# Gene therapy against Alzheimer based on adeno-associated vector E2F4DN (AAV-E2F4DN)

tetraneuron

Madrid, 28 de noviembre de 2018

GOBIERNO DE ESPAÑA MINISTERIO DE CIENCIA, INNOVACIÓN Y UNIVERSIDADES

MEDICAMENTOS INNOVADORES
Plataforma Tecnológica Española

farmaindustria

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   b) Innovative mechanisms of action
   c) Differential features facing the market
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## 1. The Institution

**Tetraneuron** is a drug discovery company, focused on the development of a **Therapy for Alzheimer's disease** (AD) and an **early Biomarker** for this neurodegenerative condition based on patents from our laboratory.

**Spin-off from the Cajal Institute**, High Council for Scientific Research (**CSIC**).

## 1. The Institution

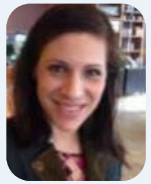
### PRINCIPALS:

**Dr. José M. Frade, PhD - Scientific Director & co-Founder**– Scientist at the Cajal Institute, Honorary Professor at the Autonomous University of Madrid, and world leader in neuronal tetraploidy

**Dr. Noelia López Sánchez, PhD – Technical Supervisor** -Senior Scientist in Tetraneuron with ample experience in neuronal tetraploidy

**Torres Quevedo Program 2017**

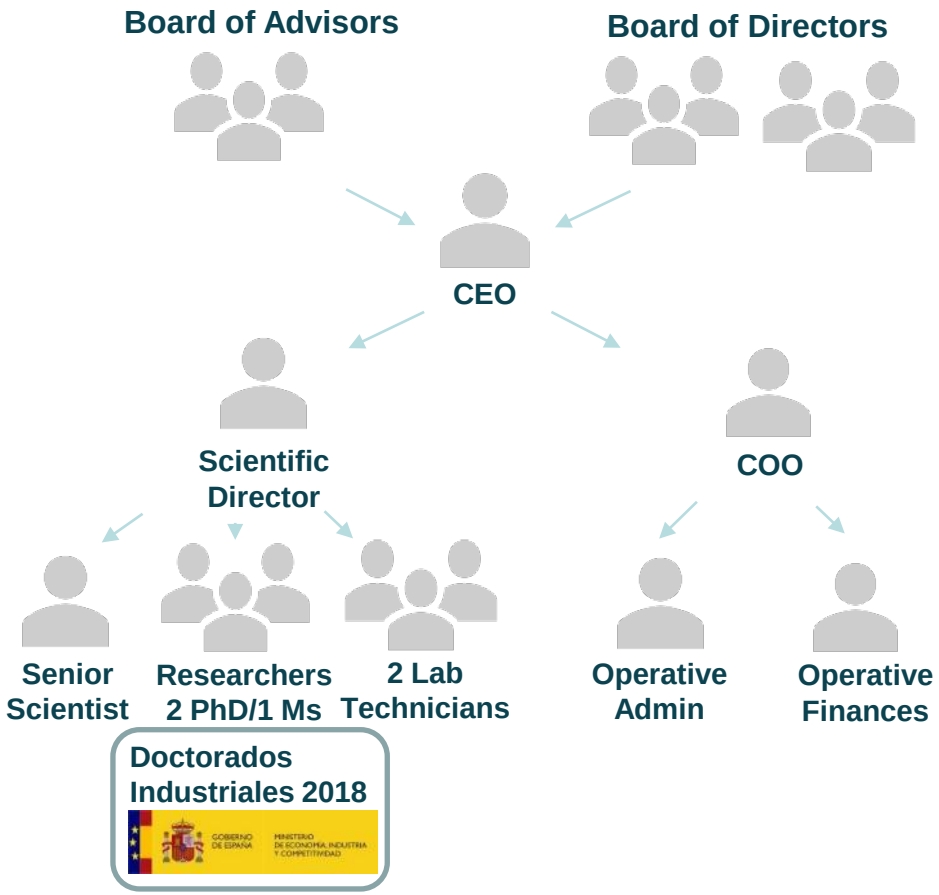
**David Mor, COO – Interim Management** – More than 15 years of experience in Management and development of scientific and sanitary spin off working with scientist , R&D entities, and VC´S



**Mercedes Poveda & Ifedes development Team – Interim Management** – More than 12 years of experience in Business Administration and Management.

## OUR TEAM

### COMPANY STRUCTURE




**Doctorados Industriales 2018**

## 1. The Institution

## PARTNERS AND COLLABORATORS

CSIC Consejo Superior de Investigaciones Científicas
Instituto Cajal
btcien Banco de Tejidos de la Fundación CIEN
BIOBANCO Hospital General Universitario de Alicante
Instituto de Investigación Sanitaria Hospital Universitario de la Princesa
Hospital Universitari Doctor Peset
Biopolo La Fe
Biobanco IMIB
Universidad de Navarra Biobanco
Asphalion
Envigo
Creatio
biobanko
PackGene
abg patentes
vivotecnia researching for you
Kaertor Foundation
Viralgen
imegen
ifedes Desarrollo de Negocio

## ADVISORY BOARD

**Dr. Manuel Pérez Alonso, PhD**
Dr. with expertise in Genetics, Professor from the University of Valencia and successful scientific entrepreneur.

**Dr. Manuel Sarasa Barrio, PhD**
Scientific Founder of Araclon Biotech in 2004. Inventor of several Biotechnology patents related to the diagnosis and treatment of AD.

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## 2. The Product (Target Indications)

**AAV-E2F4DN:** adeno-associated viral vector for neuronal expression of E2F4DN after intra-arterial administration

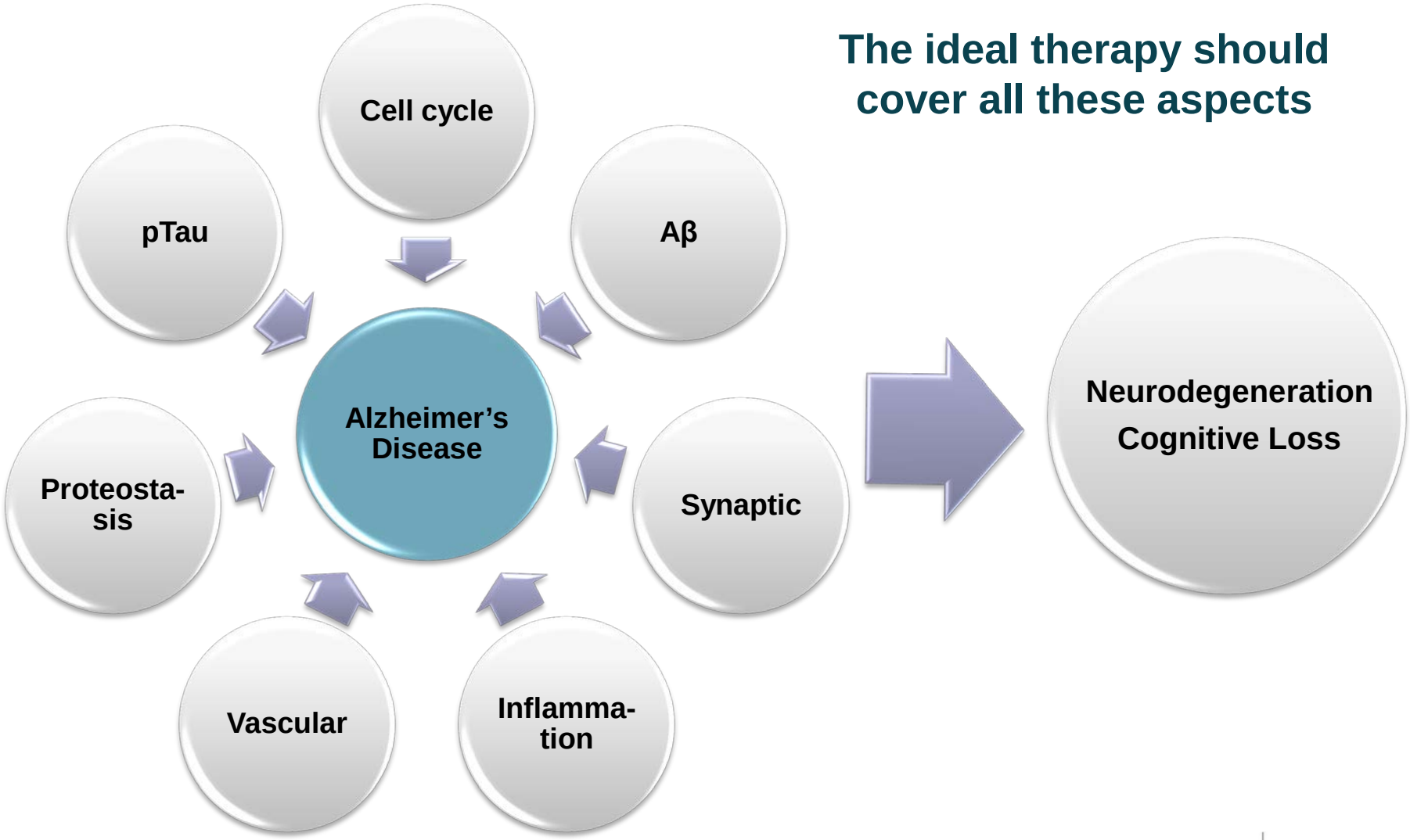
I. Gene therapy against Alzheimer's disease

II. 50 million people are currently affected / 152 million patients expected in 2050.

III. Prevents the progression of AD in asymptomatic or prodromal stages as well as in mild and moderate dementia

IV. No effective therapy for AD is currently available

## 2. The Product (Target Indications)




**The ideal therapy should cover all these aspects**

## 2. The Product (Target Indications)

- **THERAPY BASED ON E2F4DN FOR ALZHEIMER'S DISEASE**


**INTRAVENOUS DELIVERY EFFICACY**

✓ Preclinical efficacy proved in murine model of AD (5xFAD)

**REACHES THE BRAIN**

✓ Crosses the blood brain barrier

**SAFE**

✓ With no side effects
✓ Well tolerated

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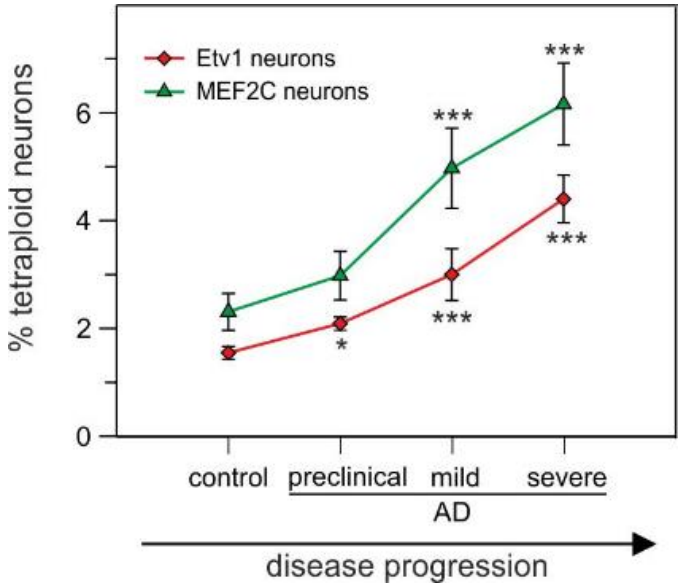
## 2. The Product (Innovative mechanisms of action)

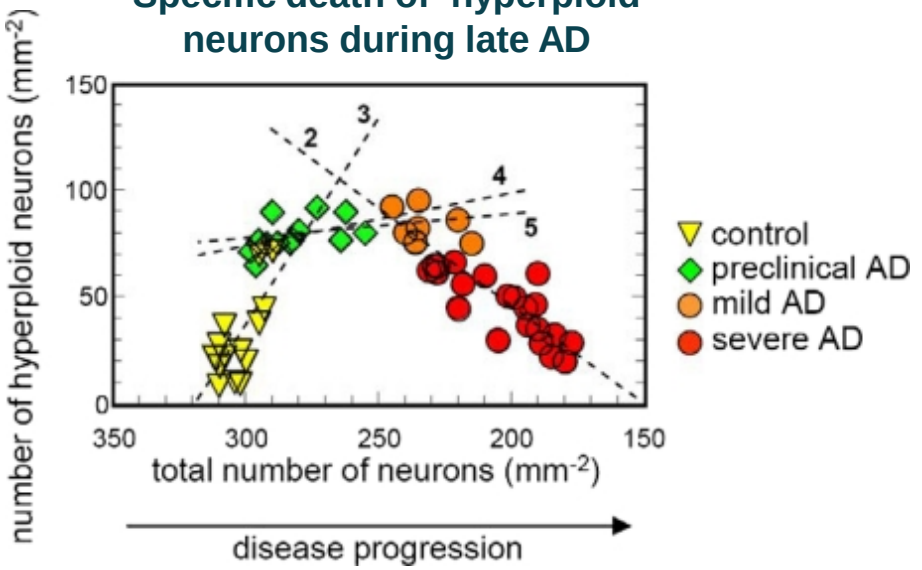
Neurons subjected to stress (excitotoxicity, trophic deprivation, Aβ,…) upregulate the expression of cell cycle regulators

Cell cycle reentry leads to DNA replication and tetraploidy

**Tetraploidy in cortical neurons during AD**




**Specific death of hyperploid neurons during late AD**

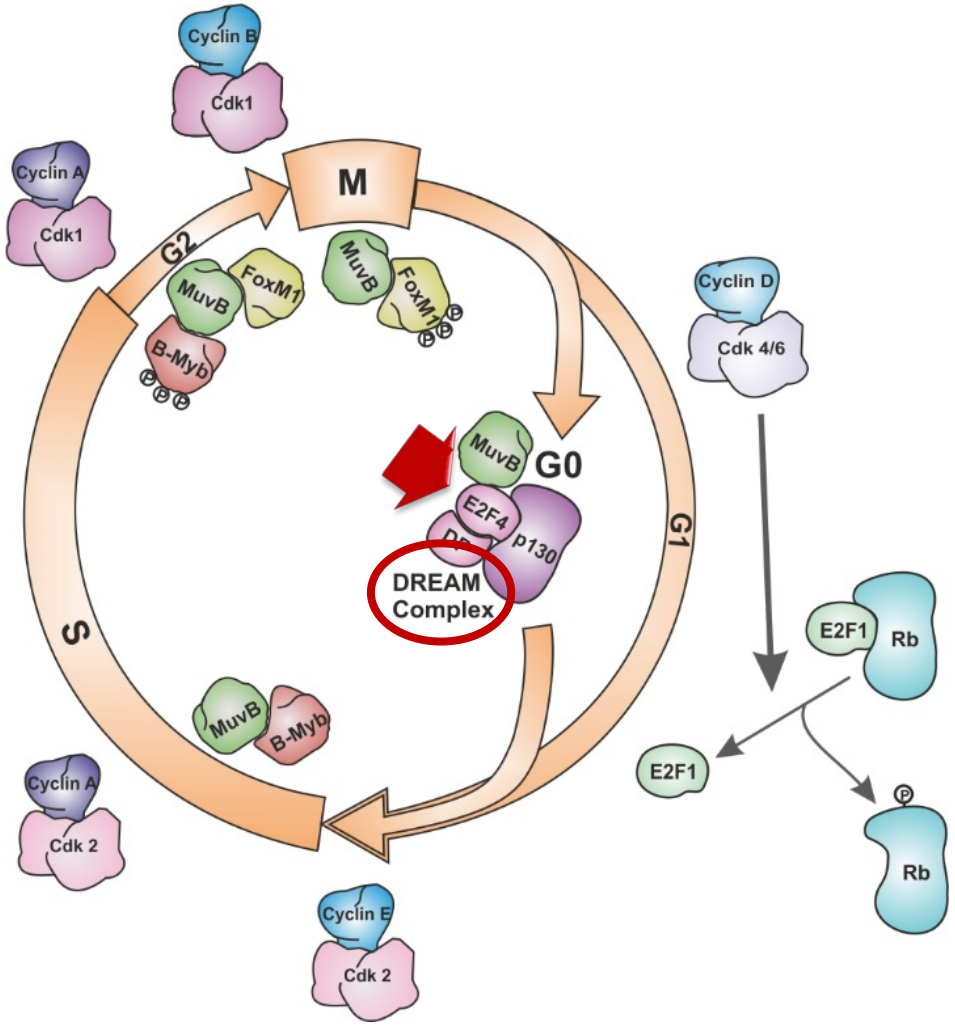


## 2. The Product (Innovative mechanisms of action)

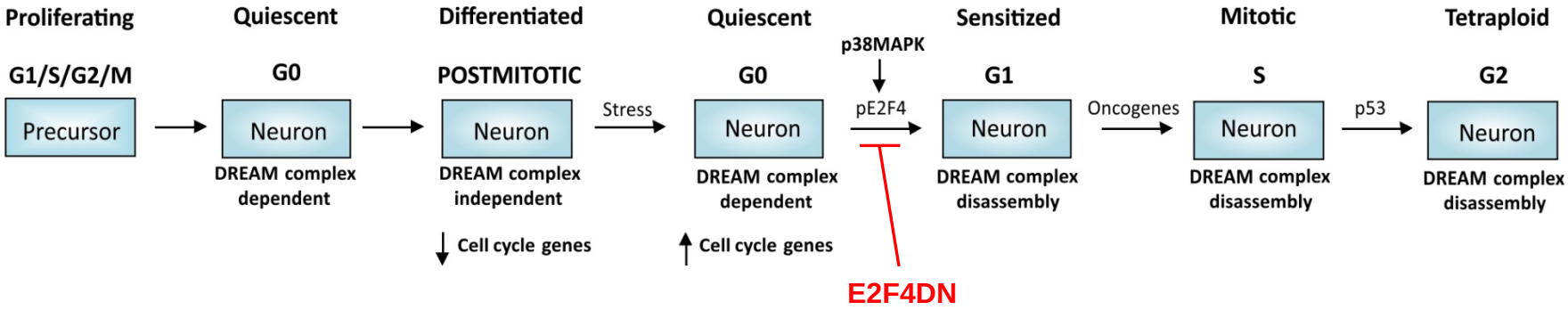
**Cell cycle in neurons leads to:**

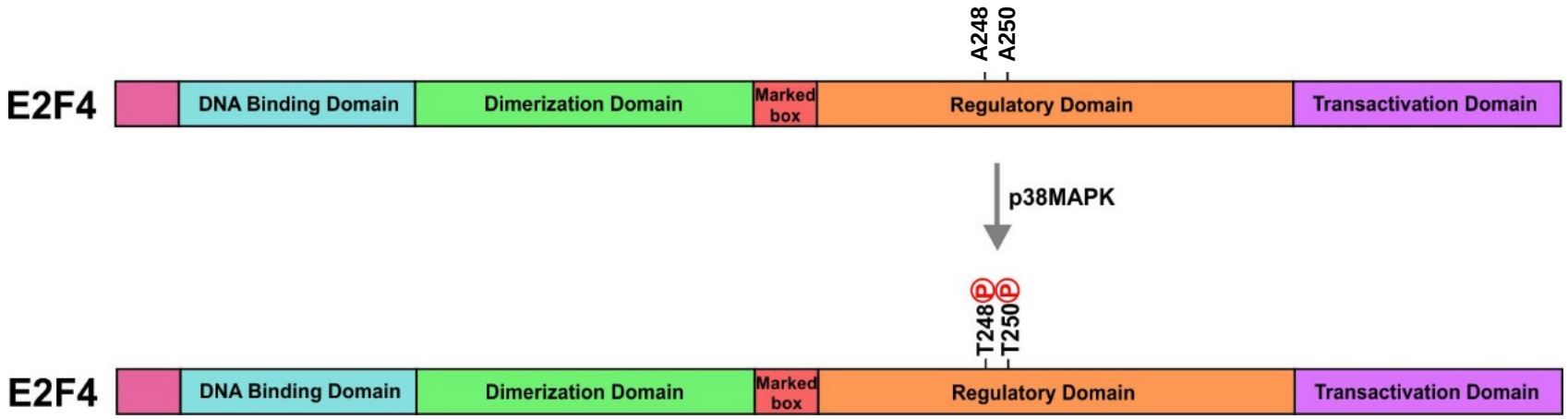
- PhosphoTau (NFTs)
- Extracellular Aβ deposits
- Synaptic dysfunction
- Gliosis

**Multi-data analysis of gene regulatory networks has related E2F4 to the AD pathogenesis**



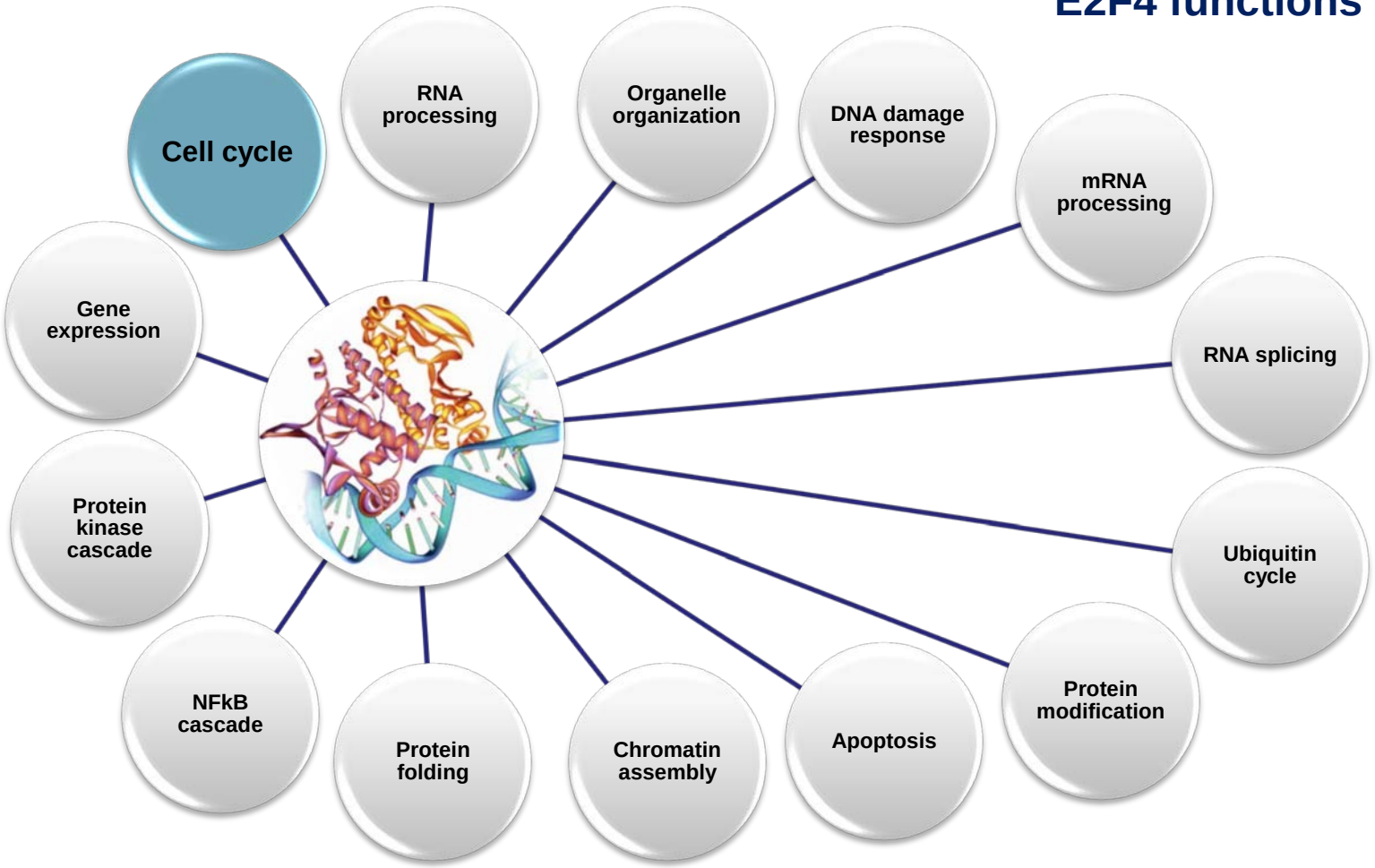
## 2. The Product (Innovative mechanisms of action)



## 2. The Product (Innovative mechanisms of action)

### E2F4 functions



## 2. The Product (Innovative mechanisms of action)

**E2F4DN transgenic mice**

**5xFAD mice (AD model) expressing E2F4DN show:**

- Blockade of neuronal tetraploidization
- Prevention of cognitive loss
  (Y-maze and Morris Water Maze training)
- Induction of a transcriptional program that promotes neuronal survival, axonal regeneration, synaptic plasticity, and enhancement of memory
- Increases the expression of genes that facilitate vascular integrity, non-cytotoxic inflammatory response through *Disease-Associated Microglía* (DAM), and facilitates neuronal "well-being"
- Potentiates Aβ aggregation (reduced cytotoxicity)

## 2. The Product (Innovative mechanisms of action)

**Therapy**

**AAV-E2F4DN is fully effective:**

Blockade of neuronal tetraploidization

Prevention of cognitive loss
(Y-maze and Morris Water Maze training)

**No side effects:**

Improved body weight gain and life expectancy

Normal activity

No tumors

Normal hepatic and spleen markers

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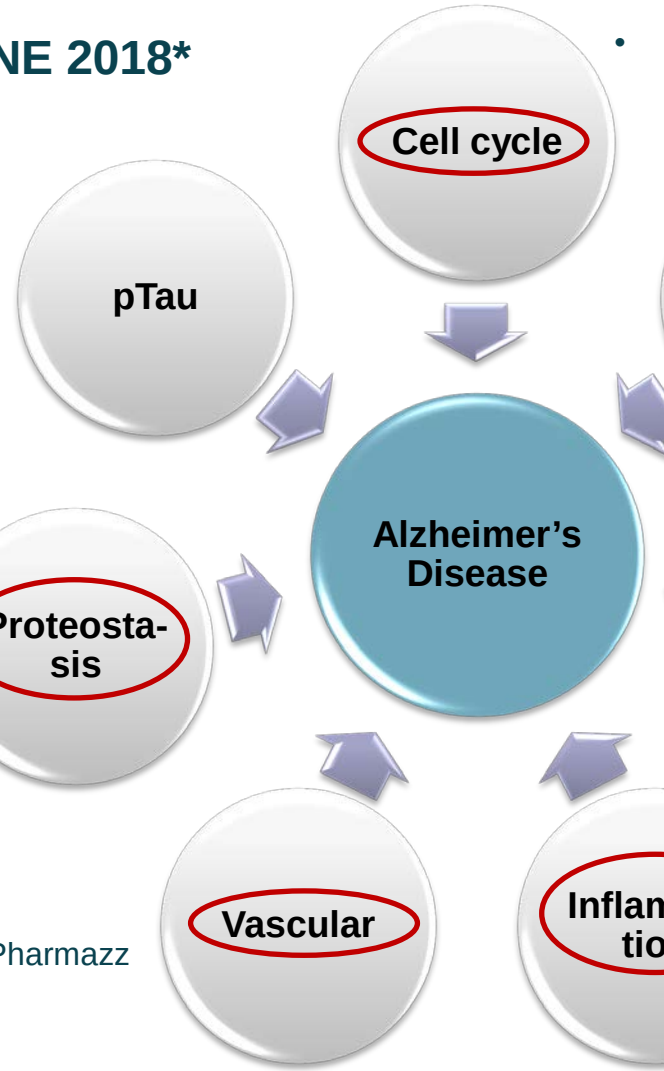
## 2. The Product (Differential features facing the market)

### PHASE I PIPELINE 2018*




- ?

- Biogen /Neurimmune
- AC immune /Janssen
- Proclara Biosciences
- Janssen
- Cortice Biosciences
- Pain Therapeutics
- Etc.

- Kyowa Hakko Kirin/ OncoTherapy Science
- AstraZeneca/Eli Lilly
- Sanofi
- H.Lundberck/Otsuka
- NeuroGenetic Ph.
- Eisai /Biogen
- Cognition Therap.
- Etc.

- ?

- Sosei / Allergan
- Tetra discover Part.
- Eisai
- Merk /Bionomics
- Lundbeck
- Suven Life Sciences

- Pharmazz

- Neuraltus Pharmaceuticals
- Denali Therapeutics
- GliaCure Inc.

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* Source: Rx Pulse Alzheimer's Disease

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## 2. The Product (Current status of development)

### November 2018

| Product | Discovery | Lead Identificaton | Preclinical Proof of Concept | Preclinical GLP Stage | Clinical Stage I and II |
|---|---|---|---|---|---|
| E2F4DN Therapy (Alzheimer) | | | | 2019-21 | 2021-24 |
| Biomarker – E2F4 (Alzheimer) | | | 2019 | 2020-21 | |
| New applications | | | | | |

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## 2. The Product (IPR protection)

**Therapy Patent**

- Use of E2F4 unable to be phosphorylated at T248/T250 **as a therapy for AD. License agreement** with CSIC (**Spanish patent No. ES2409779), issued in USA** (U.S. Patent No. 9,567,384 B2), **Japan** (Japan Patent No. 2014-534257), and in the recent months **in EU** (EU Patent No. 2783696).

**Biomarker Patent**

- Tetraneurons has also **patented the detection of E2F4 phosphorylation is blood serum as a biomarker for early diagnosis of AD** (**Spanish patent No. ES2598885**). PTC national phase in USA, Japan and EU (Tetraneuron/CSIC shared ownership at 50%)

**AAV vector**

- **License to use the AAV vector has been secured**.

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## 2. The Product (pitfalls & risks to be considered)

**1. FOR THE MECANISM OF ACTION:**

- Efficacy could be different in humans, but pThr-E2F4 can be detected in cerebral cortex from AD patients.
- Although not observed in mice, adverse side effects in humans cannot be ruled out.

**2. FOR THE USE OF THE AAV VECTORS (GENE THERAPY)**

- Another vector or administration route should be optimized if the AAV vector currently used cannot cross the BBB in non-human primates.
- Regulation approval might be slow due to the novelty of the approach. Nevertheless, regulatory institutions and developers are opening their scope to Alzheimer-specific drugs, and Gene Therapy is becoming accepted.

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## 3. Partnering Opportunities

- We seek for a partnership with big Pharma to advance quicker in our Therapy Development, with economic support and know-how in Drug development.
- Collaboration could also be developed in the line of securing options or license agreements when milestones set are reached.
- The development of an early Biomarker for Alzheimer's disease is a secondary partnering opportunity we also consider.
- Opportunities for additional IP developments for other therapeutic targets or neurodegenerative diseases.

# Thank you for your attention

**José María Frade, Ph.D.**
**Scientific Director**

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