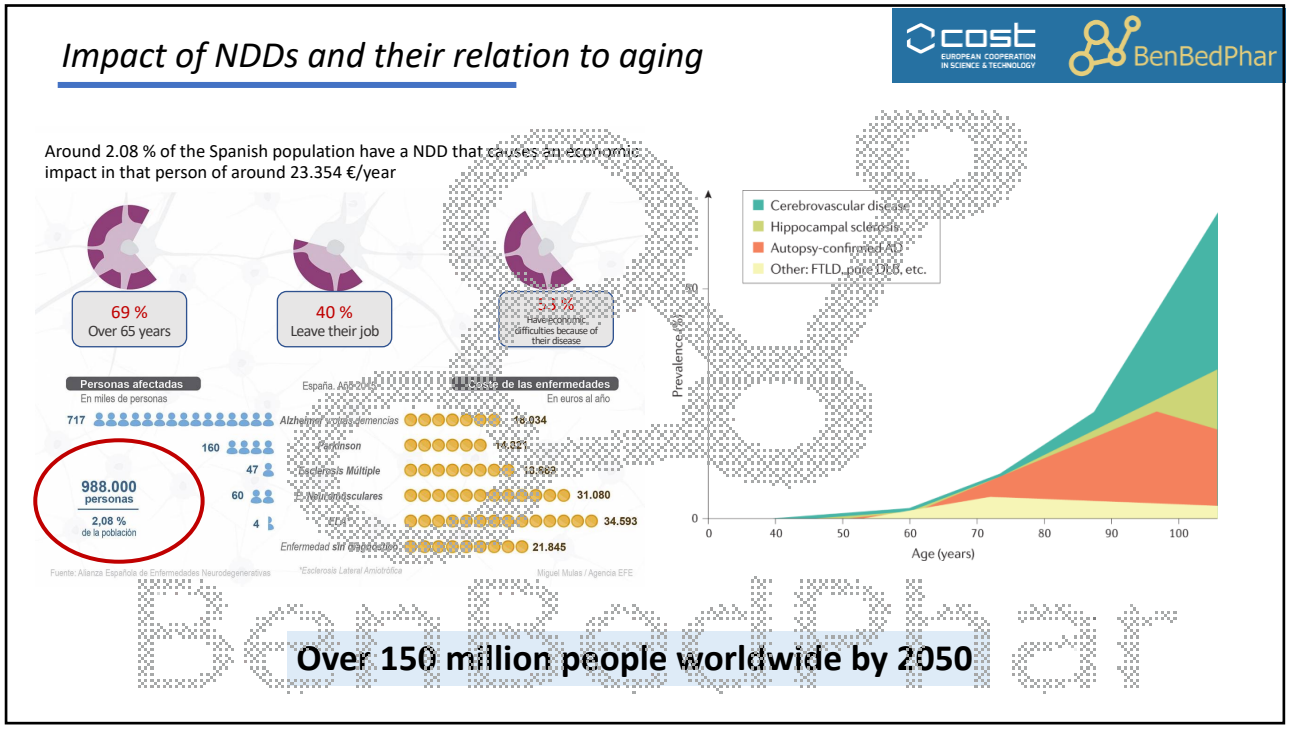

BenBedPhar Training School 2023
NRF2 in noncommunicable diseases:
From bench to bedside
June 26 - 30, 2023
Smolenice Castle, Slovakia
BenBedPhar
cost
EUROPEAN COOPERATION IN SCIENCE & TECHNOLOGY
NRF2 in neurodegenerative diseases
Prof. Manuela G. Lopez
Universidad Autonoma de Madrid
Spain

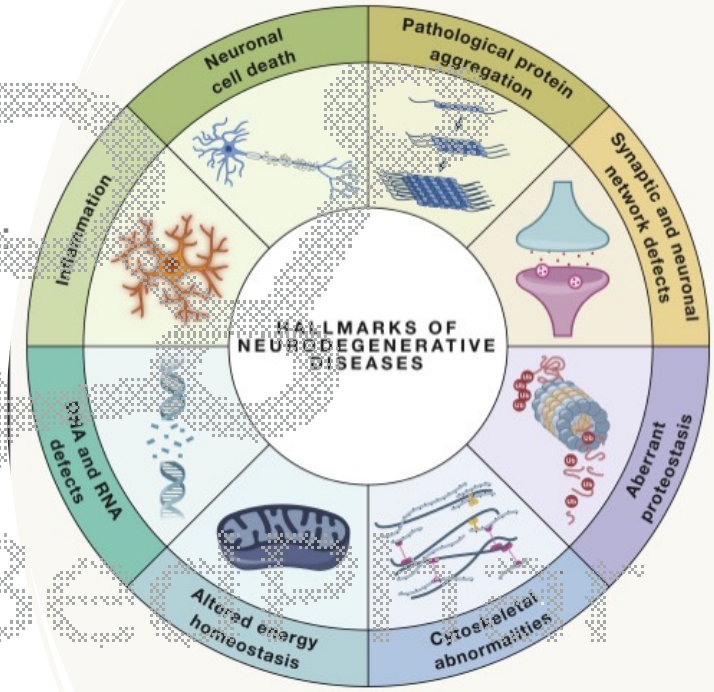
1


Impact of NDDs and their relation to aging
cost
EUROPEAN COOPERATION IN SCIENCE & TECHNOLOGY
BenBedPhar
Around 2.08 % of the Spanish population have a NDD that causes an economic impact in that person of around 23.354 €/year
69 %
Over 65 years
40 %
Leave their job
53 %
Have economic difficulties because of their disease
Personas afectadas
En miles de personas
Coste de las enfermedades
En euros al año
España. Año 2015
717
Alzheimer y otras demencias
16.034
160
Parkinson
11.021
47
Esclerosis Múltiple
10.982
60
E. Neurovasculares
31.080
4
ELA
34.593
Enfermedad sin diagnóstico
21.845
988.000
personas
2,08 %
de la población
Fuente: Alianza Española de Enfermedades Neurodegenerativas
*Esclerosis Lateral Amiotrófica
Miguel Muñoz / Agencia EFE
Cerebrovascular disease
Hippocampal sclerosis
Autopsy-confirmed AD
Other: FTLD, prion, DLB, etc.
Prevalence (%)
0
40
50
60
70
80
90
100
Age (years)
Over 150 million people worldwide by 2050

2

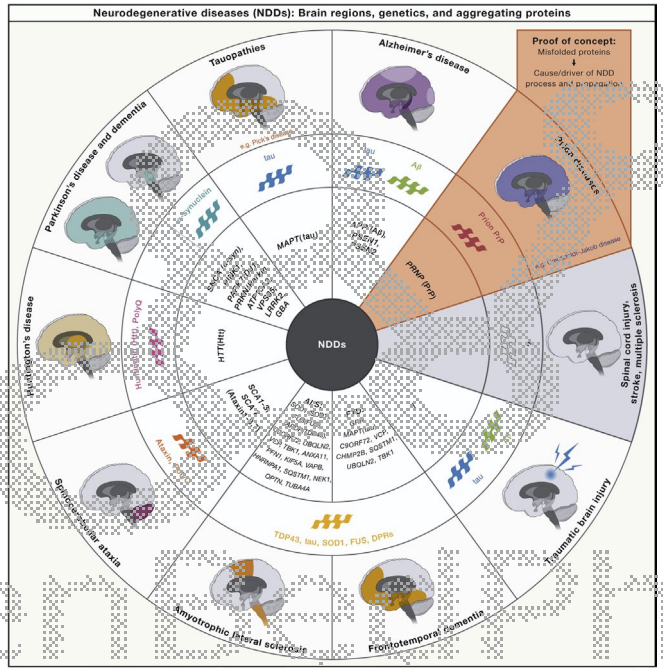
Hall marks of
Neurodegenerative diseases:

Common pathological mechanisms



Wilson et al., ***Cell*** 186, 2023 (https://doi.org/10.1016/j.cell.2022.12.032)

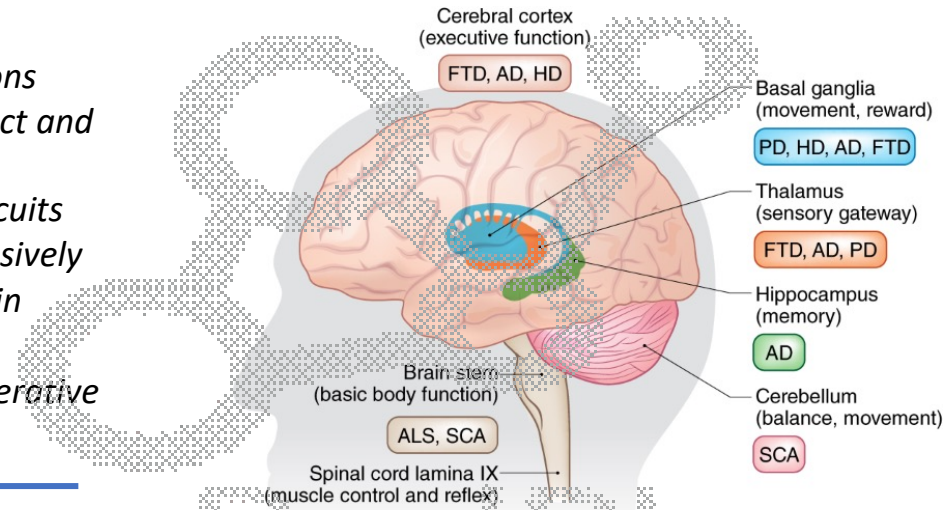
3



Wilson et al., ***Cell*** 186, 2023 (https://doi.org/10.1016/j.cell.2022.12.032)

4

Clinical manifestations reflect distinct and overlapping neuronal circuits that progressively degenerate in various neurodegenerative diseases

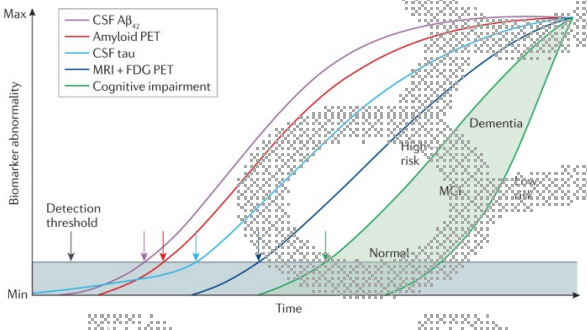


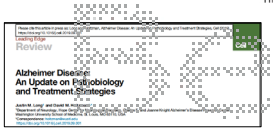
Wilson et al., ***Cell*** 186, 2023 (https://doi.org/10.1016/j.cell.2022.12.032)

5

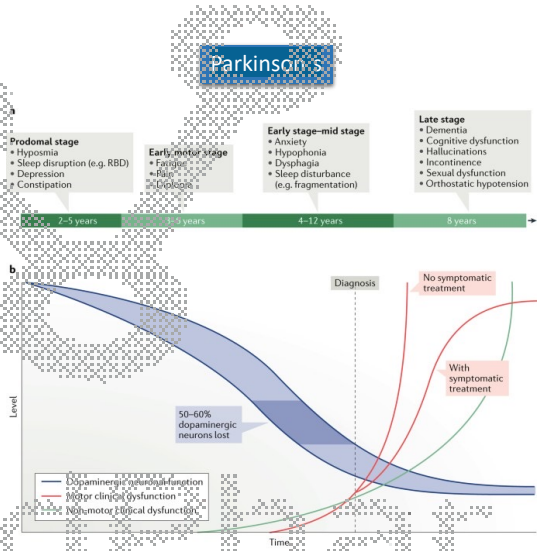
The disease starts many years before it manifest clinically

Alzheimer´s





Parkinson´s



Anthony H.V. Schapira et al., *Nature Reviews Neuroscience* volume 18, pages435–450 (2017)

6

think TOGETHER

Let´s think together on how we could find innovative tratments for AD

BenBedPhar

7

Things we need to know?

cost EUROPEAN COOPERATION IN SCIENCE & TECHNOLOGY BenBedPhar

- Which are the current treatments
  - MoA
  - **Efficacy**
  - **Security**
- Is there a need for new treatments
- What do we know about the physiopathology of AD?
- Which is the pipeline and which would be are targets?
- When would we treat the patients?
- Are there therasnostic biomarkers?

think TOGETHER

BenBedPhar

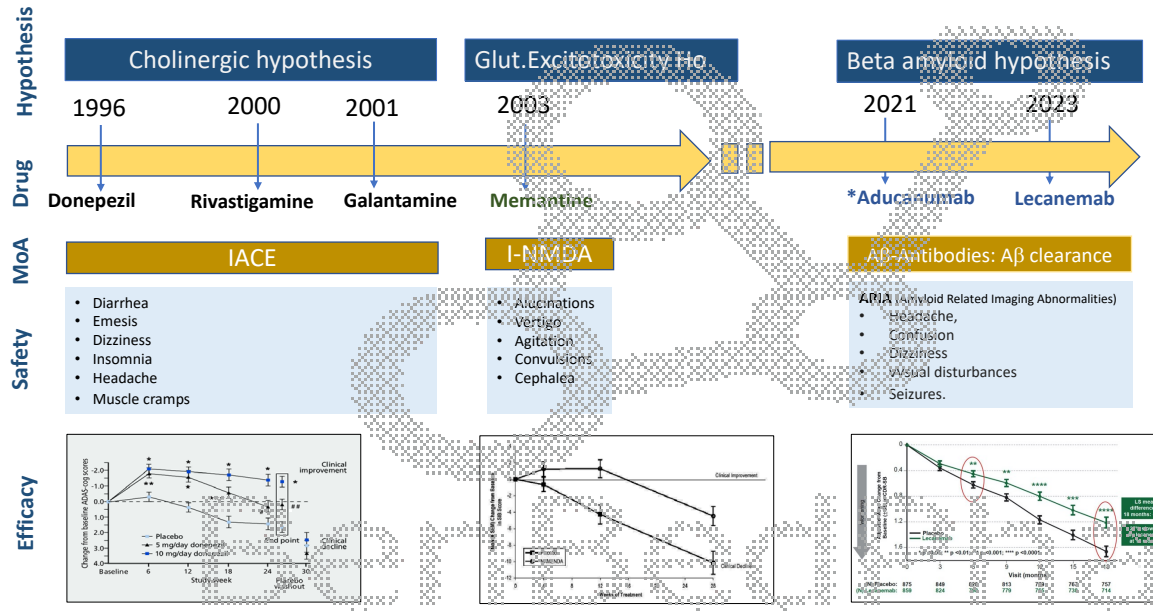
8

Things we need to know?

- **Which are the current treatments**
  - **MoA**
  - **Efficay**
  - **Security**
- Is there a need for new treatments
- What do we know about the physiopathology of AD?
- Which would be are targets?
- When would we treat the patients?
- Are there therasnostic biomarkers?

9

Available drugs for AD: MoA, safety and efficacy



10

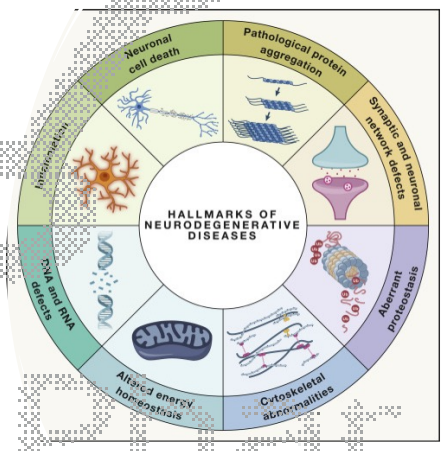
Things we need to know?

- Which are the current treatments
  - MoA
  - Efficay
  - Security
- **Is there a need for new treatments**
- What do we know about the physiopathology of AD?
- Which is the pipeline and which would be are targets?
- When would we treat the patients?
- Are there therasnostic biomarkers?

11

Things we need to know?

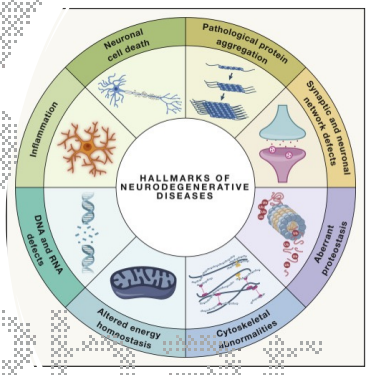
- Which are the current treatments
  - MoA
  - Efficay
  - Security
- Is there a need for new treatments
- **What do we know about the physiopathology of AD?**
- Which is the pipeline and which would be are targets?
- When would we treat the patients?
- Are there therasnostic biomarkers?



12

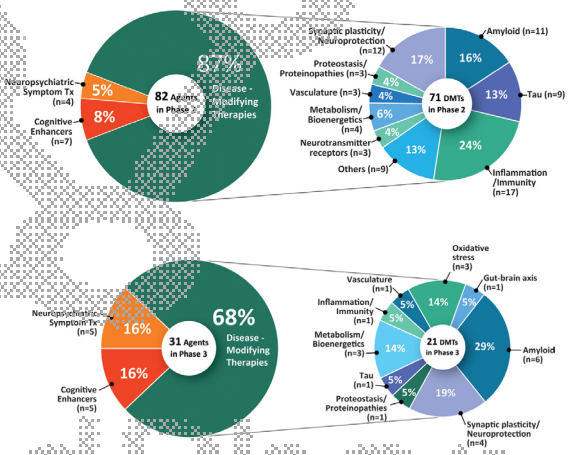
Things we need to know?

- Which are the current treatments
  - MoA
  - Efficay
  - Security
- Is there a need for new treatments
- What do we know about the physiopathology of AD?
- **Which is the pipeline and which would be are targets?**
- When would we treat the patients?
- Are there therasnostic biomarkers?



13

Which is the AD development pipeline

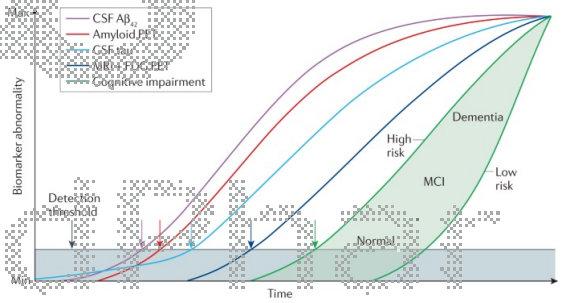


Cummings et al., *Alzheimer's Dement*. 2022; 8:e12295

14

Things we need to know?

- Which are the current treatments
  - MoA
  - Efficay
  - Security
- Is there a need for new treatments
- What do we know about the physiopathology of AD?
- Which would be are targets?
- **When would we treat the patients?**
- **Are there therasnostic biomarkers?**

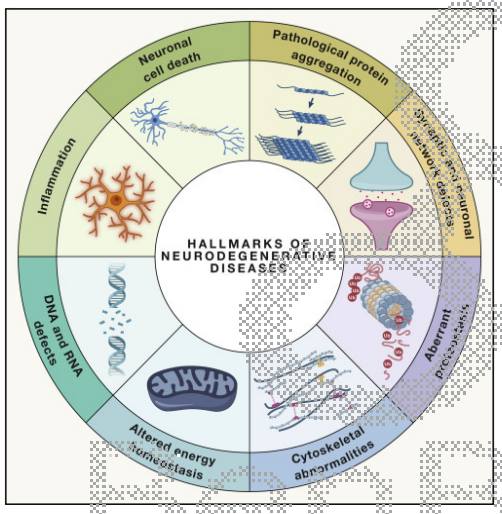


15

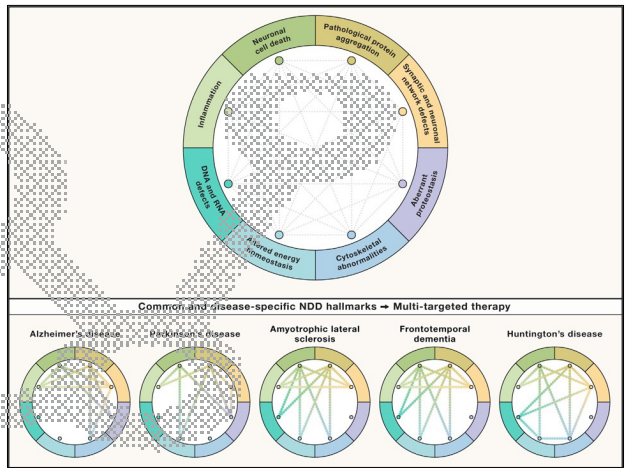
The Multitarget drug strategy for AD: Can NRF2 be a candidate?

16

Rationale for the Multitarget Strategy (MTDs)



Better opportunities to validate in the future efficacy in other NDDs



Compared to combination of drugs:
- Same ADME
- Same PK
- Potential less side effects
- Better compliance for the patient

17

Steps we need to address:

- Selection of the Target: rationelle to target Nrf2
- Selection of the Disease Model
- Proof of Concept

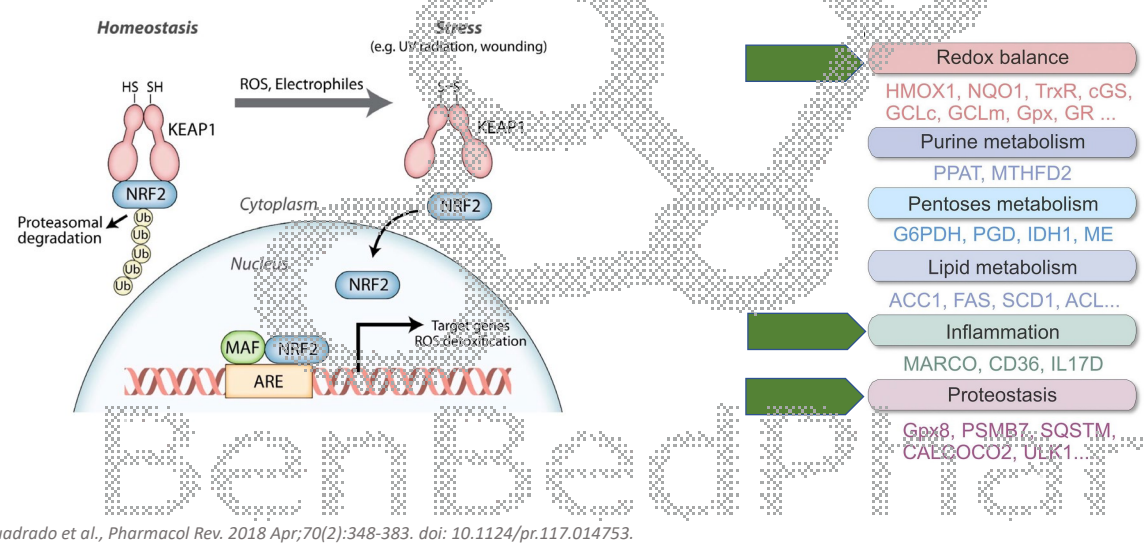
18

SELECTION OF THE TARGET: Nrf2

We should have evidence that lead us to think that acting on that target, which is implicated in the pathology of the disease, would be beneficial for our disease (AD)

19

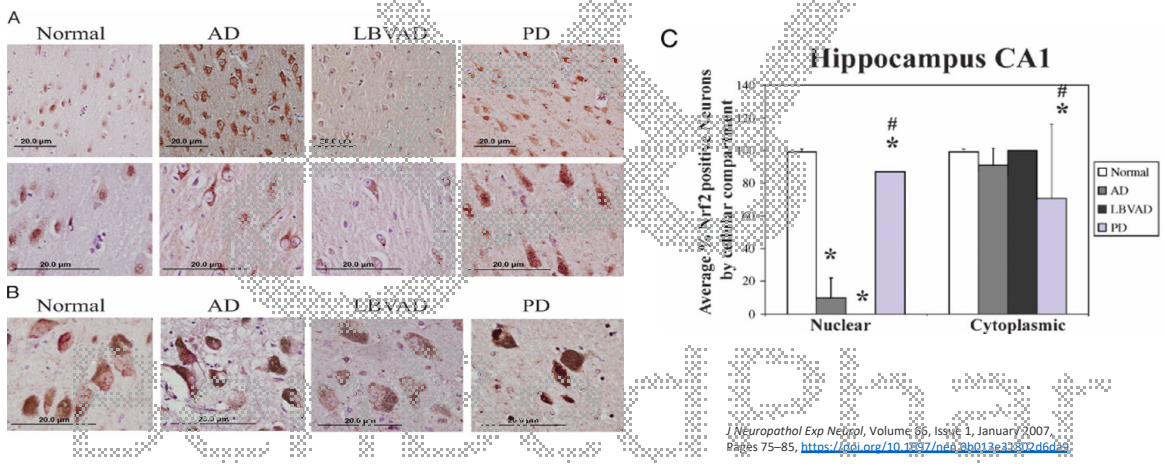
Nrf2 regulates different pathways implicated in AD



Cuadrado et al., Pharmacol Rev. 2018 Apr;70(2):348-383. doi: 10.1124/pr.117.014753.

20

Nrf2 expression patterns are altered in hippocampal neurons of Alzheimer disease and Lewy body variant of Alzheimer disease and neurons of the substantia nigra in Parkinson disease



J Neuropathol Exp Neurol, Volume 66, Issue 1, January 2007, Pages 75–85, https://doi.org/10.1097/nen.0b013e31802d6da9

21

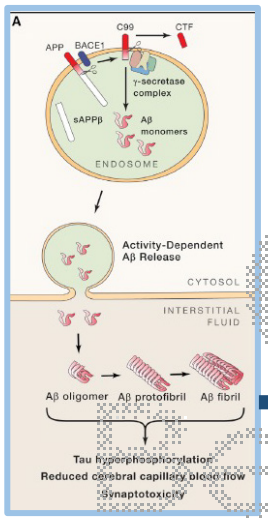
SELECTION OF THE DISEASE MODEL

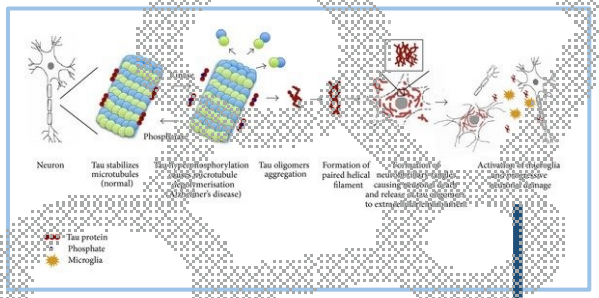
It should recapitulate those pathological mechanisms/symptoms implicaated in the human disease

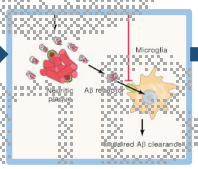
22

Pathological markers in AD

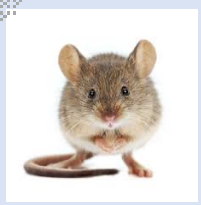
Beta-amyloid plaques (Aβ) **Neurofibrillary tangles (Tau)**







Neuroinflammation

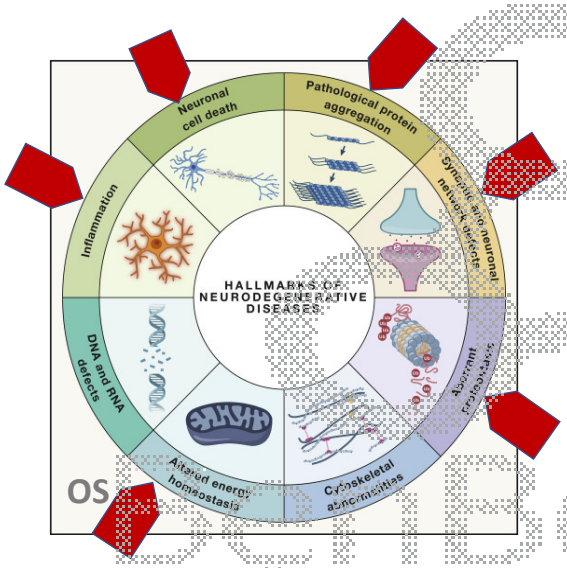


Transgenic mouse

Amyloidopathy (Aβ) + Tauopathy (Tau)

23

Model validation: We should be able to reproduce pathological pathways related to NDDs



- ✓Oxidative stress
- ✓Neuroinflammation
- ✓Tauopathy
- ✓Alt. Macroautophagy
- ✓Cognitive impairment

24

PROOF OF CONCEPT (PoC)

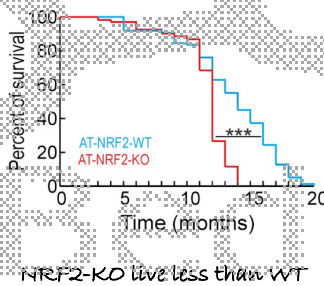
We need to demonstrate that acting on our target we are going to obtain the expected result

25

PoC Target

AD Mouse
APP/Tau Mouse

AT-NRF2-WT

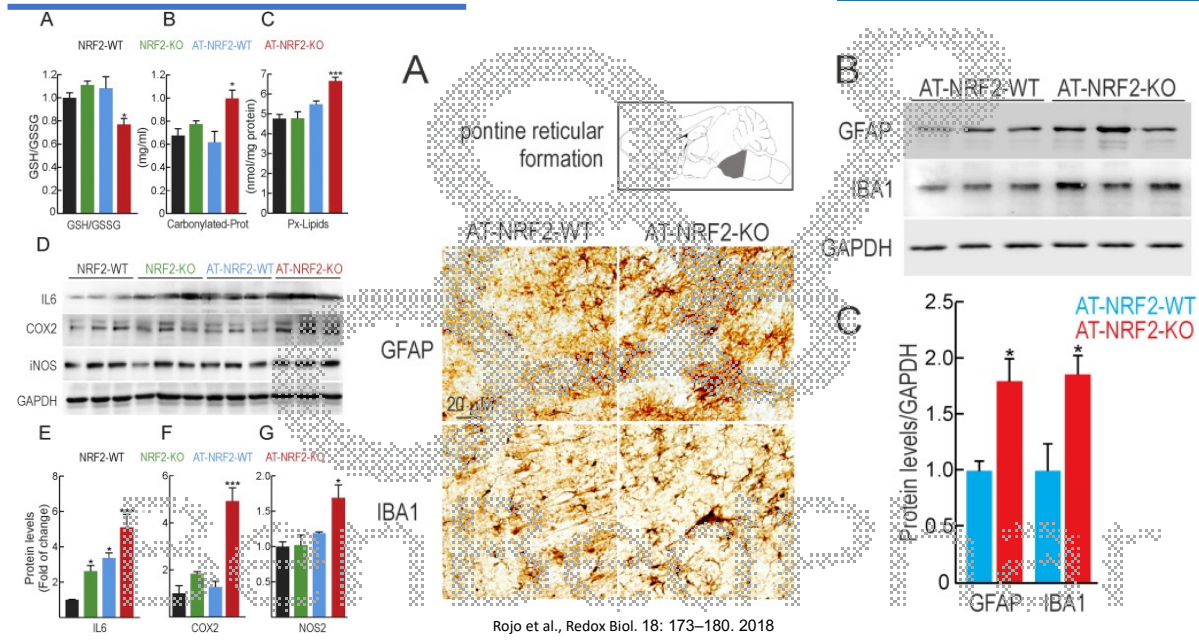


AT-NRF2-KO

NRF2-KO live less than WT

26

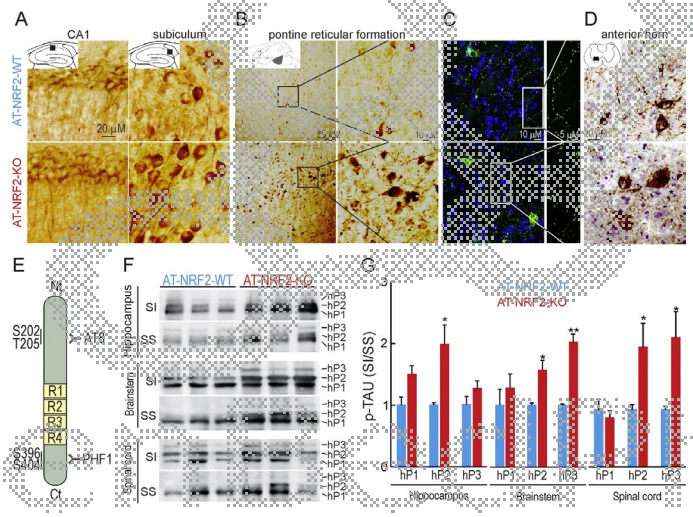
Neuroinflammation and oxidative markers are exacerbated in the absence of NRF2.



Rojo et al., Redox Biol. 18: 173–180. 2018

27

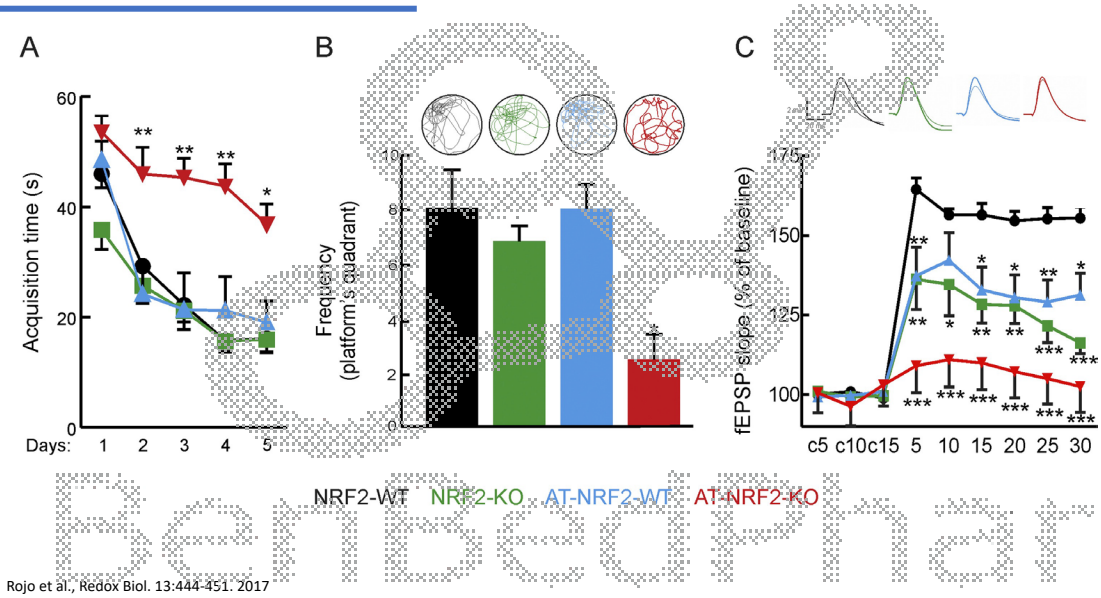
Lack of NRF2 leads to more tauopathy



Rojo et al., Redox Biol. 13:444-451. 2017

28

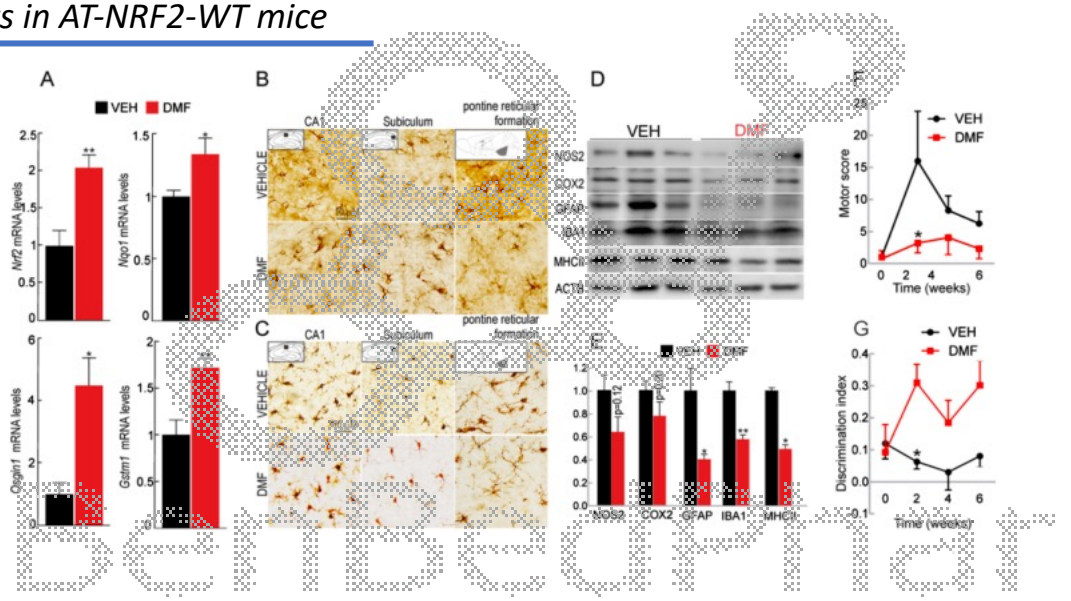
NRF2 deficiency impairs long term potentiation and spatial learning and memory



Rojo et al., Redox Biol. 13:444-451. 2017

29

The NRF2 inducer DMF improves memory and motor deficits in AT-NRF2-WT mice



Rojo et al., Redox Biol. 18: 173–180. 2018

30

31

PPI-NRF2 inducers as innovative therapies for NNDs

NRF2 4 AD

S2017/BMD-382-CM

Desarrollo de fármacos activadores de NRF2 para terapias innovadoras de la enfermedad de Alzheimer

Comunidad de Madrid

Dirección General de Investigación e Innovación Tecnológica

VICEPRESIDENCIA, CONSEJERÍA DE EDUCACIÓN Y UNIVERSIDADES

Tau-NeuroDiscovery

P2022/BMD-7230-CAM-22

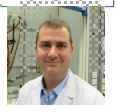
Optimización y validación *in vivo* de fármacos innovadores para el tratamiento de tauopatías

GT1
(Manuela G. Lopez)
Coordinator
UAM/IFTH

GT2
(Antonio Cuadrado)
UAM/IIB

GT3
(Maribel Rodriguez-Franco)
IQM-CSIC

GT4
(Rafael León)
IQM-CSIC

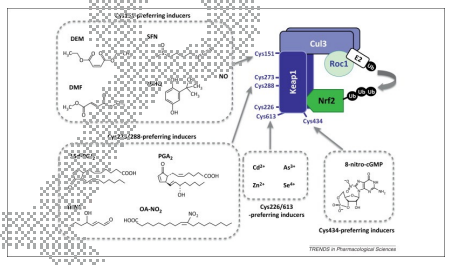


BenBedPhar

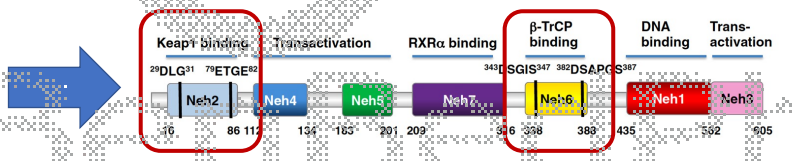
32

Pharmacological modulation of Nrf2

- **Electrophilic compounds-** covalent adducts with the sulfhydryl groups of cysteins in Keap-1 by oxidation or alkylation
  - Curcumin
  - Resveratrol
  - Sulforaphane
  - CDDO-methyl- Bardoloxone
  - Dimethyl fumarate

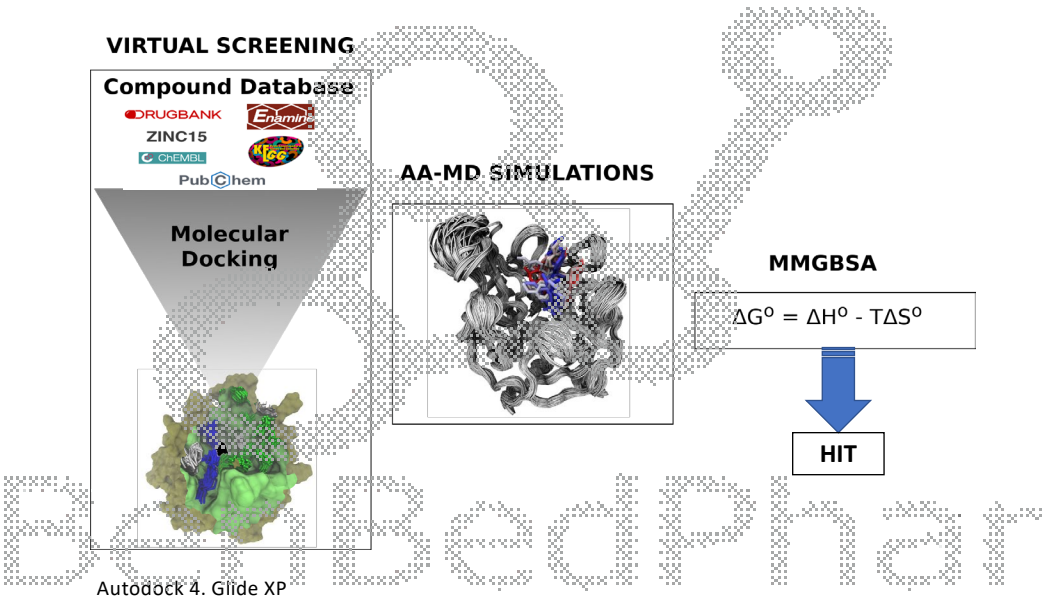


- **Protein-protein inhibitors (PPIs)**



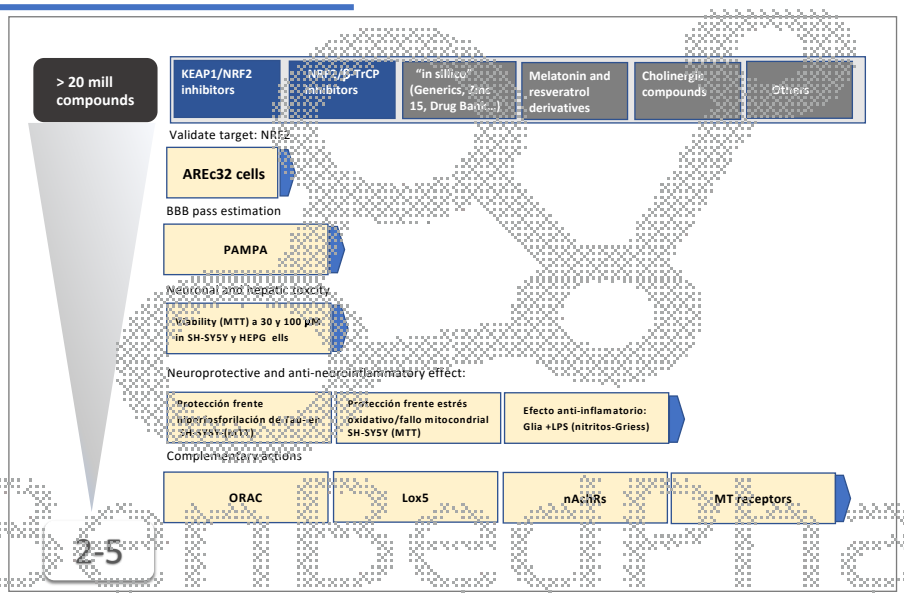
33

Computational screening platform



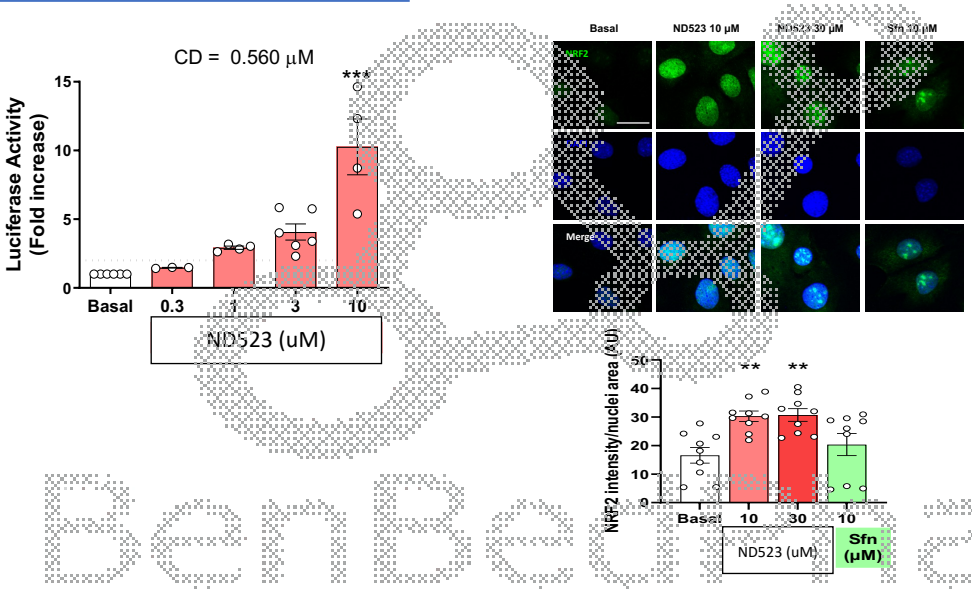
34

In vitro pharmacological screening of the compounds



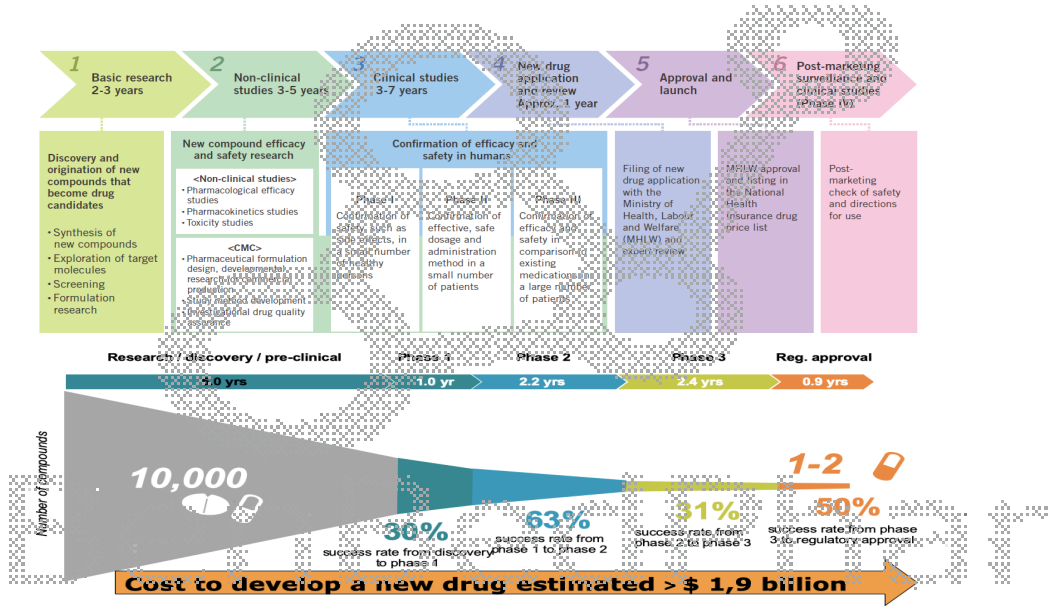
35

KEAP1-NRF2 PPI lead compound



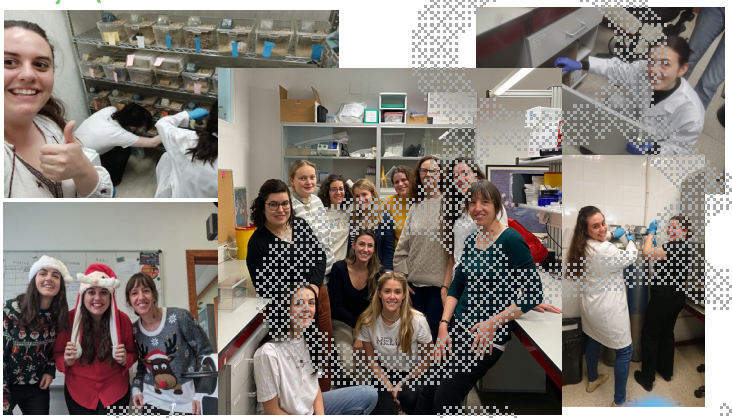
36

Drug reseach and development Process



37

NeuroProtectionLab



http://neurodiscovery-ndd.com/gt1 manuela.garcia@uam.es

Posdocs
Elena Tortosa (Captación de talento CM-modalidad 1)
Elsa Cortés (Juan de la Cierva)
Catalina Requejo (Contrato posdoctoral)
Laura Hautrive Milanesi (Contrato posdoctoral)

Predocs
Eric del Sastre (FPU)
Lucía Vigueira (FPU)
Angela Gomez (FPU-UAM)
María de la Fuente (Contrato Predoctoral)

TFMs
Carlota Siguero
Marta Mirón
Iciar Luna

Erasmus Plus
Sophie Reid

Tecnico de Gestión
Alejandra Quiroja

Madrid
Ref. B2017/BMD-3827 (NRF24AD-CM) Convocatoria Biomedicina 2017

UNIÓN EUROPEA
Fondos estructurales
Invertimos en su futuro

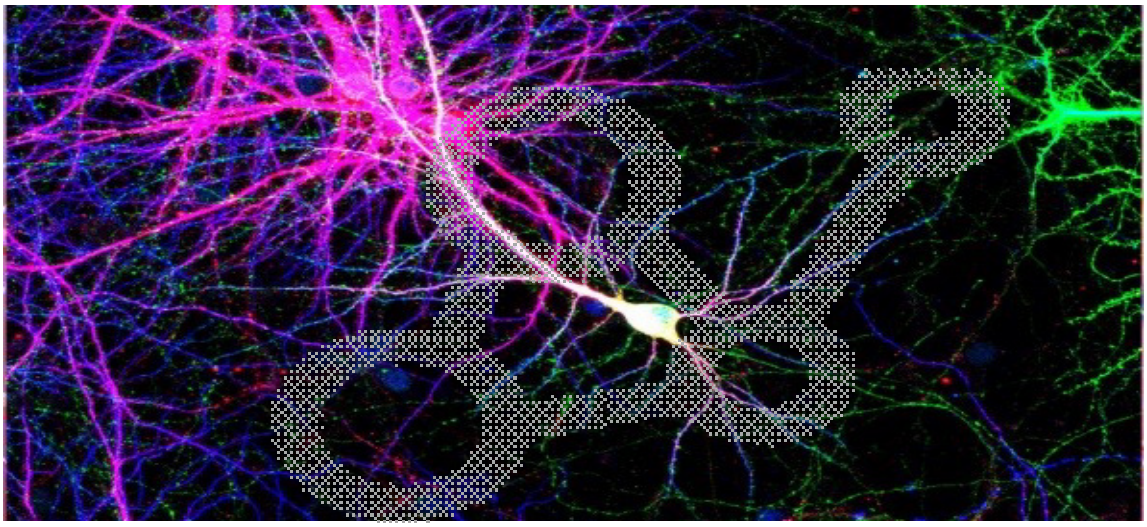
GOBIERNO DE ESPAÑA MINISTERIO DE ECONOMÍA Y COMPETITIVIDAD

cost EUROPEAN COOPERATION IN SCIENCE & TECHNOLOGY

Collaborators
- Antonio Cuadrado (UAM-CSIC)
- Rafael León (IQM-CSIC)
- MI Rodríguez-Franco (IQM-CSIC)
- Ana María Cuervo (I. Albert Einstein)
- JA Bernal (CNIC)

TEÓFILO HERNANDO
INSTITUTO TEÓFILO HERNANDO FUNDACIÓN TEÓFILO HERNANDO

38



(NeuroprotectionLab)

Thank you for your attention

39