

## BACKGROUND

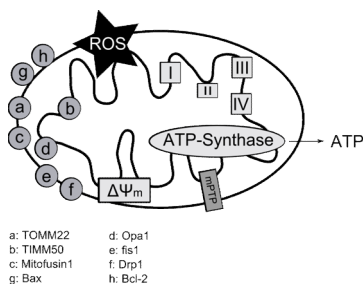
Neurodegenerative diseases are one of the major challenges of the 21st century. The United Nations estimate that the number of people suffering from age-related neurodegeneration, particularly Alzheimer's disease (AD), will exponentially increase from 25.5 million in 2000 to an estimated 114 million in 2050. The risk of AD grows exponentially with age, doubling approximately every 5 to 6 years. Cells in the central nervous system are affected by aging and react to aging, as indicated by a decline of several physiological abilities including sensory, motor, and cognitive functions. Aging cells are affected by increasing amounts of oxidative stress, perturbed energy homeostasis, accumulation of damaged proteins and lesions in their nucleic acids on the molecular level and by impaired function of signaling mechanisms and altered gene expression at the cellular level.

## GOALS

Our interdisciplinary team is dedicated to explore the underlying mechanisms of brain ageing and of neurodegenerative diseases. The main focus is the modulation of mitochondrial and synaptic dysfunction and stroke-related damage by food-based prevention and intervention. Therefore we use various *in vitro* and *in vivo* models of aging and Alzheimer's Disease.

## METHODS

### Mitochondrial Dysfunction



- Isolation of dissociated brain cells and metabolic active mitochondria
- Isolation and purification of mitochondrial membranes
- High Resolution Respirometry (Oxygraph-2k, Oroboros), activity of complexes (I-IV)
- Mitochondrial membrane potential ( $\Delta\Psi_m$ ) (Rhodamin123, TMRE)
- ATP levels
- Mitochondrial mass markers (Citrate synthase activity, Mitotracker green, cardiolipin content)
- Gene expression of relevant genes (quantitative RT-PCR), e.g. mRNA levels of PGC1- $\alpha$ , PPAR $\gamma$ , CREB, NRF-1, TFAM, Sirt1
- Levels of mitochondrial proteins (Western blot) (a-h)
- Membrane fluidity
- Mitochondrial swelling (mPTP opening)
- ROS production (FACS), lipid peroxidation products (protein carbonyls, malondialdehyde)
- Antioxidant enzymes (glutathione peroxidase, glutathione reductase, superoxide dismutase, catalase)



Oxygraph-2k, Oroboros

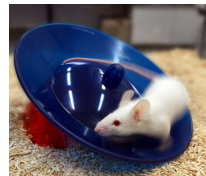


### Behavioral Dysfunction

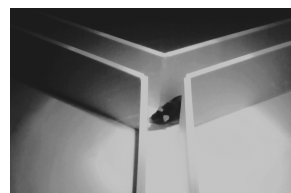
- Passive avoidance
- Social recognition
- Object recognition
- Y-maze
- Rotarod
- Open Field
- Nesting
- Burrowing
- Enrichment: Running Wheels, Mazes



Rotarod



Running Wheel

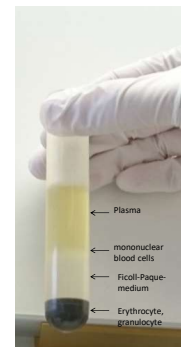


Y-Maze

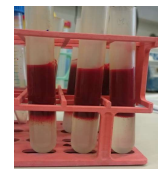
### Human Biomarker

in close cooperation with the clinic for general medicine (Prof. Pantel, Dr. Matura) and the clinic for neuroradiology (Dr. Pilatus), Frankfurt

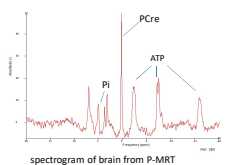
- Mitochondrial function of isolated lymphocytes (High Resolution Respirometry, Mitochondrial membrane potential, ATP levels, WB, qPCR)
- Imaging of energy metabolites (P-MRT)
- Cognitive tests
- Nutrition and activity survey



Separated blood fractions

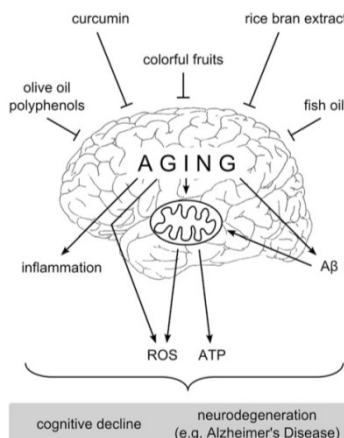


Blood-Ficoll-gradient



spectrogram of brain from P-MRT

## LEADS UNDER INVESTIGATION



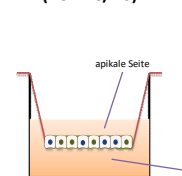
## MODELS

### *in vitro*

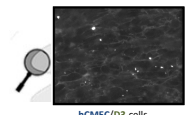
- SH-SY5Y cells
- SY5Y-Mock cells
- SY5Y-APP (695) wt cells
- PC12neo cells
- PC12sw cells
- Cellular model of human blood-brain barrier (hCMEC/D3)

### *in vivo*

- NMRI mice
- C57/BL6 mice
- CD1 mice
- Thy1-APP751 SL mice
- SAMP8 and SAMR1 mice



Schematic picture of transwell-system with monoculture of BBB



hCMEC/D3 cells

## PUBLICATIONS

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- Hagl S, Asseburg H, Heinrich MA, Sus N, Blumrich EM, Dringen R, Frank J, Eckert GP. Effects of long-term Rice Bran Extract supplementation on survival, cognition and brain mitochondrial function in aged NMRI mice. *NeuroMolecular Medicine*, 2016, 18(3):347-63.
- Bhatia HS, Baron J, Hagl S, Eckert GP, Fiebich BL. Rice Bran Derivatives Alleviate Microglia Activation: Possible Involvement of MAPK Pathway. *J Neuroinflammation*, 2016, 13(1):148.
- Muller WE, Eckert A, Eckert GP, Fink H, Friedland K, Horr R, Ihl R, Kasper S, Moller HJ. Ginkgo-Spezialextrakt 761 (Tebonin) - Ein präklinisches und klinisches Update im Wandel klinischer und aetiopathogenetischer Konzepte der Alzheimer-Demenz. *Psychopharmakotherapie*, 2016, 23(3):102-19 [in German].
- Pohland M, Hagl S, Pellowiska M, Wurglics M, Schubert-Zsilavecz M, Eckert GP. MH84 - A novel  $\gamma$ -secretase modulator/PPAR $\gamma$  agonist - improves mitochondrial dysfunction in a cellular model of Alzheimer's disease. *Neurochem Res*, 2016, 41(1-2):231-42.
- Hagl S, Berressem D, Grewal R, Grebenstein N, Frank J, Eckert GP. Rice bran extract improves mitochondrial dysfunction in brains of aged NMRI mice. *Nutr Neurosci*, 2016, 19(1):1-10.

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