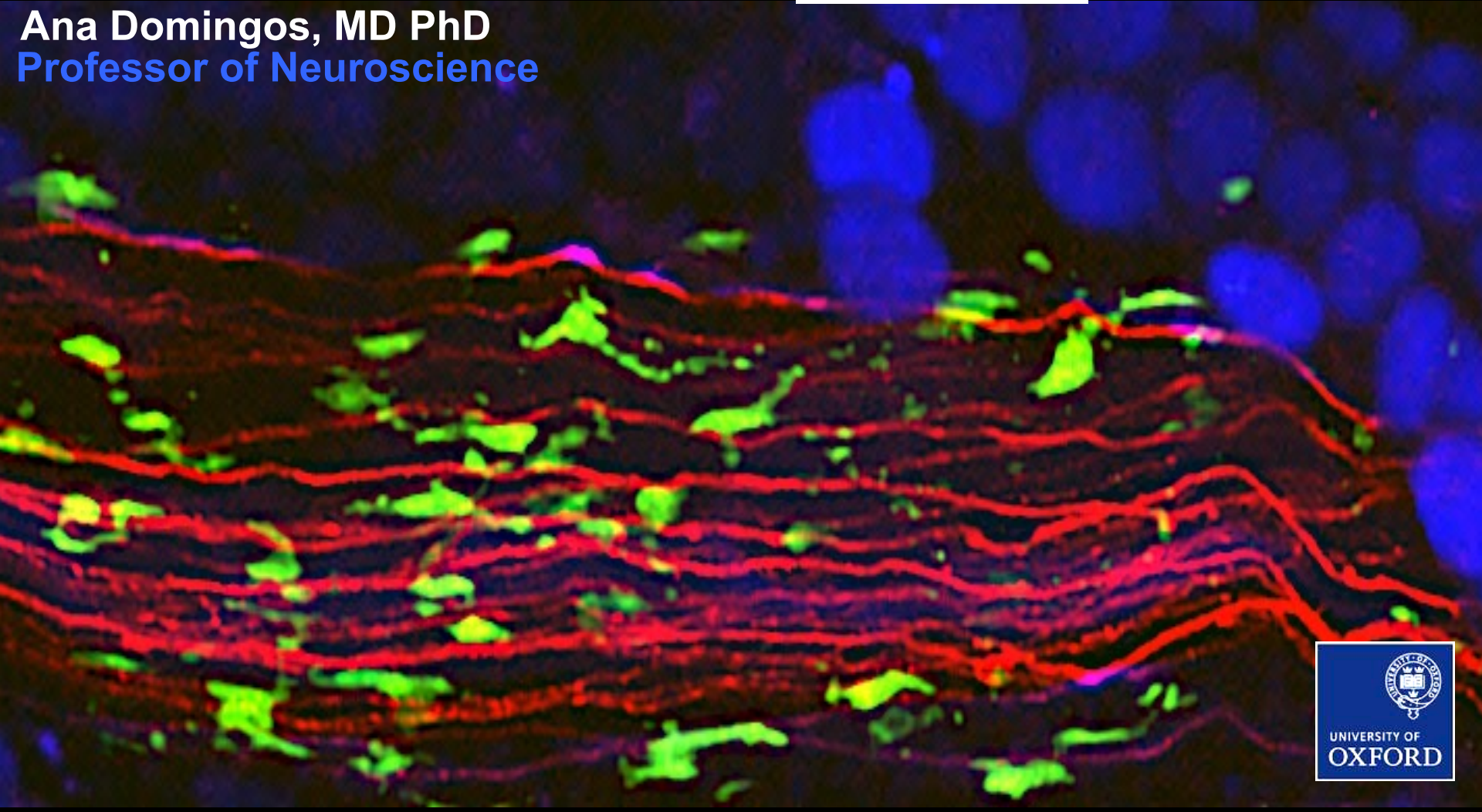


Sympathetic Neuroimmunity in Obesity

Understanding Brain-Body Interactions to Advance Brain Health
A Virtual Workshop

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Ana Domingos, MD PhD
Professor of Neuroscience



G2 Film & Music

Crazy in love
Superstar marriages
- can they last?



All the rage
On tour
with Idles

Reviews
Christina Aguilera ★★★
Hereditary ★★★★★



Friday
13 June 2018
Issue No. 51,426
theguardian.com
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The Guardian

Angry Tory
rebels
May's
ame

Heather
Anne F

There
short
rebu

TIME

THE WEIGHT LOSS TRAP



Low carb. Low fat.
Paleo. Vegan.
Flexitarian.
Why your diet isn't working
By Alexandra Sifferlin

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The Hidden Forces
Behind the Obesity Epidemic—
And How We Can End It

A BIG



CRISIS

Deborah A. Cohen, MD

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JUNE 2018 HEALTH AWARENESS.CO.UK

The Obesity Epidemic

Media
Power

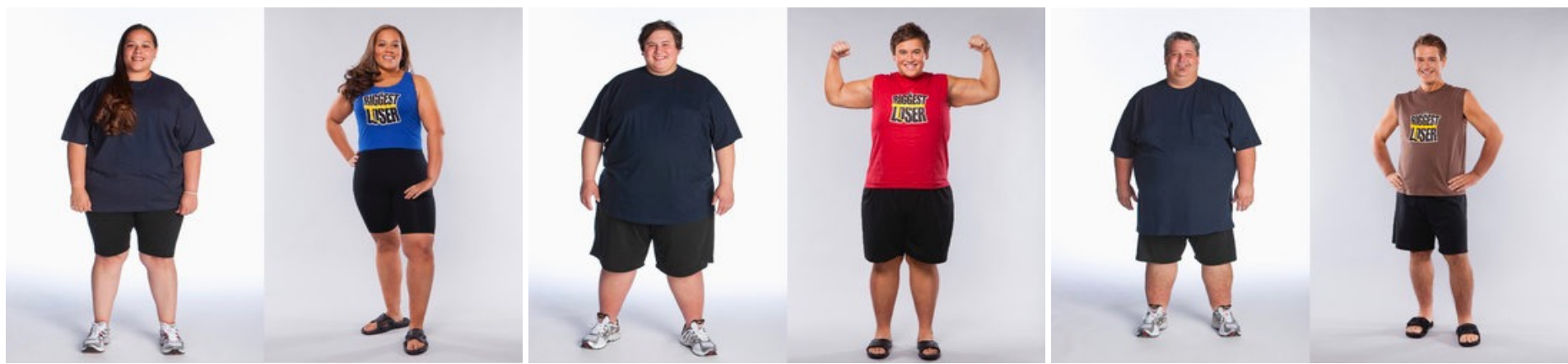


Nearly one in
four children are
overweight
says Caroline Cerny
from the Obesity Health
Alliance.
P2

14 & 15 November 2018
Olympia, London

Conference & Exhibition
FREE TO ATTEND

... professionals the real-world skills and relevant knowledge to help
care for, and empower, people affected by **obesity, diabetes**
and their related conditions.



The New York Times

THE SCIENCE OF FAT

After 'The Biggest Loser,' Their Bodies Fought to Regain Weight

Contestants lost hundreds of pounds during Season 8, but gained them back. A study of their struggles helps explain why so many people fail to keep off the weight they lose.

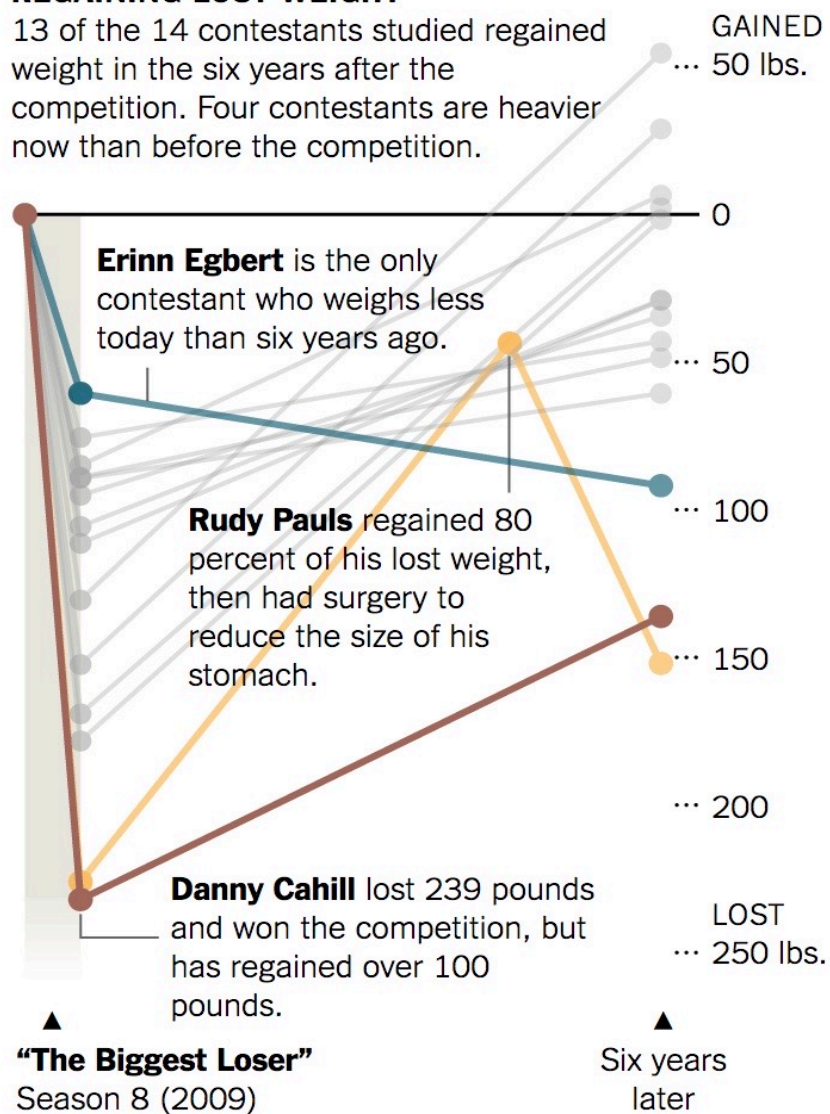


Biggest Losers Fight a Slower Metabolism

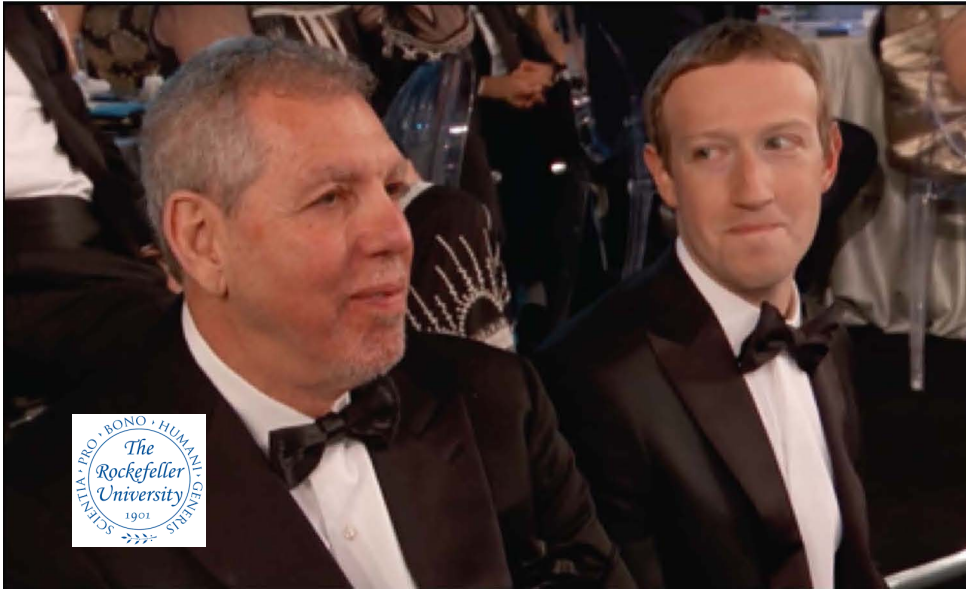
A study of contestants from “The Biggest Loser” found their metabolisms slowed during and after the competition, making it difficult to maintain weight loss.

REGAINING LOST WEIGHT

13 of the 14 contestants studied regained weight in the six years after the competition. Four contestants are heavier now than before the competition.



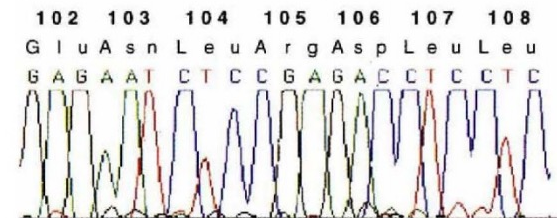
The identity of the signal encoded by the *ob* gene: LEPTIN, conserved in mice and humans



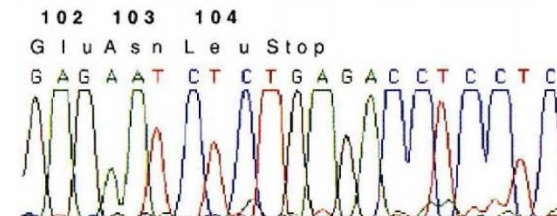
Jeffrey M. Friedman

-Lasker Award 2014

-Breakthrough Award 2020



C57BL/6J



C57BL/6J *ob/ob*

Zhang Y, et al, Friedman JM
Positional cloning of the mouse obese gene and its human homologue. Nature 1994

Recombinant leptin therapy reverses congenital leptin deficiency

3 yo , 40 Kg



6 yo , 29 Kg



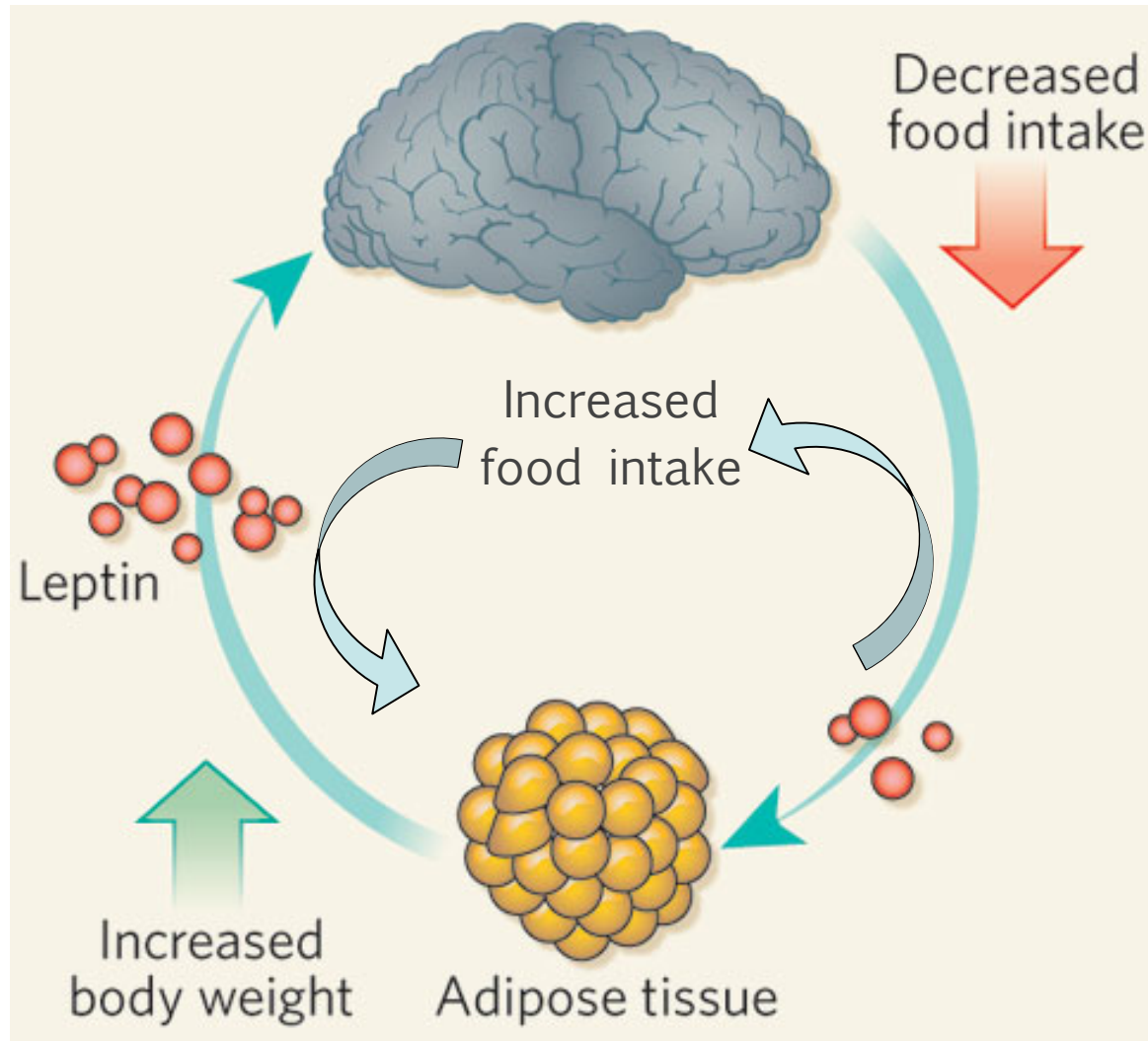
Montague CT, Farooqi IS, et al, O'Rahilly S. Congenital leptin deficiency is associated with severe early-onset obesity in humans. Nature. 1997

Farooqi et al O'Rahilly S. Effects of recombinant leptin therapy in a child with congenital leptin deficiency, NEJM .1999

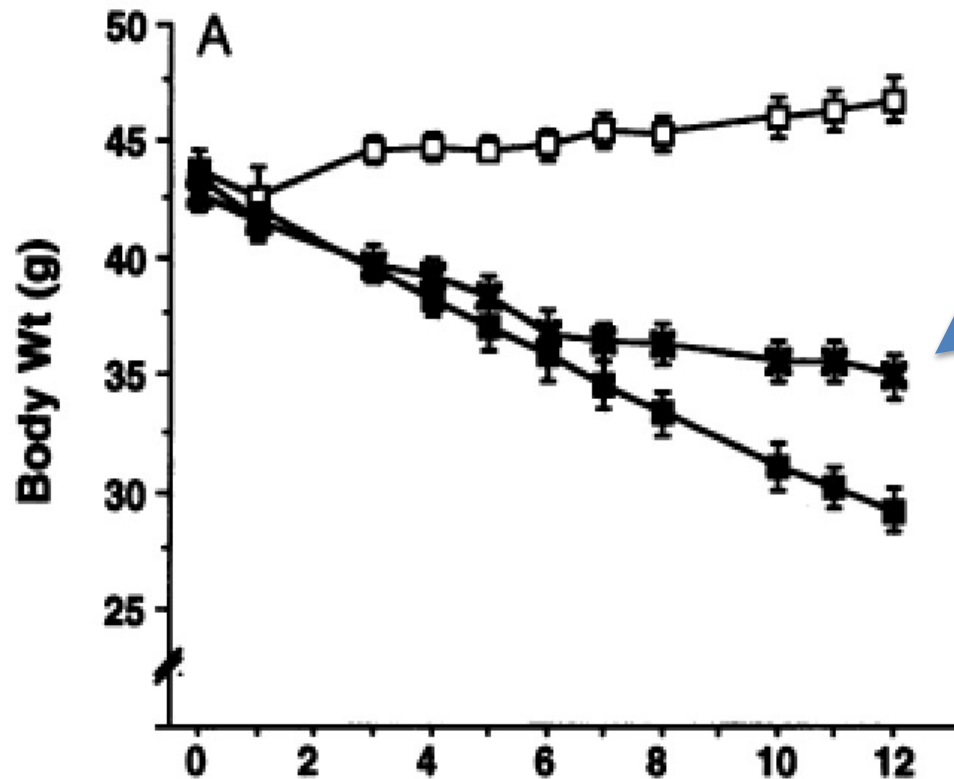
Body weight homeostasis

Leptin: an adipostat

The neuroendocrine loop of leptin action



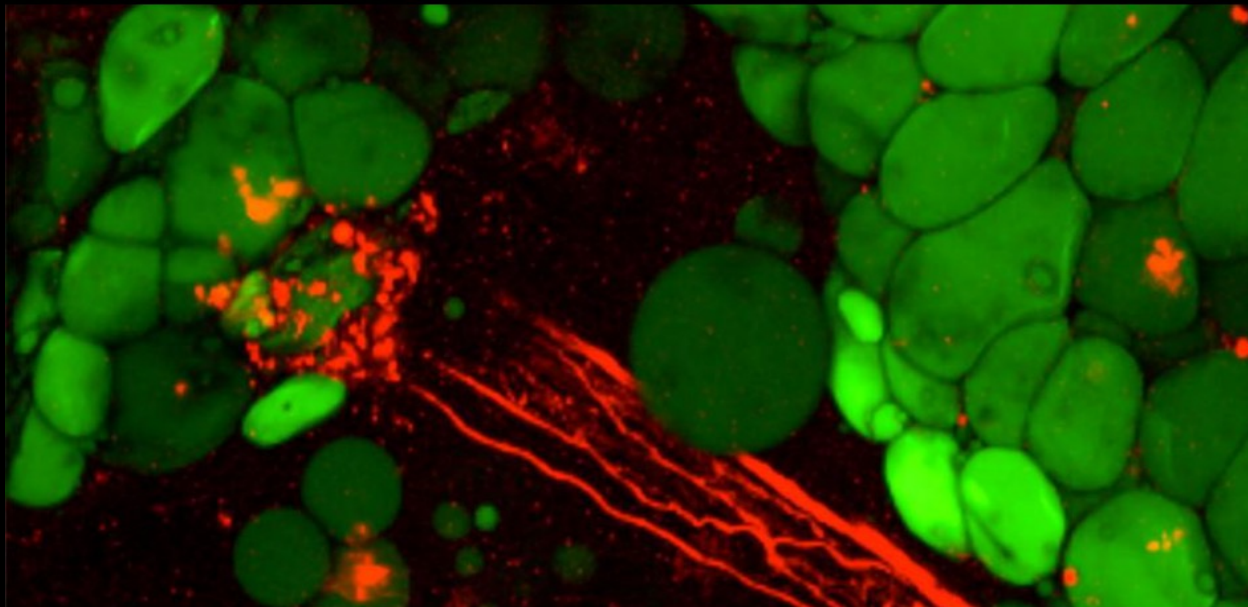
The weight loss effect of leptin action is not solely mediated by suppression of food intake



Ob/ob mice that are Pair-fed
To leptin-treated ob/ob mice
Do not lose weight to the same
extent



ob/ob



Bundles of nerves (red) that surround some fat cells (green) are key to fat breakdown—and weight loss.

Ana Domingos, Instituto Gulbenkian de Ciência

A closer look at the nerves that slim down your fat cells

Sympathetic Neuron-Adipose Connections Mediate Leptin-Driven Lipolysis

Zeng, et al,
Domingos
Cell, 2015

nature
REVIEWS **NEUROSCIENCE**

© Tony Lilley/Alamy Stock Photo



AUTONOMIC NERVOUS SYSTEM

Zapping fat in WAT

A Sympathetic View on Fat by Leptin

Cell

Luis Varela¹ and Tamas L. Horvath^{1,*}

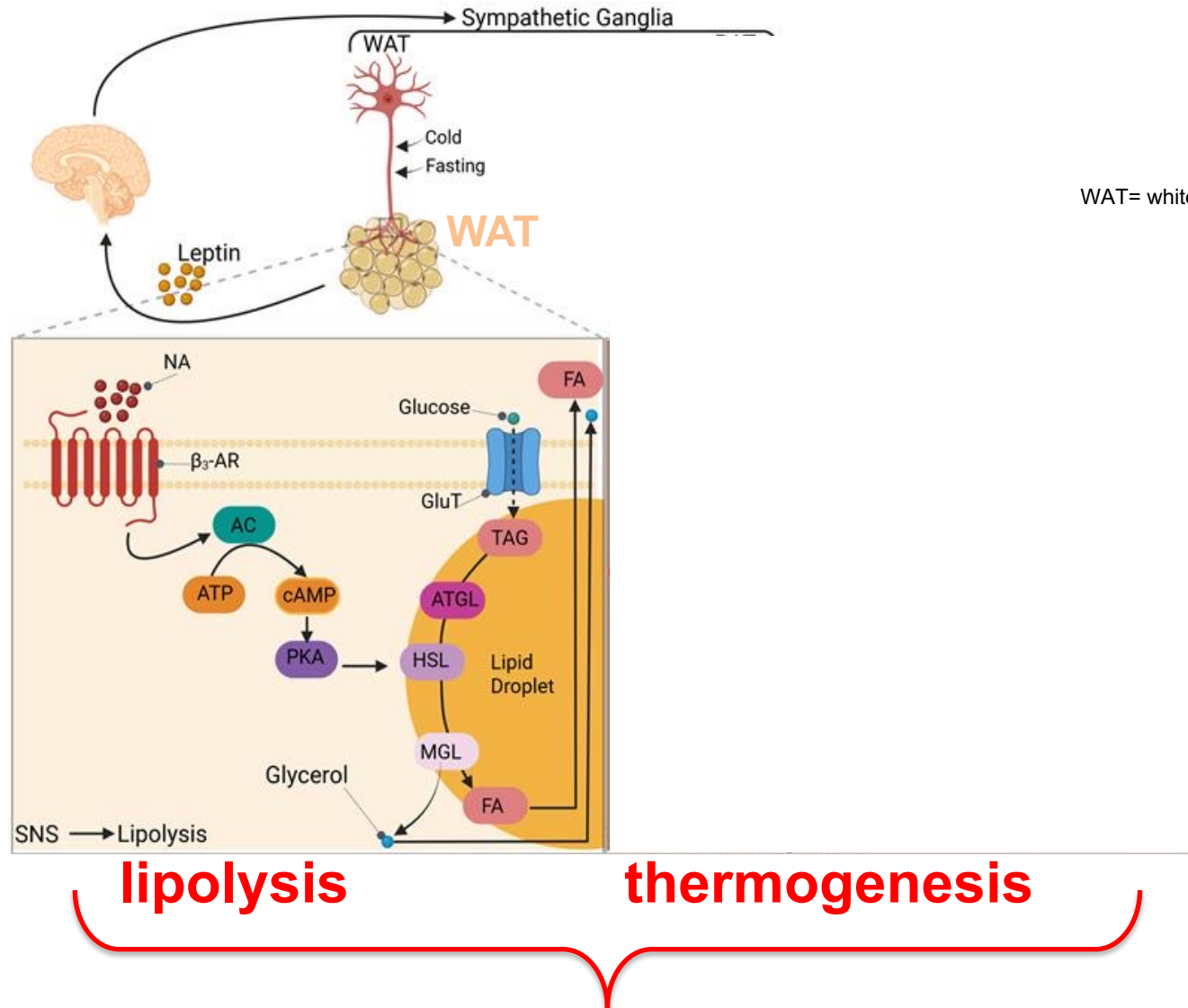
¹Program in Integrative Cell Signalling and Neurobiology of Metabolism, Section of Comparative Medicine, Yale University School of Medicine, New Haven, CT 06520, USA

*Correspondence: tamas.horvath@yale.edu

<http://dx.doi.org/10.1016/j.cell.2015.09.016>

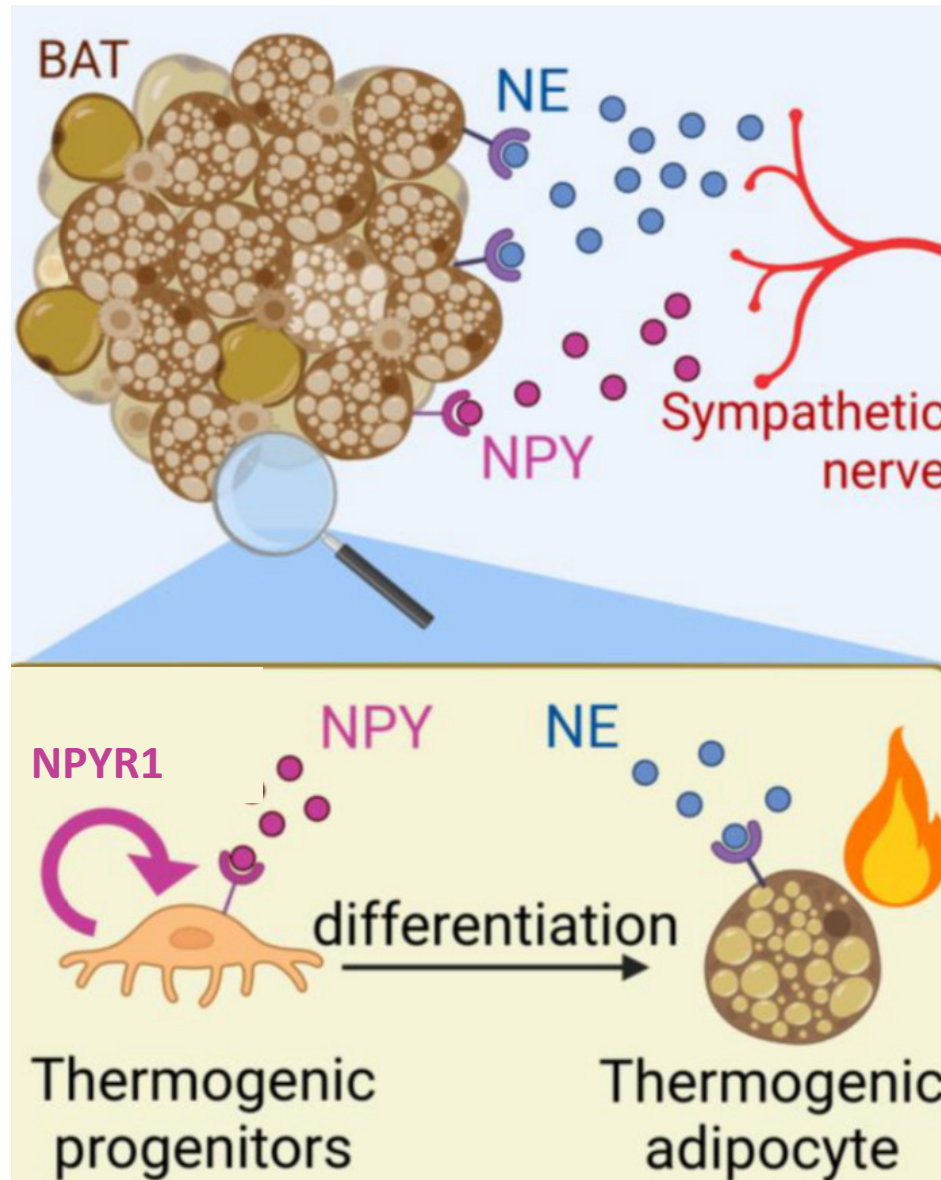
The Neuroendocrine Loop of Leptin action

Beyond appetite regulation

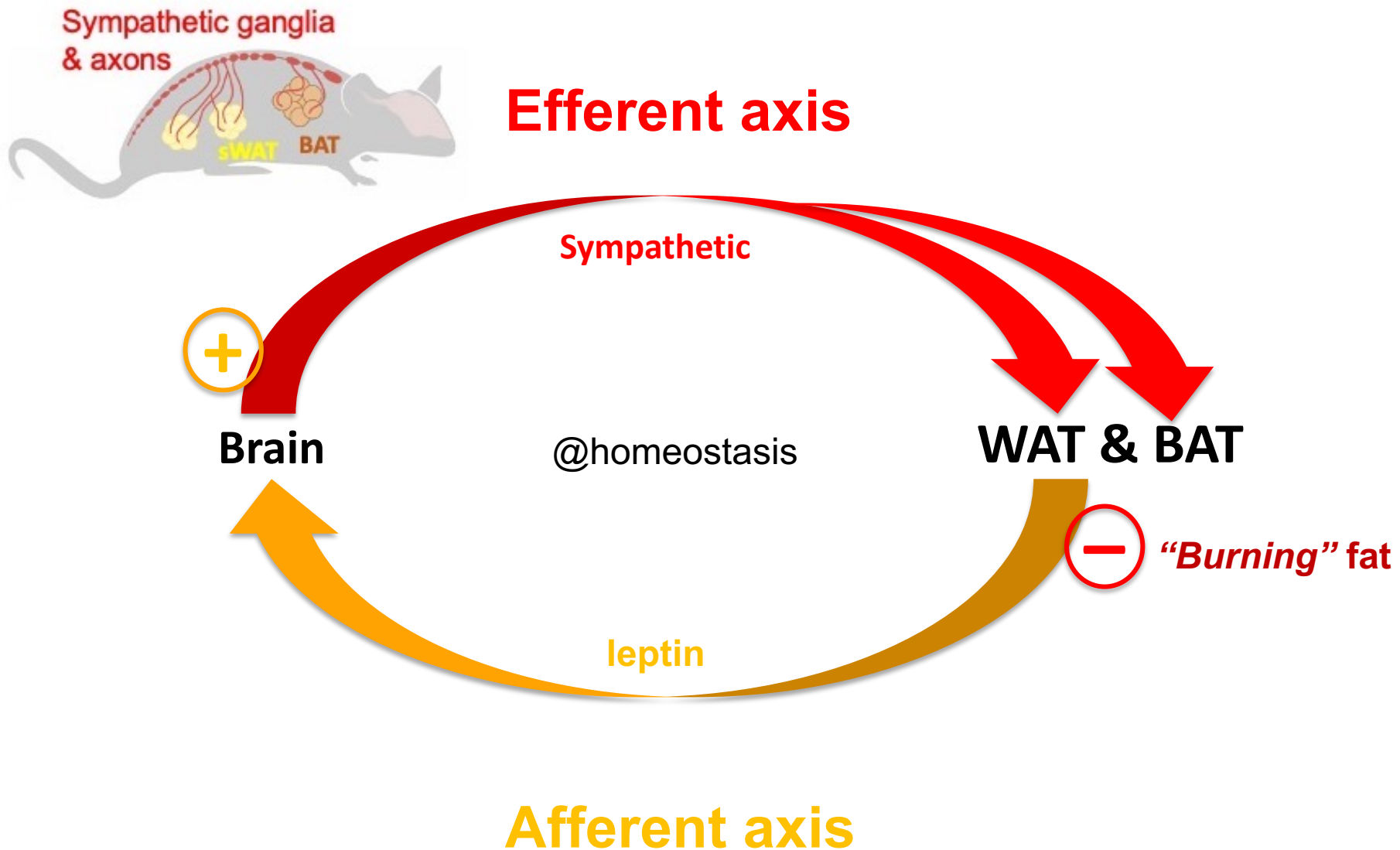


Legend:
WAT= white adipose tissue (AT)
BAT=Brown AT

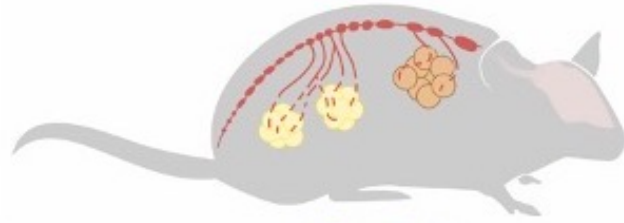
Sympathetic Neuropeptide Y protects from obesity by sustaining thermogenic adipocytes.



The Neuroendocrine Loop of Leptin

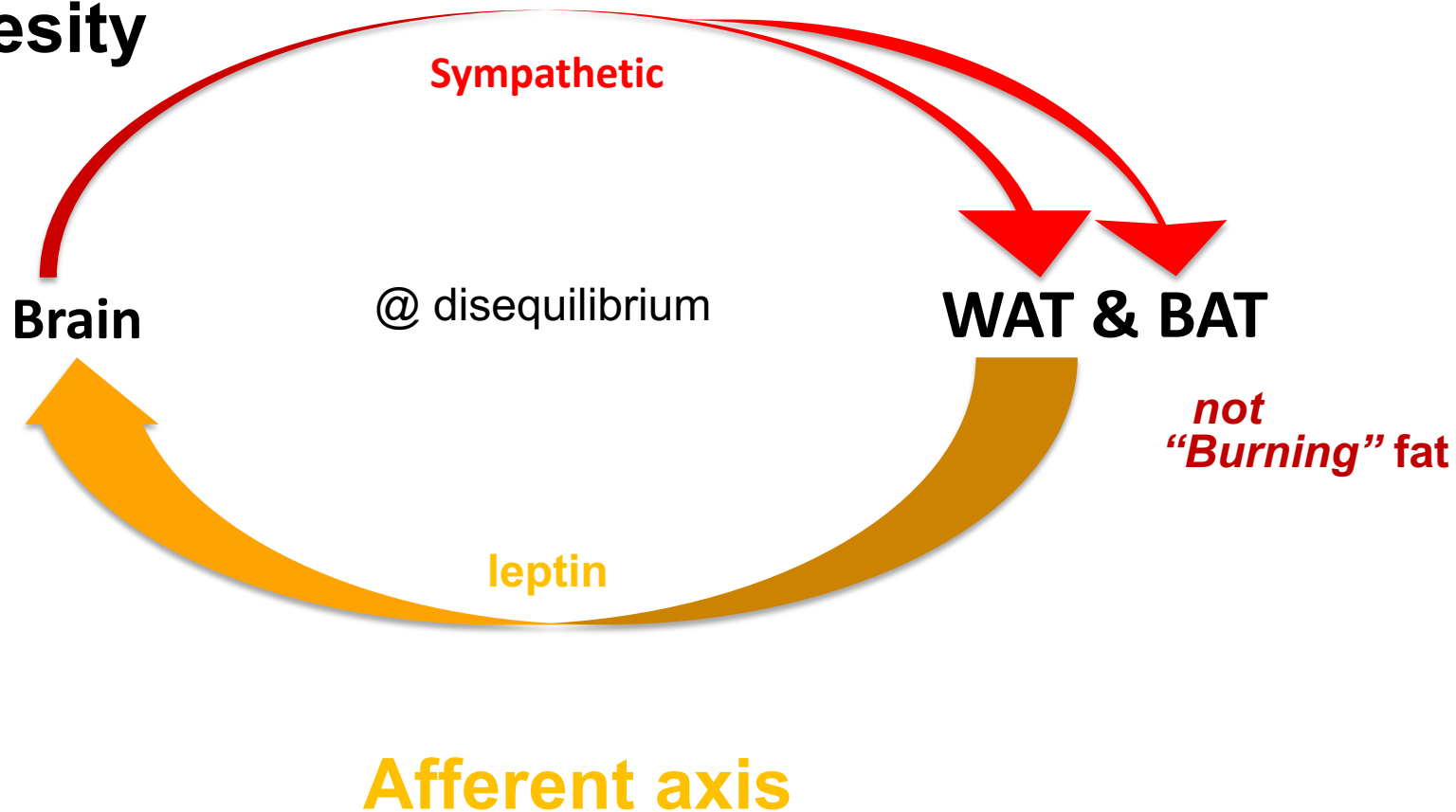


The Neuroendocrine Loop of Leptin

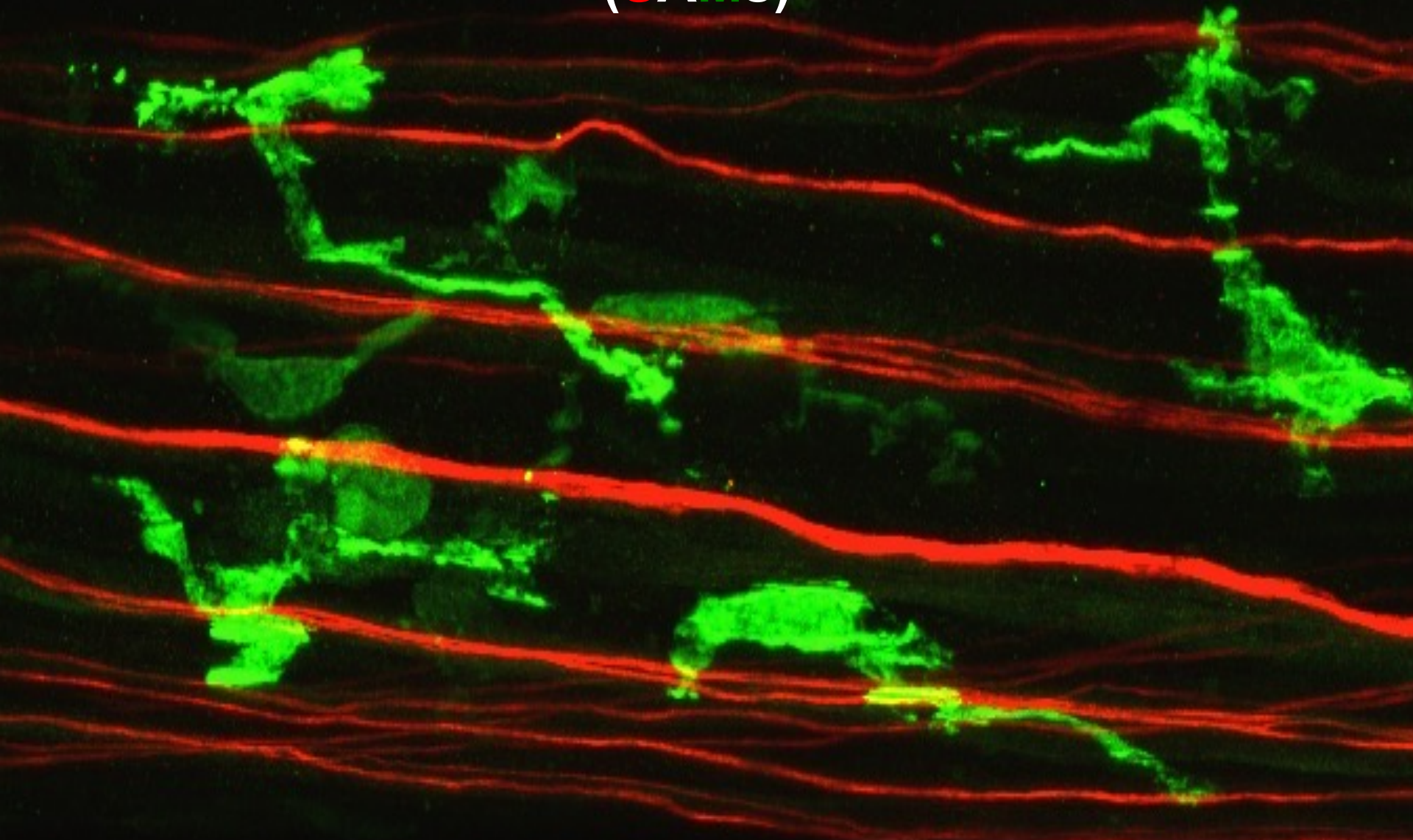


Obesity

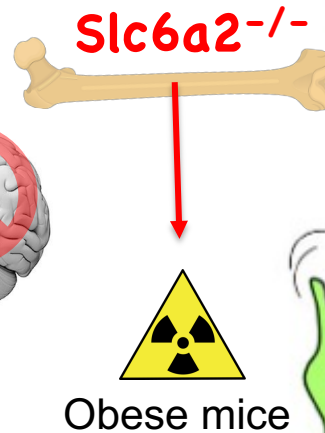
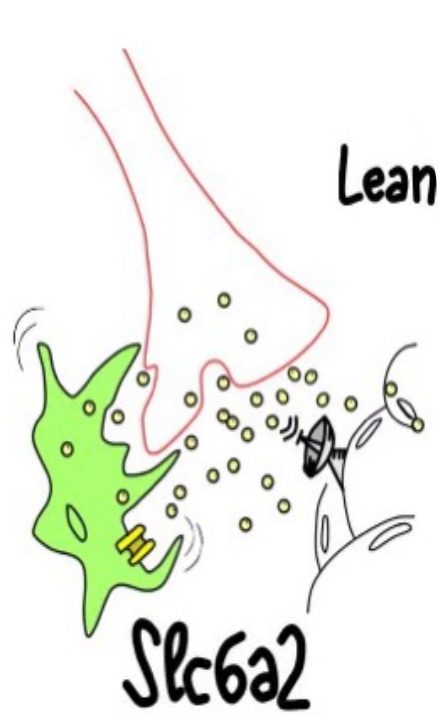
Efferent axis



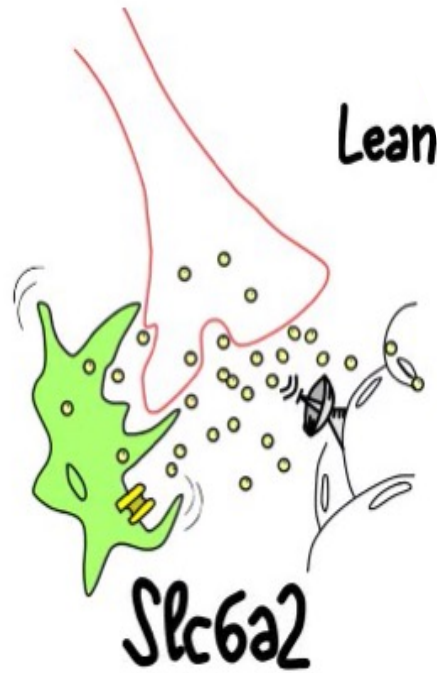
Sympathetic associated macrophages (SAMs)



SAMs
contribute to
Obesity
By importing
And
metabolizing
norepinephrine



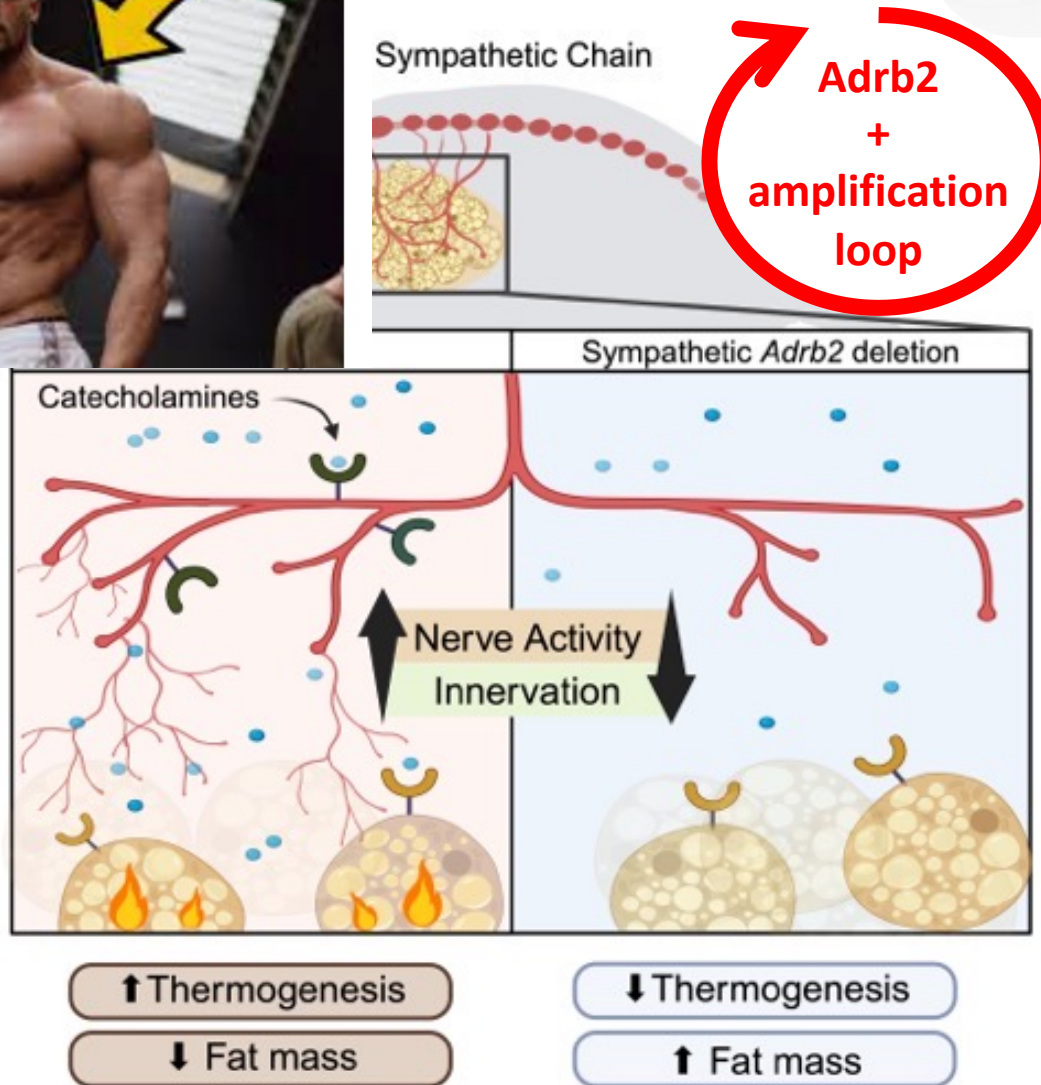
If **SAMs**
Mop up
Norepinephrine
On top of
the neurons
Then...



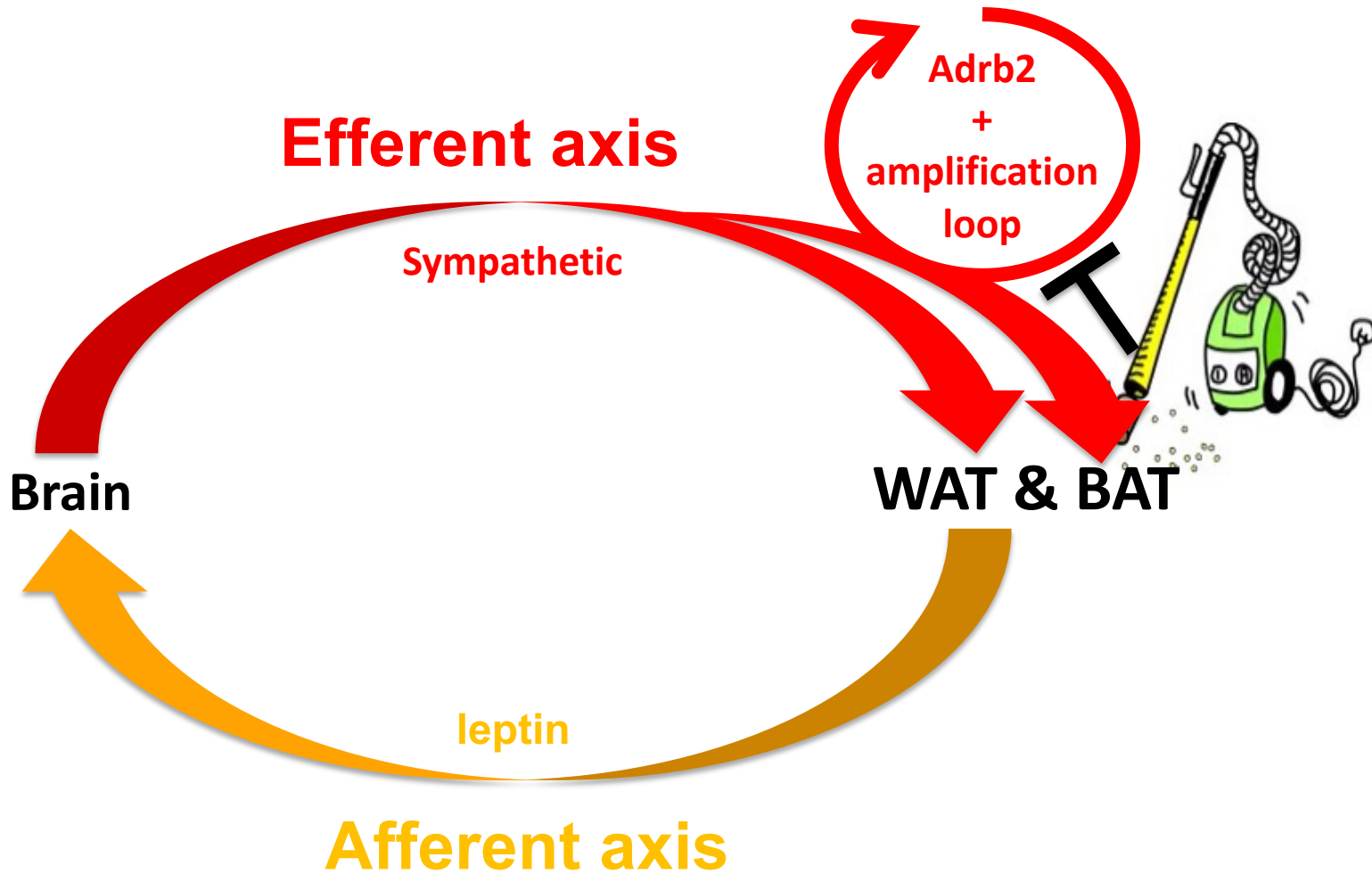
Does
norepinephrine
influence the
neurons?



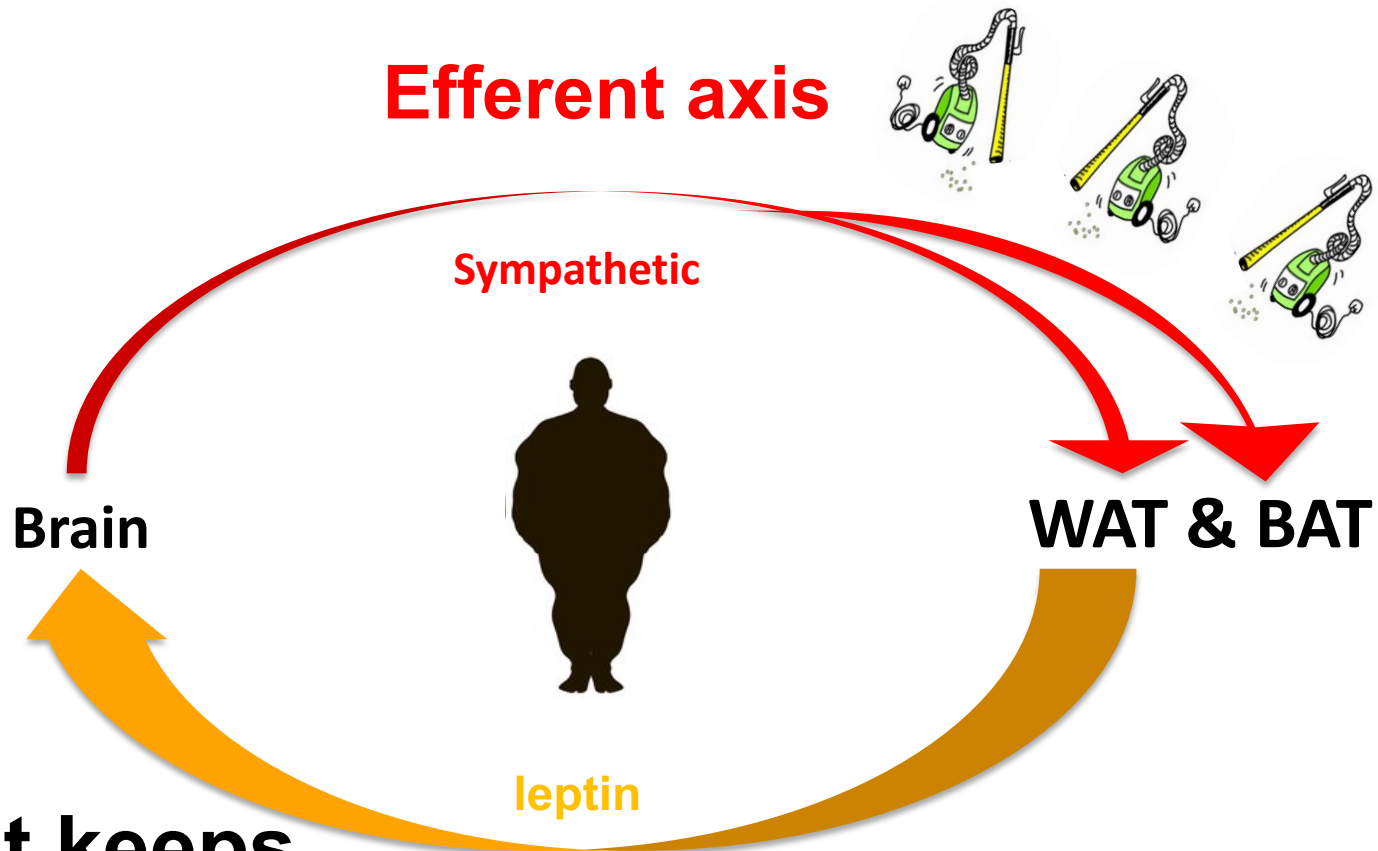
Adrb2 agonists *burn fat* via sympathetic neurons



SAMs keep the noradrenergic autocrine positive feedback under control



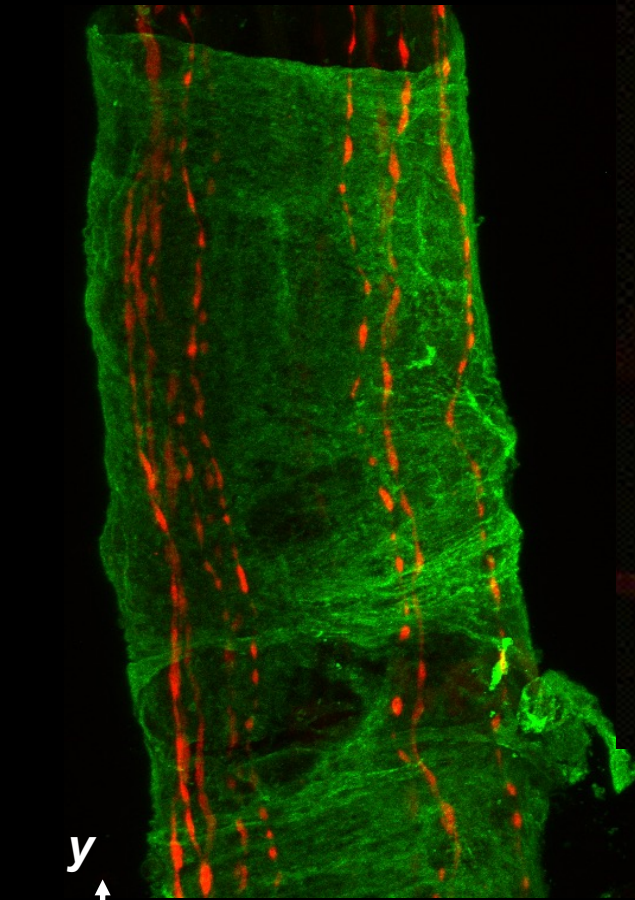
Macrophages dispose of **norepinephrine**, weakening the **efferent** arm in the neuroendocrine loop of **leptin**



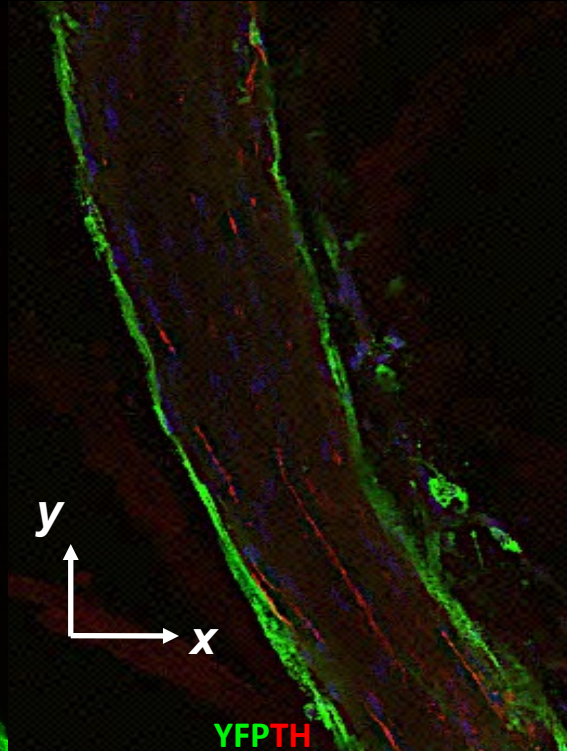
What keeps
SAMs away?

Afferent axis

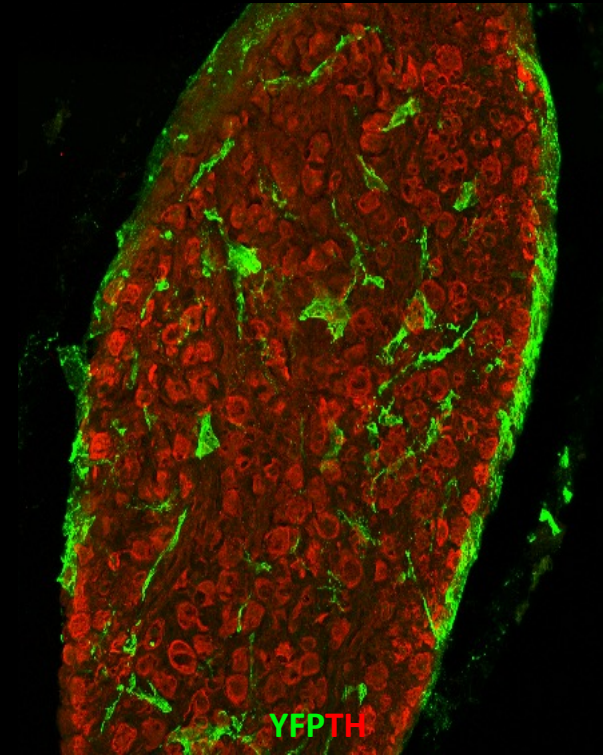
Sympathetic perineurial barrier cells (SPCs)



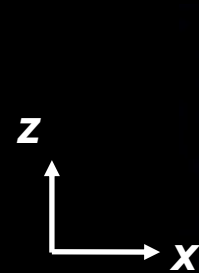
TH



YFP TH

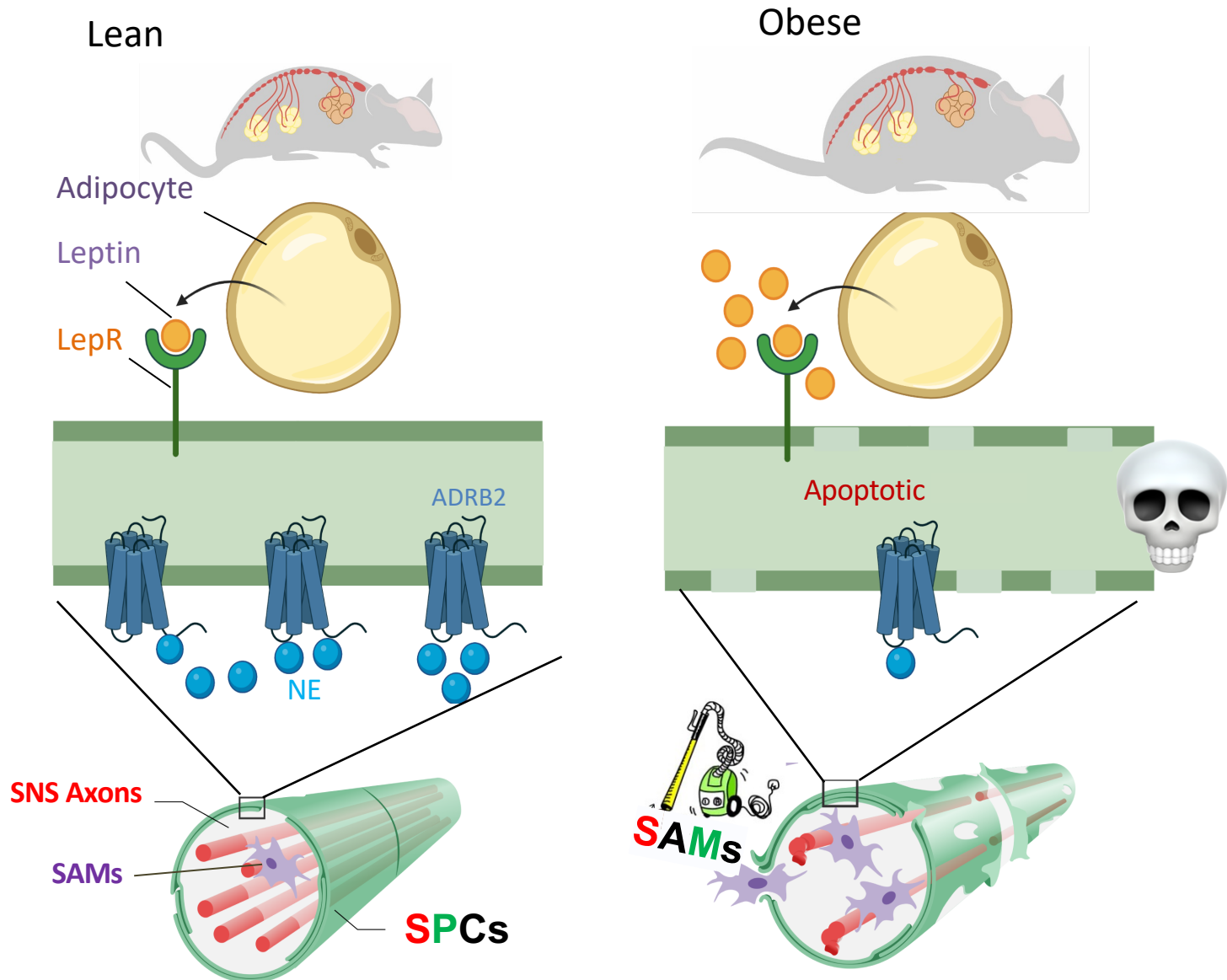


YFP TH



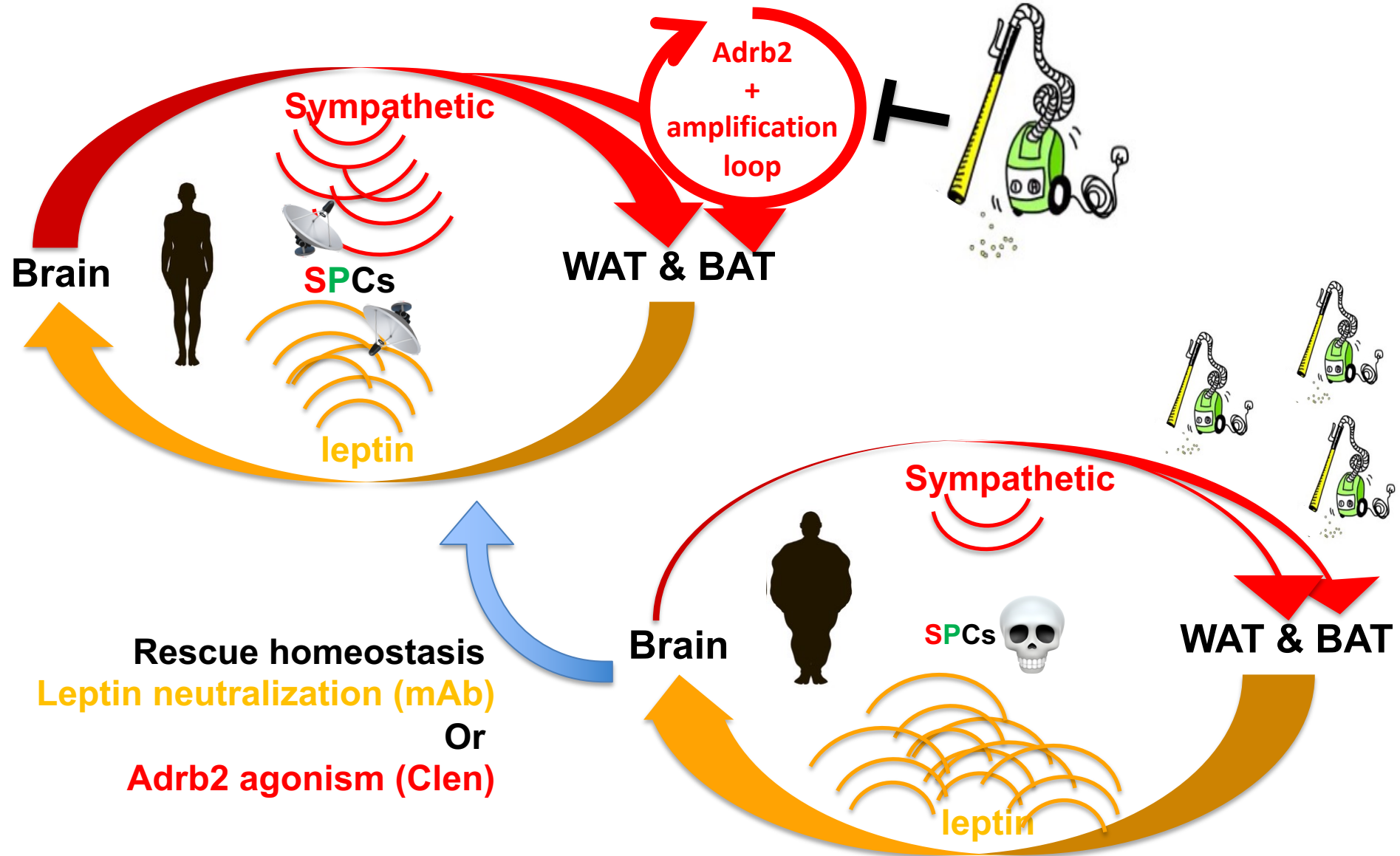
YFP TH DAPI

SPCs integrate leptin with its sympathetic outflow to protect against obesity



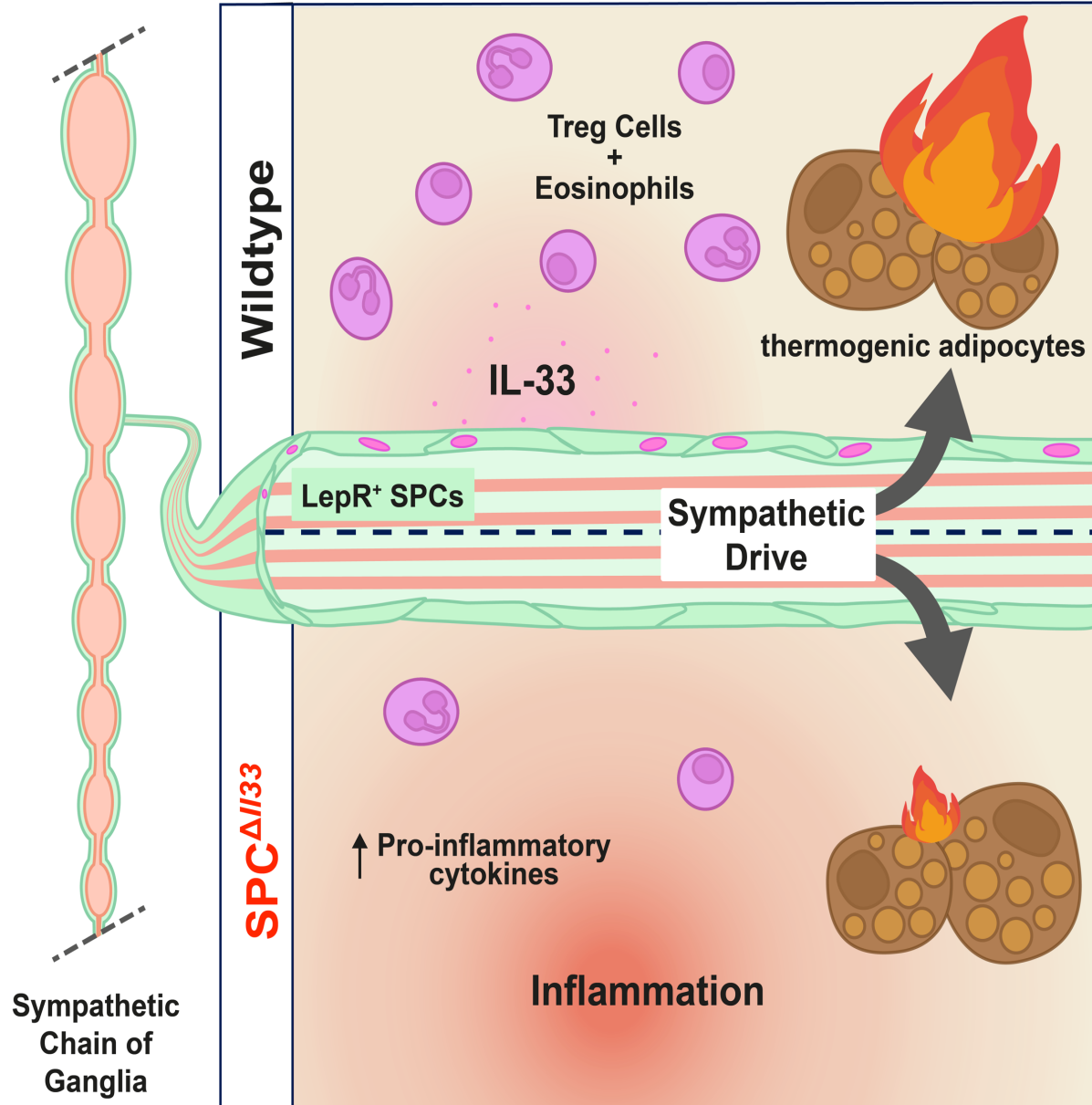
Under review

SPCs integrate leptin with its sympathetic outflow to protect against obesity

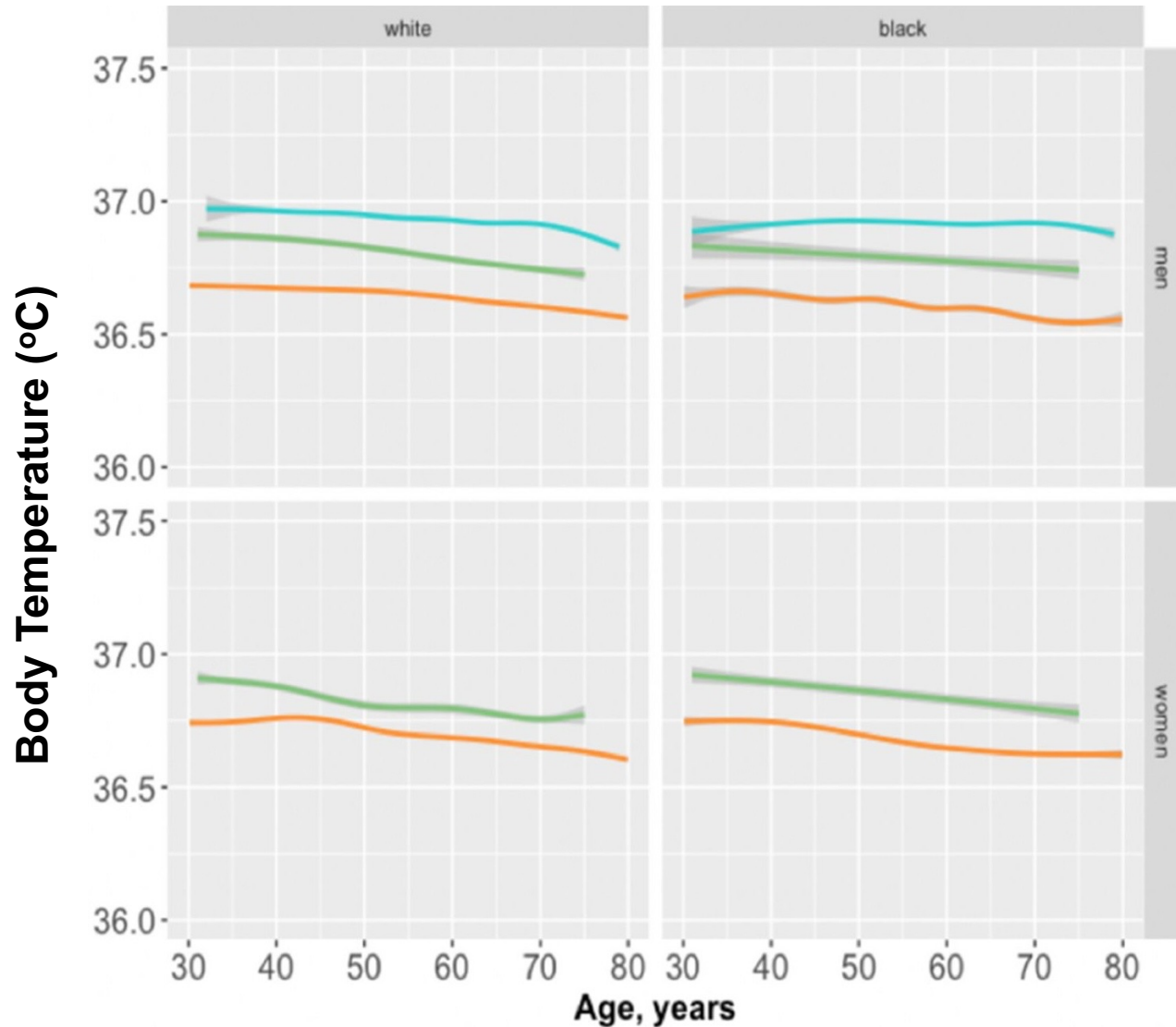


Brown Adipose Tissue

Immunomodulatory
LepR⁺ perineurial cells
protect against obesity
by facilitating
Leptin-mediated
thermogenesis



Decreasing human body temperature in the United States since the Industrial Revolution



Time period of the measurement 1860-1940 1971-1975 2007-2017



Howard Hughes
Medical Institute



National Institute of
Diabetes and Digestive
and Kidney Diseases



Sofia Lundh, NN



Wing Cheung



Kamal Rahmouni
Iowa Univ



Dan Li



David
Oliveira



Licio Velloso
UniCamp



Rocksana
Pirsgalska
Champ



Enrique
Maldonado, NN



Cyrielle
Maroteau, NN



Florent
Ginhoux, A*



Karin Ziegler,
TUM



Gitalee
Sarker



Shingo
Kajimura, HMS



Yitao Zhu



Miguel
Vasques
Champ