PHAGO
New therapeutic strategies for Alzheimer's Disease

Dr Angela Hodges, KCL

# TARGETING TREM2 AND CD33 OF PHAGOCYTES FOR TREATMENT OF ALZHEIMER'S DISEASE

ALZHEIMER EUROPE CONFERENCE

THE HAGUE | 24TH OCTOBER 2019

imi efpia

# PHAGO – a public private partnership

## Industry Partners

Janssen Pharmaceutica NV
Andreas Ebneth, Derya Ayaz

Sanofi -Aventis
Laurent Pradier

Eli Lilly
David Collier

F. Hofmann-La Roche
Markus Britschgi

AbbVie
Knut Biber

AstraZeneca AB
Damian Crowther

H/S Lundbeck
Sandra Vergo

Orion Pharma
Sanna Janhunen

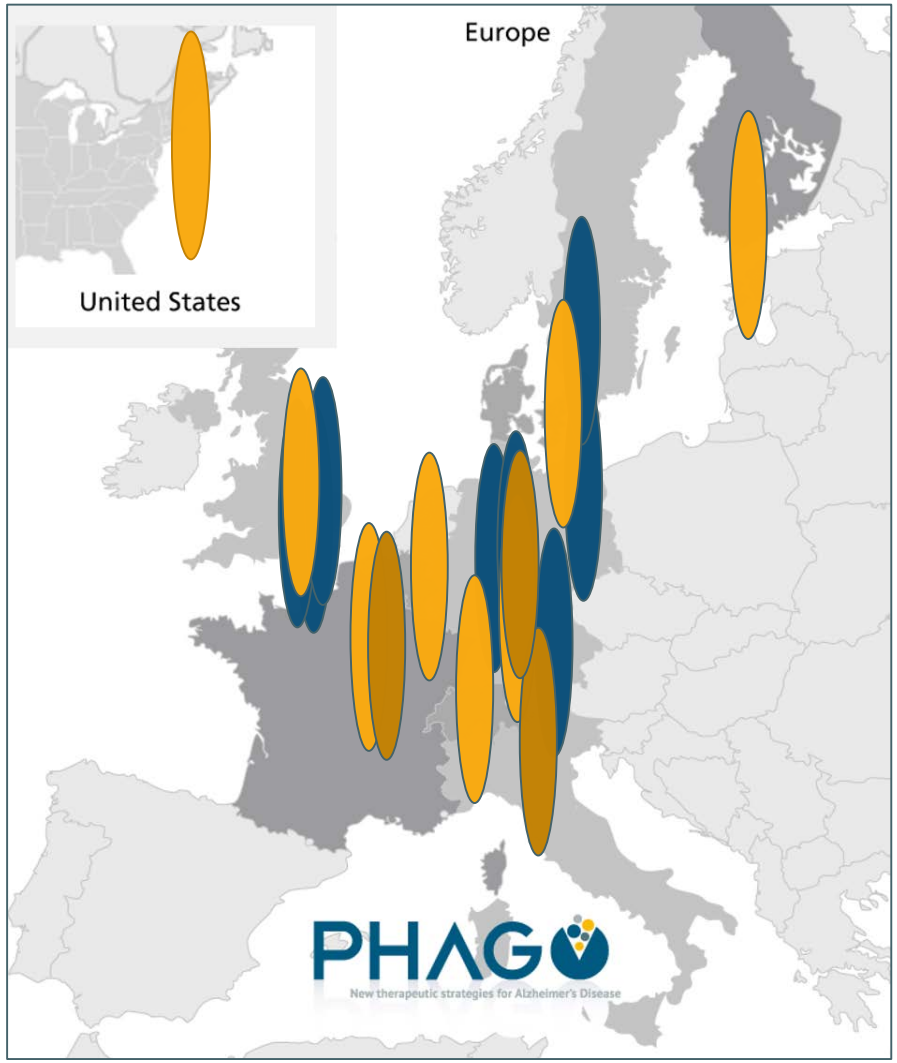
EISAI Inc.
Peter Atkinson

ARTTIC S.A.S
Claudia Pfander, Gabriele Wagner

## SME Partners

Axxam SpA
Loredana Redaelli

Life & Brain GmbH
Oliver Brüstle, Mona Mathews




## Academic Partners

University Hospital of Bonn
Harald Neumann, Jochen Walter

King's College London
Angela Hodges, Federico Turkheimer, Marios Politis, Antony Gee

German Center for Neurodegenerative Diseases – DZNE
Christian Haass (Munich), Michael Heneka (Bonn)

Charité
Frank Heppner

University College London
Jennifer Pocock, John Hardy

University of Cambridge
Guy Brown, Peter St. George-Hyslop

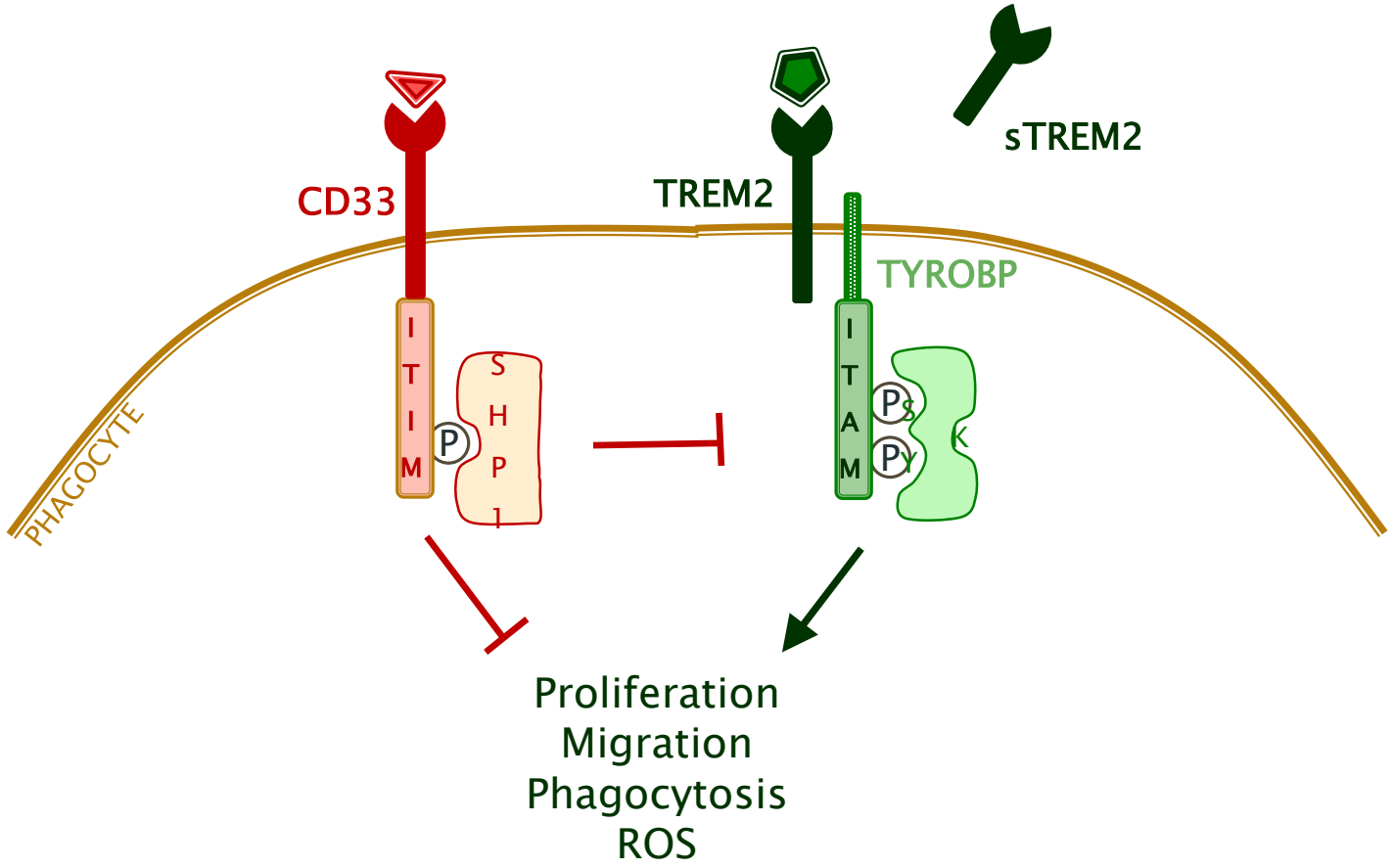
University of Gothenburg
Henrik Zetterberg

Fraunhofer Institute, St. Augustin
Martin Hofmann-Apitius

# TREM2 and CD33

Sialo-proteins, sialo-lipids

Anionic oligo-saccharides, lipids and ApoE



# PHAGO Objectives

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

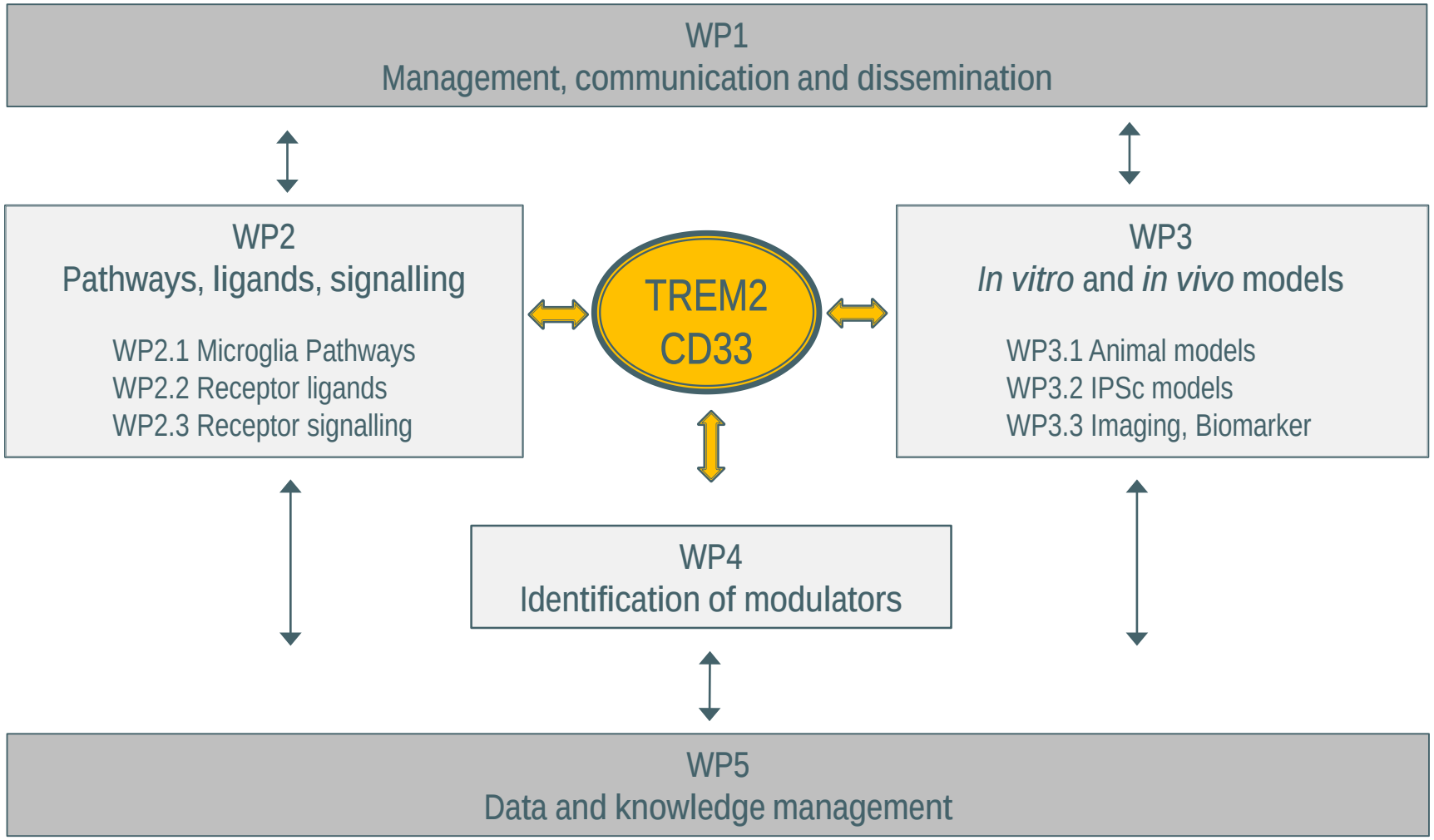
- to generate new knowledge on phagocytosis and neurodegeneration
- to acquire key knowledge on the role of TREM2/CD33 in AD
- to generate innovative tools for investigating TREM2/CD33
- to develop and validate assays targeting TREM2/CD33

# PHAGO Approach

Combining the expertise of a multidisciplinary and international consortium:

- Genetics, bioinformatics and systems biology
- Positron emission tomography (PET)–imaging of AD patients
- Microglial biomarkers
- Induced pluripotent stem cell (iPSC) technologies
- Cellular screening assays
- Advanced knowledge database

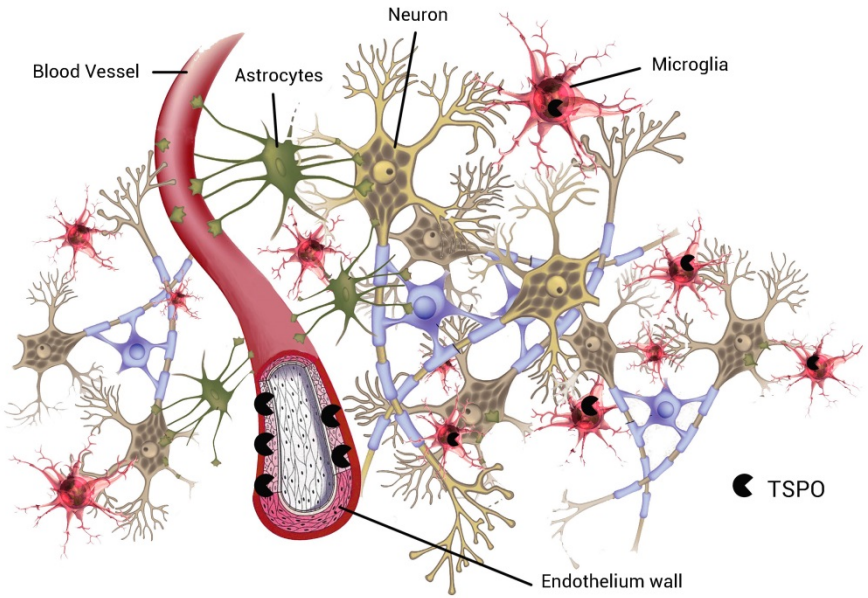
# PHAGO Structure



# WP2 – Pathways, ligands and signalling

## Identification of

- novel AD risk genes within microglial pathways
- downstream genes/pathways with alterations in TREM2 and CD33 expression in disease and model systems
- TREM2 and CD33 ligands to elucidate function and generation of agonists/antagonists as tool compounds



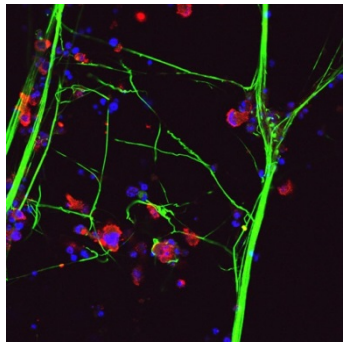
Neuronal structures and activation marker TSPO, KCL

## Characterization of TREM2- and CD33 metabolism and signalling

- establishment of assays for TREM2- and CD33 dependent signalling, phagocytic activity and migration
- characterization of signalling pathways and how TREM2- and CD33-dependent signalling interact to regulate microglia/ macrophage function

# WP3 –AD models, TREM2 and CD33

*In vivo* AD mouse models to determine the effect of activating/inhibiting TREM2 and CD33



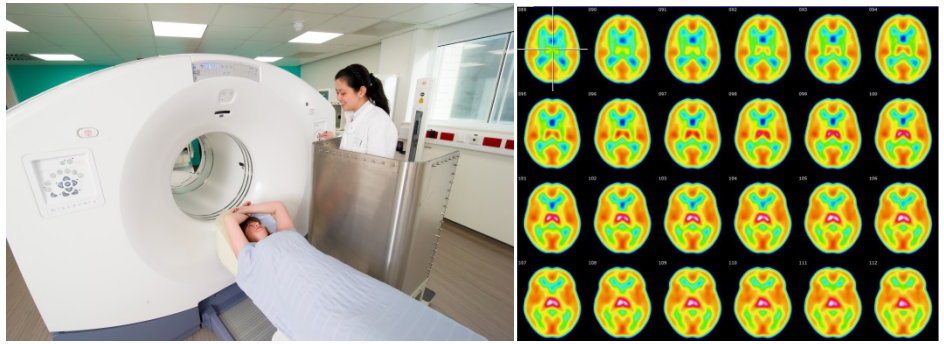
Macrophages with iPS-derived neurons, UKB

Novel *in vitro* tools:

- human iPSC with disease relevant variants of TREM2/CD33
- iPSC derived microglia and macrophages for functional studies and drug screening

## Imaging in AD patients

- Study microglia activation in patients with/without TREM2 disease risk variants
- Patient CSF analysis for microglial disease biomarkers

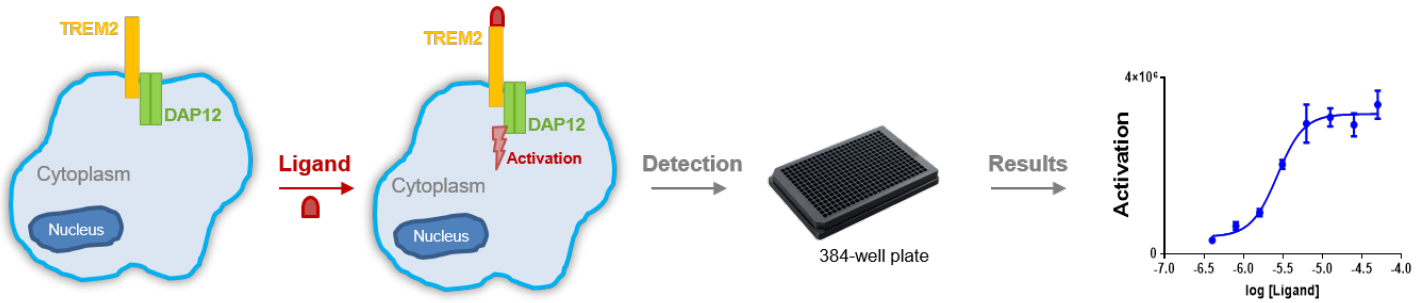


PET Center (left) PET MRI scan (right), KCL

# WP4 – Modulators of TREM2 / CD33

## Identification of modulators by screening

- Assay development for HTS technology
- Pilot screen for small molecule activators (Trem2) or inhibitors (CD33)




TREM2 assay for HTS, Axxam

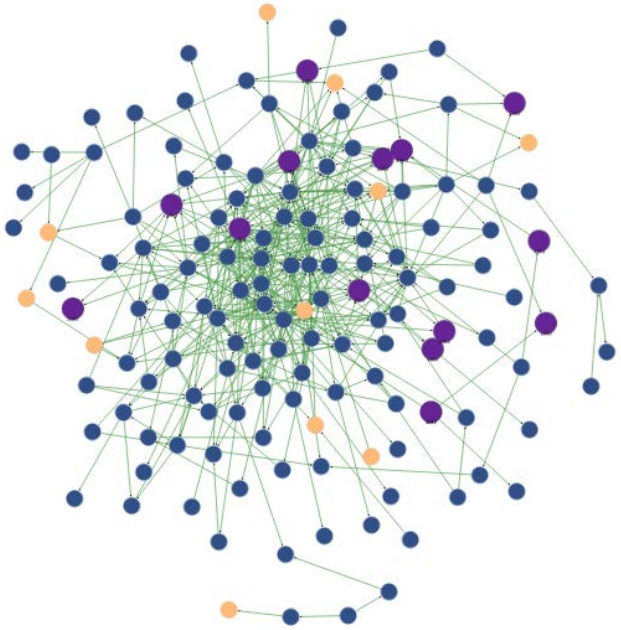
## Modelling of interactions

- X-ray structure of CD33 and TREM2 ectodomains
- Modelling of interactions with ligands

# WP5 – Data and knowledge management

Establish platform for data and knowledge management and sharing data across the project:

- Ensure interoperability of quality standards
- Ensure storage, visualization and access to data generated across project
- System biology for data validation



Cluster analysis, Fraunhofer

# Results

- PHAGO has studied the shedding of TREM2 as well as TREM2 and CD33-signalling pathways of phagocytosis. The identification of the exact cleavage side of TREM2 in its ectodomain at H157 has been revealed.
- PHAGO has generated iPSCs with disease relevant genetic variants of TREM2. The iPSC lines are available at the EBiSC repository (https://cells.ebisc.org/).
- PHAGO described the generation of human iPSC derived from microglial like cells from patients with early-onset dementia caused by variants in the immune receptor gene TREM2.
- PHAGO has started to generate TREM2 and CD33 reporter systems and assays to support screening and drug development campaigns.
- The crystal structure of CD33/SIGLEC3 complexed with natural ligands was determined.
- PHAGO established a knowledge platform with -omics data from PHAGO partners enriched with literature data from public resources.
- PHAGO has aligned different public and own resources to get an overarching transcriptome fingerprint of human microglia.
- Transcriptome data of TREM2 KO mice reveals that loss of Trem2 in microglia leads to widespread disruption of cell co-expression networks in mouse brain.

# PHAGO list of publications

- **Small Molecule Binding to Alzheimer's Risk Factor CD33 Promotes Aβ Phagocytosis**
  iSCIENCE – Miles et al., 2019
- **"TREM2 triggers microglial density and age-related neuronal loss"**
  GLIA – B. Linnartz-Gerlach et al., 2019
- **"Loss of TREM2 function increases amyloid seeding but reduces plaque-associated ApoE"**
  Nature Neurosci. – S. Parhizkar et al., 2019
- **"Loss of Function of TREM2 Results in Cytoskeletal Malfunction in Microglia"**
  JNNB – A.E. M. Phillips et al., 2018
- **"Effective Knockdown of Gene Expression in Primary Microglia With siRNA and Magnetic Nanoparticles Without Cell Death or Inflammation"**
  Front. Cell. Neurosci. – A. Carrillo-Jimenez et al., 2018
- **"The Trem2 R47H Alzheimer's risk variant impairs splicing and reduces Trem2 mRNA and protein in mice but not in humans"**
  Mol. Neurodegeneration – X. Xiang et al., 2018
- **"Human Induced Pluripotent Stem Cell-Derived Microglia-Like Cells Harboring TREM2 Missense Mutations Show Specific Deficits in Phagocytosis"**
  Cell Reports – P. Garcia-Reitboeck et al, 2018
- **"Loss of Trem2 in microglia leads to widespread disruption of cell co-expression networks in mouse brain"**
  Neurobiol. Aging – G. Carbajosa et al., 2018
- **"An Alzheimer associated TREM2 variant occurs at the ADAM cleavage site and affects shedding and phagocytic function"**
  EMBO Molecular Medicine – K. Schlepckow et al, 2017
- **"TREM2 shedding by cleavage at the H157-S158 bond is accelerated for the Alzheimer's disease-associated H157Y variant"**
  EMBO Molecular Medicine – P. Thornton et al., 2017

# External collaborations

## (New) collaborations with other AD-related consortia/partners

| | |
|---|---|
| ADAPTED | to improve the transcriptome analysis of samples |
| IMPRiND | to use the tau-seeding mouse models |
| Neuronet Efficiently Networking European Neurodegeneration Research | to increase the outreach and knowledge about ND |
| EBiSC European Bank for Induced pluripotent Stem Cells | to supply iPSCs to the scientific community |
| AETIONOMY | to provide basis for WP5 developments |
| EPAD European Prevention of Alzheimer's Dementia Consortium | to provide access to biosamples for CFS analysis |
| AMP-AD | as first collaboration between an IMI project and NIH |

www.phago.eu

https://www.linkedin.com/in/phago-project/

@phago_imi


- This project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking (IMI2 JU) under grant agreement No. 115976.
- This Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation programme and the European Federation of Pharmaceutical Industries and Associations (EFPIA).