An iPSC technology development collaboration – a critical component to enable ADAPTED

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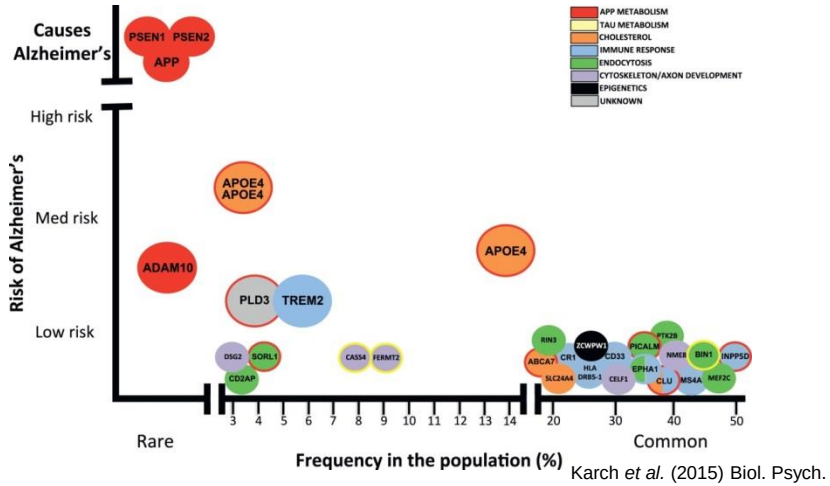
22 & 23 October 2018 • IMI Scientific Symposium • Brussels, Belgium

ADAPTED Project Objectives

→ Understand the biological impact of the biggest risk factor for Alzheimer's Disease (AD): **APOE4**



Karch *et al.* (2015) Biol. Psych.

OBJECTIVES:

1. ***Increased APOE understanding****: Clarification of the role of APOE as a risk factor in the development of AD*
2. *Identification of promising entry points (**targets**) for the treatment of AD*
3. *Generation and validation of selected high value **APOE-related model systems***
4. *Uncover the basic scientific evidence required to progress the development of a **stratified** approach*

Total budget, duration and current status

- Committed EFPIA in-kind contribution: € 3 million
- IMI-JU funding: € 3,5 million
- 3 year project: Oct 1, 2016 - Sept 30, 2019

Project Participants & Organization

- Project jointly led by
  - Fundació ACE (Institut Català de Neurociències Aplicades, Barcelona (coordinator)
  - AbbVie (leader)
- 3 EFPIA participants (AbbVie, Janssen and Biogen)
- 10 Academic/non-profit research organizations/SMEs
- 5 Countries (Germany, Netherlands, Spain, UK, USA)
- 5 Work Packages

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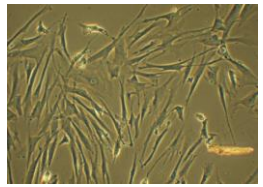
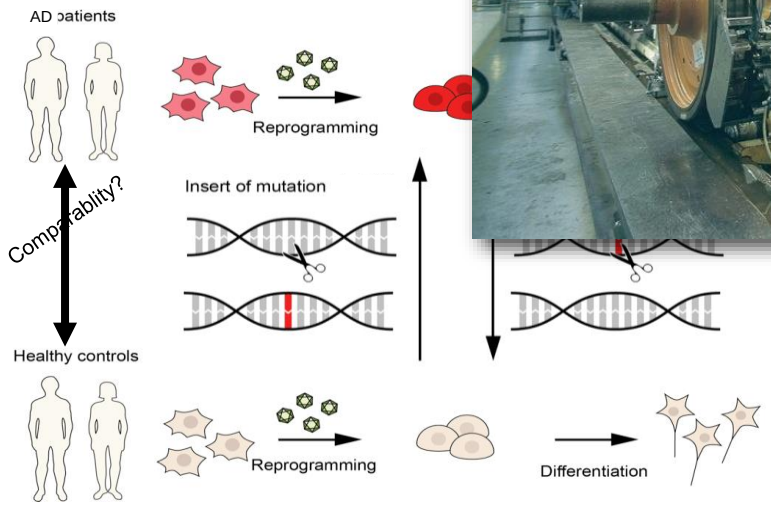
Understanding Neurodegenerative Diseases: APOE in Alzheimer's Disease

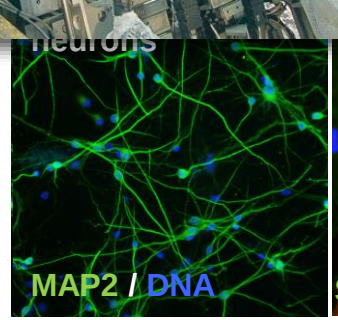


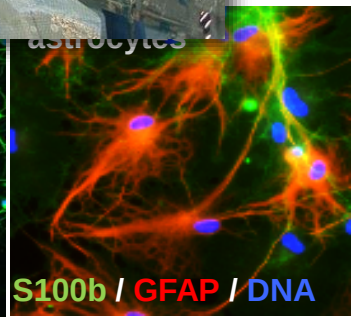
skin fibroblasts

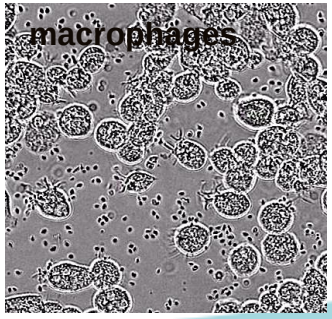
OCT4

nan induced pluripotent stem cells (hiPSCs)
ES cell - like
imitless self renewal!









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The Task

Generation of 5 different APOE genotypes in 3 different iPSC lines

APOE genotypes:

- APOE 2/2
- APOE 3/3
- APOE 3/4
- APOE 4/4
- APOE KO

Parental lines:

- 19 year old male donor (original APOE genotype: APOE 3/4)
- 78 year old female donor (original APOE genotype: APOE 3/3)
- 72 year old male donor (original APOE genotype: APOE 4/4)

Modified from DOI: 10.1038/mt.2016.1

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Results and Lessons Learned

- About 20% of the clones don't pass the DNA SNP array analysis
  - → DNA SNP array analysis before and after banking – ideally from 3 independent clones
  - → First QC to be done
- Low efficiencies of the CRISPRs
  - → Chemically modified CRISPRs (higher stability) – much more efficient
- Polyclonality instead of pure clones
  - → Single cell production of a gene-edited clone
- Introduction of indel mutations instead of homologous recombination
  - → Insertion of silent mutations that prevent the CRISPR from recutting

Our Achievement: Three sets of high quality isogenic iPSC lines

- Biweekly update rythm
- Sharing expertise and knowledge

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