Harald Neumann, UKB &
Andreas Ebneth, JPNV

on behalf of PHAGO

PHAGO –INFLAMMATION AND AD: MODULATING MICROGLIA FUNCTION – FOCUSSING ON TREM2 AND CD33

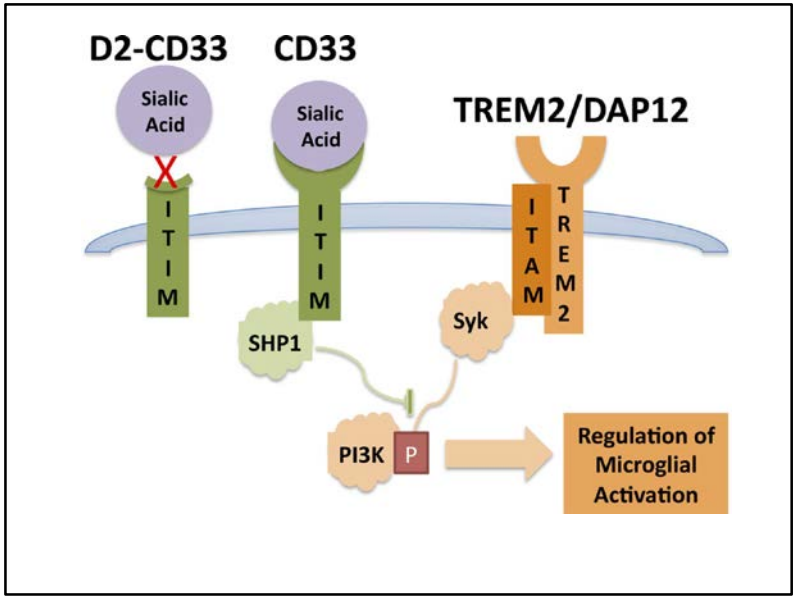
AETIONOMY Final Symposium

Bonn, 29/11/2018

Project starting point

Novel AD risk genes:

- TREM2 (loss of function?)
- CD33 (increased expression?)



Malik et al. J. Neurosci. 2013;33:13320-13325

PHAGO: Targeting TREM2 and CD33 of phagocytes for treatment of Alzheimer's disease

Project objectives

Identify druggable points of interaction in TREM2 and CD33 signaling to modulate phagocytes for treatment of AD

- Generate innovative tools for TREM2/CD33
- Develop and validate assays for TREM2/CD33
- Explore whether a decrease or an increase of phagocytic activity and/or cytokine release causes or prevents neurodegenerative phenotypes

Project key features

Key Data

- Project start 11/ 2016
- Funding period 5 years
- IMI funding € 8.8 million
- EFPIA contribution € 9.1 million

Project Lead & Coordinator

- Janssen Pharmaceutica (lead)
- University Hospital of Bonn (coordinator)

Project Participants & Organization

- 8 EFPIA partners
- 3 SMEs
- 8 public institutions

Scientific Advisors

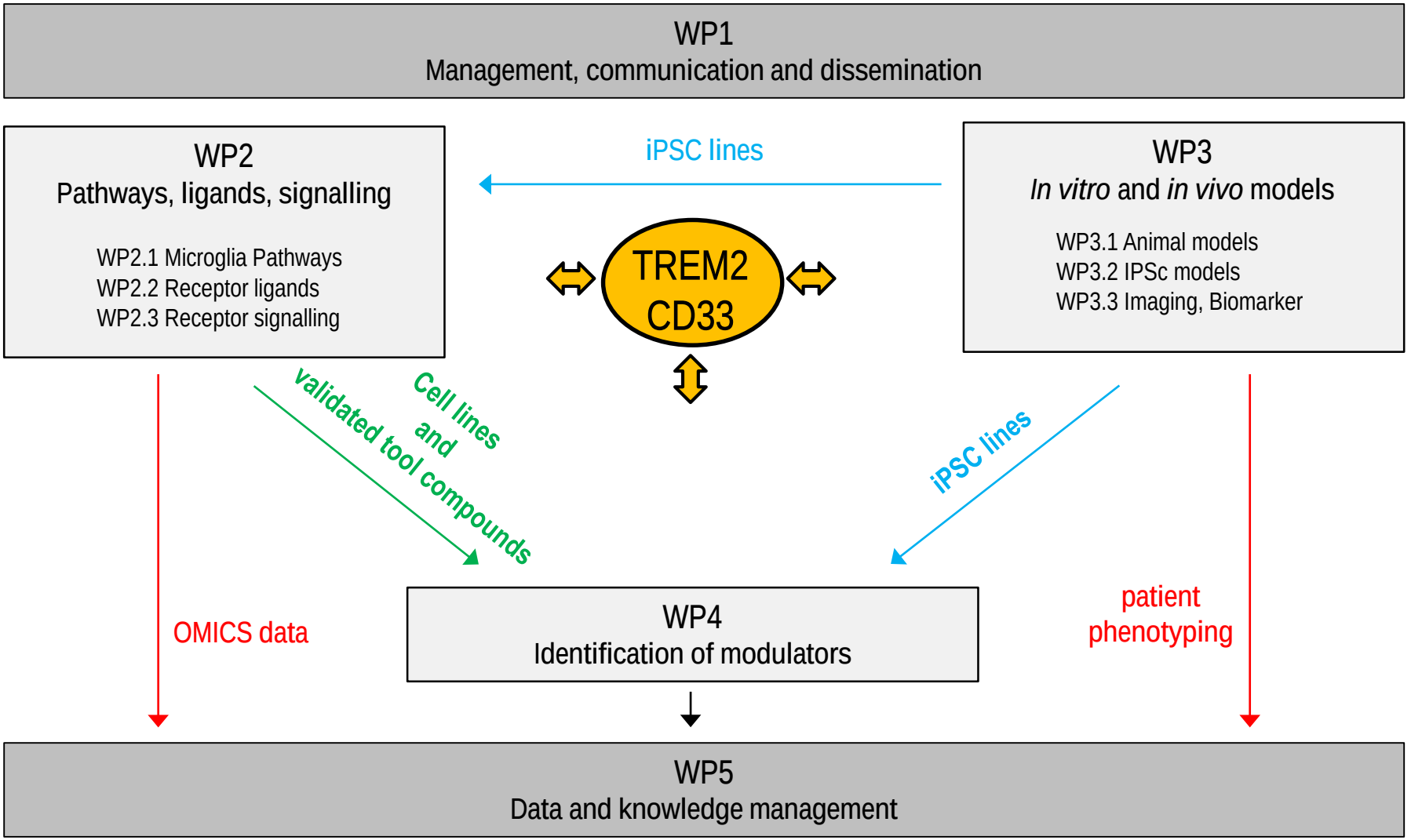
- Hugh Perry, University of Southampton, UK
- Fred Van Leuven, Emeritus KU Leuven, Belgium
- John Kemp, CSO Syndesi Therapeutics, Belgium

Ethics Advisors

- Nils Hoppe, Leibniz Universität Hannover, Germany
- Hub Zwart, Radboud University Nijmegen, The Netherlands

PHAGO
New therapeutic strategies for Alzheimer's Disease

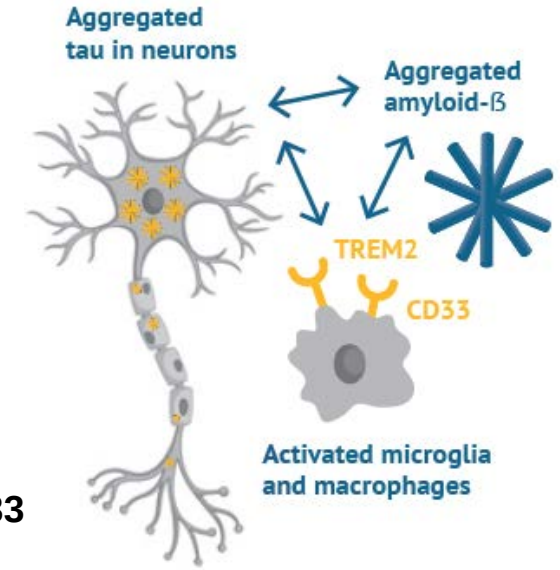
Project Structure



Project output (after 2 years)

Open access publications

- P. Garcia-Reitboeck (2018) Cell Reports
- X. Xiang et al. (2018) Mol. Neurodegeneration
- A. Carrillo-Jimenez et al. (2018) Front. Cell. Neurosci.
- G. Carbajosa et al. (2018) Neurobiol. Aging
- K. Schlepckow et al. (2017) EMBO Molecular Medicine
- P. Thornton et al. (2017) EMBO Molecular Medicine



Several tools related to TREM2/CD33

Several *in vitro* assay systems related to TREM2/CD33

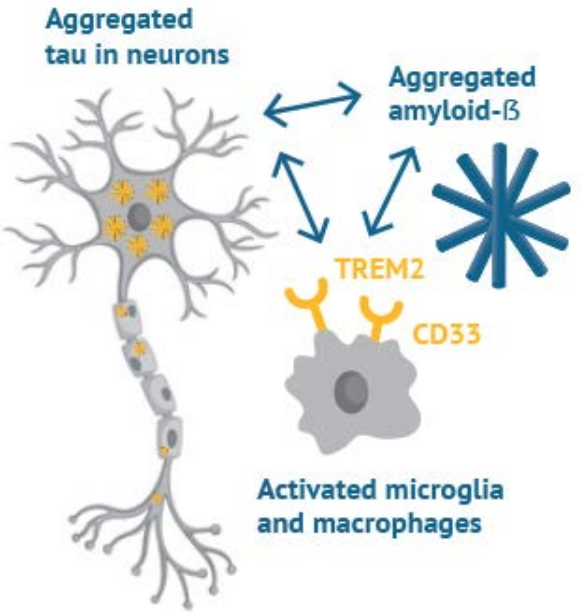
Several iPSCs related to TREM2/CD33

PHAGO
New therapeutic strategies for Alzheimer's Disease

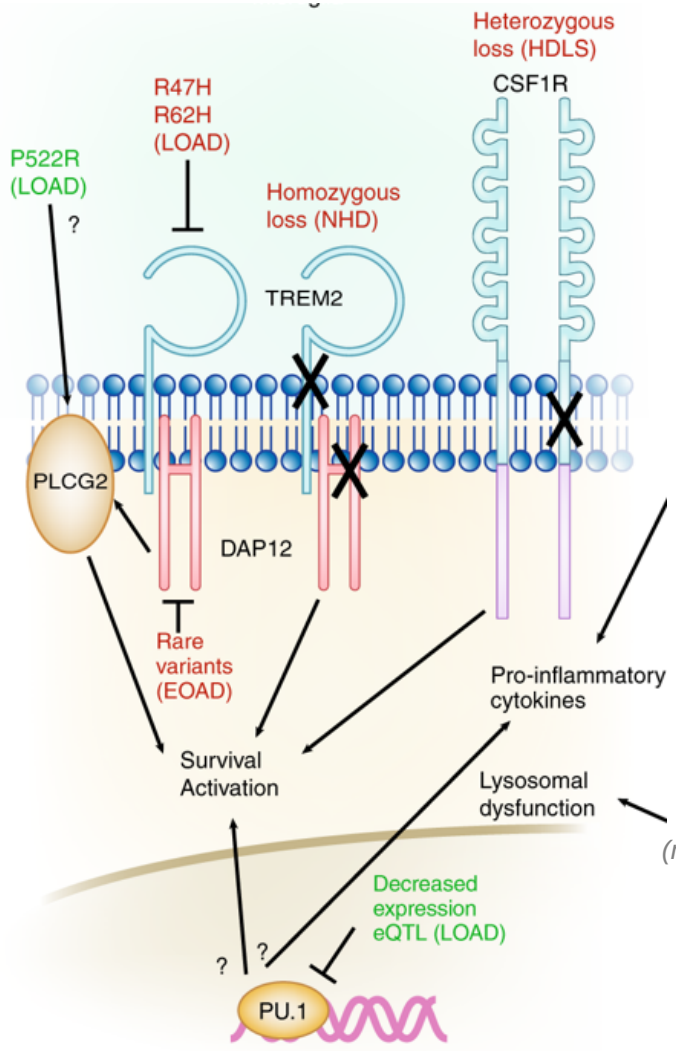
Two key questions for me as PHAGO coordinator

Should we activate or block microglia (e.g. via TREM2/CD33)?

At which stage show microglia increased or decreased activity?



Should we activate or block microglia?

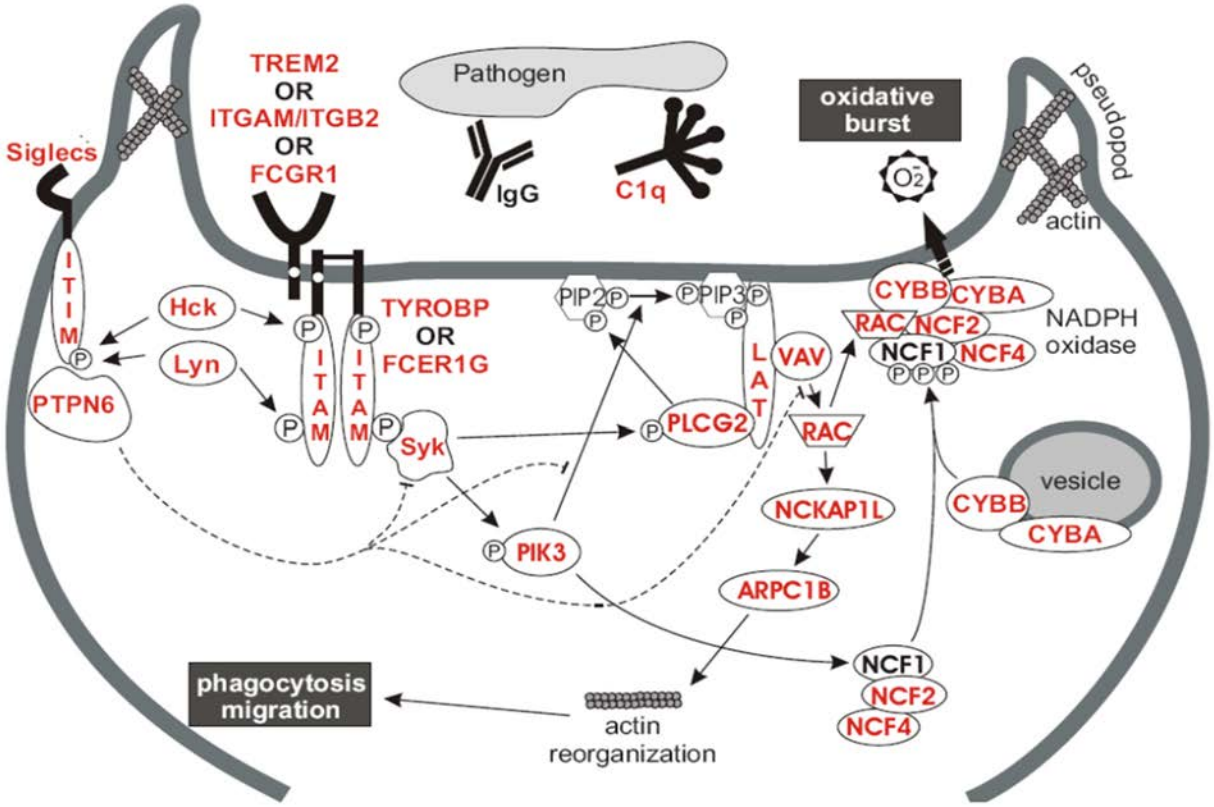


(modified from Song WM and Colonna M, 2018 Nat. Immunol.)

Neurodegeneration is linked to a loss-of-function of the activatory genes TREM2, TYROBP and CSFR1

But: neuroprotection is linked to decreased expression of the activatory transcription factor PU.1

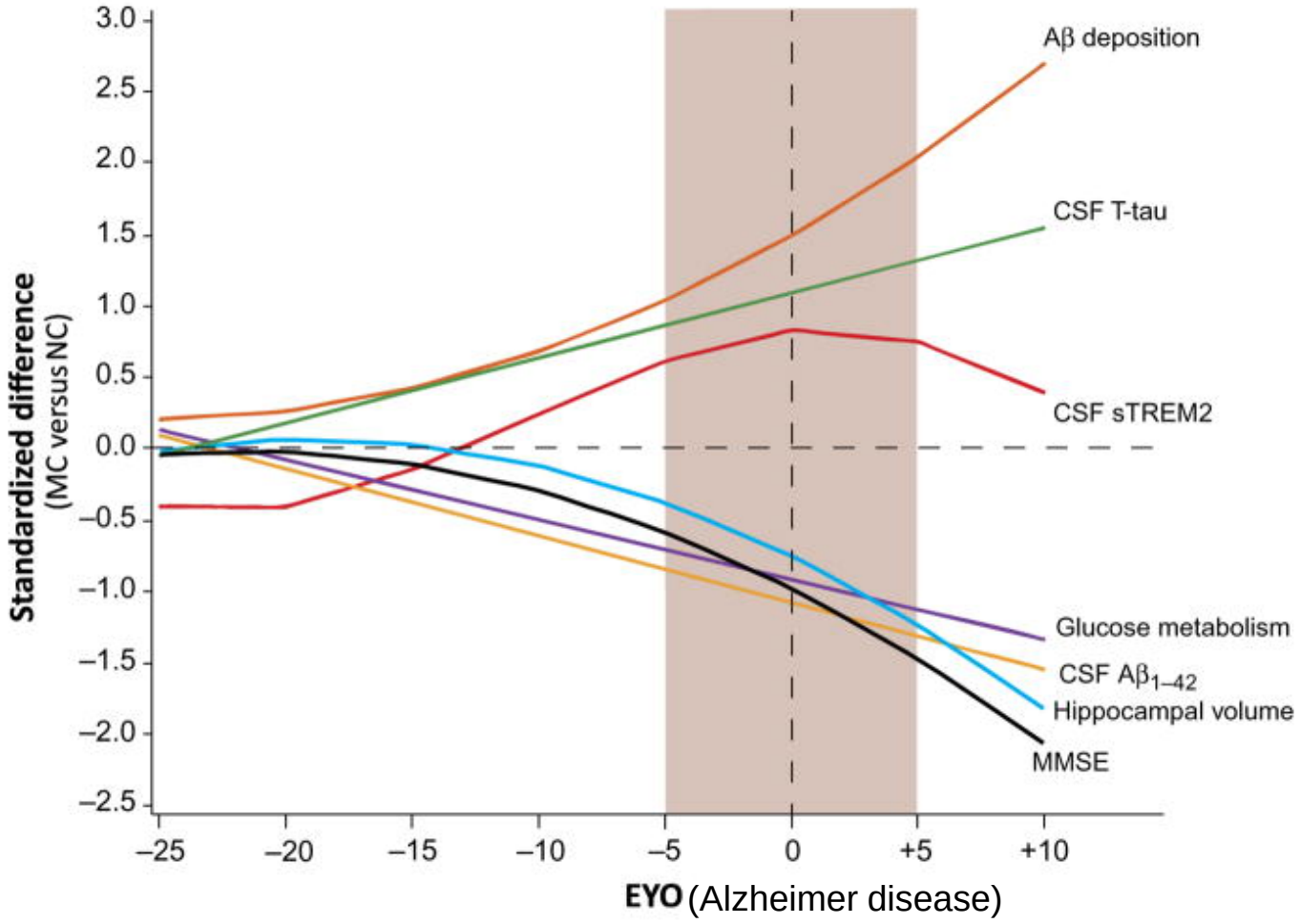
Should we activate or block microglia?



Zhang et al , Cell 2013

And: neurodegeneration is linked to increased gene transcription of the activatory genes TREM2 and TYROBP at late stage AD

At which stage show microglia increased or decreased activity?



from Suárez-Calvet et al, Sci Transl Med 2016

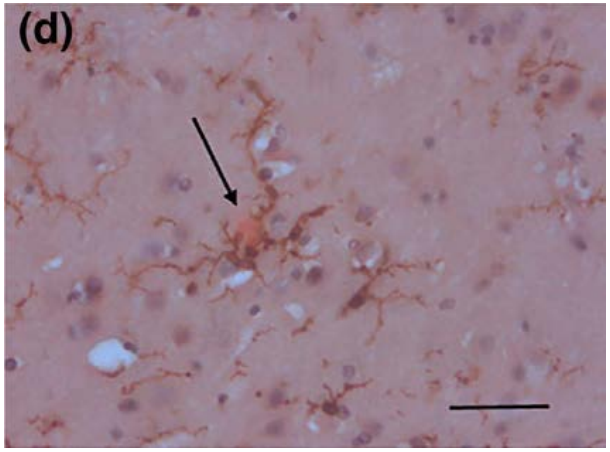
Decreased sTREM2 at 25 years before AD onset, but increased sTREM2 at onset

At which stage show microglia increased or decreased activity?

Neuropathology of 66 non-demented subjects (Streit et al, 2018):

- 100% had tau neurofibrillary degeneration
- 35% had amyloid-β deposits
- 8% had microglial activation

Activated microglia (iba1-brown) around
a small Congo red-positive amyloid



from Streit et al GLIA 2018

tau and amyloid is detected long before AD onset, but microglia activation might come late

THANK YOU

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