TRANSLATIONAL MEDICINE – FROM ANIMAL MODELS TO iPSC TECHNOLOGIES

Room:	**Aalmarktzaal**
Time:	**Monday 15:00 to 16:30**
Chairs:	**Amalia Dolga, Ingrid Dijkgraaf, Karien de Rooij**
Organizing FIGON-partner(s):	**NVF, ZonMw, NVT**

Invited lectures:

15:00 – 15:30 **A human ex vivo model for liver diseases, the missing link in liver disease research**
Prof. Peter Olinga, University of Groningen

15:30 – 16:00 **Animal models for psychiatric diseases**
Dr. Aniko Korosi, University of Amsterdam

Selected abstracts:

16:00 – 16:15 **A translational modeling approach to predict the brain unbound pharmacokinetic profiles of Alzheimer's patients and cognitively healthy elderlies**
M.A.A. Saleh – Leiden University

16:15 – 16:30 **Mitochondrial metabolism alterations in familial Alzheimer's disease neuroprogenitor cells**
Dr. Marina Trombetta-Lima – University of Groningen

Indicated speaker time includes 5 minutes for discussion

NVF Dutch Pharmacological Society ZonMw NVT TOXICOLOGIE

A human ex vivo model for liver diseases, the missing link in liver disease research

Prof. Peter Olinga, University of Groningen

Liver disease is a leading cause of mortality worldwide, especially due to nonalcoholic fatty liver (NAFL). Adequate animal models that truly describe the progression from NAFL to non-alcoholic steatohepatitis (NASH), fibrosis and liver cancer are lacking. Such species differences, a common denominator in animal research, hamper translation. Therefore, development of a “humanized” NAFL model is thus essential to elucidate the pathophysiological mechanisms of NAFL disease progression. Human precision-cut liver slices are an ex vivo model that can mirror the multicellular and multi-organ characteristics of human NAFL/NASH, liver fibrosis and cancer.

A translational modeling approach to predict the brain unbound pharmacokinetic profiles of Alzheimer's patients and cognitively healthy elderlies

M.A.A. Saleh[1], J. Bloemberg[1], J. Elassaiss-Schaap[1,2], E.C.M. de Lange[1]

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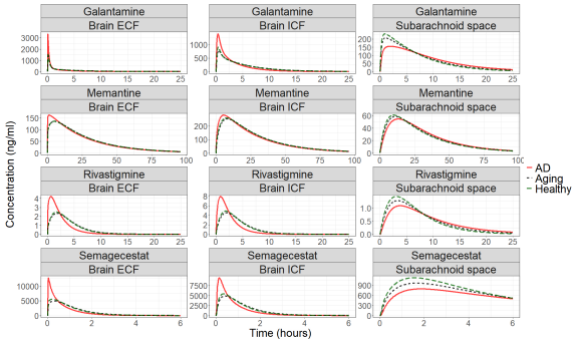
Alzheimer's disease (AD) drug development has suffered a high failure rate that could be attributed in part to poor pharmacokinetics in patients, either insufficient drug exposure or inadequate pharmacokinetic profile (PK) at the brain extracellular ($brain_{ECF}$) and intracellular fluid ($brain_{ICF}$) [1]. Poor PK could result in a lack of drug efficacy and/or an unacceptable side effects. Unbound PK at $brain_{ECF/ICF}$, the drug target sites, is the driver of CNS drug (side) effects. Measuring such profiles, while indispensable for drug development, is challenging due to the ethical restrictions of human brain sampling, the inadequate information obtained by imaging, and the context dependency of cerebrospinal fluid (CSF) as a surrogate for unbound brain PK [2,3]. We have previously published LeiCNS-PK3.0, a CNS physiologically based PK (PBPK) model that can predict human $brain_{ECF}$ and CSF PK with less than two-fold error [2]. The mechanistic and physiological framework of LeiCNS-PK3.0 allows interpopulation translation by accounting for pathophysiological alterations of the system.

Aims

The goal of this research is to predict the impact of healthy aging and AD on brain PK. To this goal, we have translated LeiCNS-PK3.0, by incorporating the aging and AD-related CNS physiological changes in the model.

Methods

An extensive literature search in PUBMED was performed to identify the AD- and aging-related changes of CNS physiology. LeiCNS-PK3.0 was re-parameterized based on the literature search results. Model simulations were performed for 4 AD-relevant drugs: memantine, rivastigmine, galantamine, and semagacestat, comparing the PK of a young adult, a 75-year-old cognitively healthy elderly, and a 75-year-old mild AD patient. Model simulations were performed in R (version 4.0.3) using RxODE (version 0.9.2-0).



Results / Conclusions

LeiCNS-PK3.0 simulations suggest that the $brain_{ECF/ICF}$, and CSF PK of AD patients are different than those of young and age-matched cognitively healthy elderlies. As shown in the figure, $brain_{ECF/ICF}$ C_{max} of galantamine increased by 200%, of memantine by 120%, of rivastigmine by 160%, of semegacestat by 200%. Thus, AD might impact the brain and CSF PK in a drug dependent manner. This study highlights the importance of accounting for the altered physiology when translating PK between populations.

References

1. De strooper. Cell. 2014. Doi: 10.1016/j.cell.2014.10.016
2. Saleh et al. J. Pharmacokinet. Pharmacodyn. 2021. Doi: 10.1007/s10928-021-09768-7
3. Saleh and de Lange. Pharmaceutics. 2021. Doi:10.3390/pharmaceutics13010095

Mitochondrial metabolism alterations in familial Alzheimer's disease neuroprogenitor cells

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Introduction

The significant increase in life expectancy in the last 60 years urges the handling of age-associated diseases. Alzheimer's disease (AD) is currently considered the major cause of dementia. However, despite being one of the most studied neurodegenerative diseases, little therapeutic progress was achieved in the last decades. Familial Alzheimer's disease comprises of 5% of the cases and display an early onset, making it a valuable model for the study of the disease. One of the hallmarks of AD is its mitochondrial metabolism disruption.

Aims

To investigate the metabolic mechanisms which are altered in AD.

Methods

We successfully generated and characterized neuroprogenitor cells (NPCs) from familial AD, their respective isogenic controls, and healthy subjects-derived iPSCs. Our differentiation protocol makes use of a 15 days 3D embryoid body formation step, followed by FACS sorting of the NPC population (CD271-, CD44-, CD184+, CD24+, CD15-/+) which renders a population of more than 90% NPC. The overall expression of metabolic pathways proteins was determined by proteomics. Metabolic activity was assessed by measurements of mitochondrial respiration, glycolytic rate, and metabolic substrate usage.

Results/ Conclusions

We report an overall decrease in glycolytic proteins expression and substrate usage, OCR and ECAR parameters. Our results indicate that metabolic alterations are already perceivable in AD-derived NPCs, which can be a target for early intervention.

References:

1. N. Gunhanlar *et al*., Mol Psychiatry 23, 1336-1344 (2018).
2. M. Oksanen *et al*., Stem Cell Reports 9, 1885-1897 (2017).
3. M. Trombetta-Lima *et al*., Cell Calcium 94:102362 (2021).