Project title: Computational systems biology versus human aging: Targeting cellular aging and senescence through metabolic modeling

Project leader: Dr. Marian Breuer

Function: Assistant Professor

Collaborators: Dr. Michiel Adriaens, Prof. Dr. Ilja Arts

Proposal (250 words):

Introduction: The aging of populations creates a major public health burden around the world. Aging involves intertwined processes on cellular and tissue levels. In particular, cellular senescence, a heterogeneous phenotype of permanent growth arrest, is an important driver of aging in tissues. Interventions against aging, e.g. by targeting this senescent state, could extend the healthy lifespan and contribute to regenerative medicine. Cellular senescence has significant ties to metabolism, suggesting potential intervention strategies; however, these ties need to be characterized further.

Hypothesis and Objectives: This project will study the metabolic changes accompanying cellular aging and in particular senescence with the goal of identifying possible new signatures and biomarkers, as well as possible metabolic targets for more selective and specific drugs against senescent cells.

Setting and Methods: Metabolic networks of young, aged and senescent human cells will be reconstructed using omics data like transcriptomics and metabolomics. *In silico* metabolic modeling will be used to analyze and compare metabolic features between conditions. This comparison will not only shed light on the metabolic signatures of cellular aging and senescence, but also identify intervention targets that could revert the aging process at cellular level.

Impact: The discovery of specific metabolic intervention targets will aid the development of more specific anti-senescence drugs. The development of metabolic signatures and biomarkers could aid in the identification and monitoring of senescent cells, which would be necessary to study the efficacy of anti-senescence drugs. Overall, this project will aid the development of anti-aging precision medicine – ultimately promoting healthy aging in the population.

Requirements candidate: Highly motivated student with good English communication skills and proactive and resolute attitude. The ideal candidate would have a foundation in biochemistry and cellular metabolism on the one hand, and some computational skills on the other hand, preferably in Matlab. Applications with background in only the biochemical or computational side are still welcome, if the applicant can make a case for being able to catch up in the other aspect.

Keywords: Biological Foundations of Human Health and Diseases, Major New Drugs Discovery, Computational Biology, Systems Biology, Metabolic Modeling, Aging

Top 5 selected publications:

1. **M. Breuer**, T. M. Earnest, C. Merryman, K. S. Wise, L. Sun, M. R. Lynott, C. A. Hutchison III, H. O. Smith, J. D. Lapek Jr., D. J. Gonzalez, V. de Crécy-Lagard, D. Haas, A. D. Hanson, P. Labhsetwar, J. I. Glass, Z. Luthey-Schulten **"Essential Metabolism for a Minimal Cell"** *eLife* (2019), 8:e36842. Citations (Web of Science): 75

2. D. Haas, A. M. Thamm, J. Sun, L. Huang, L. Sun, G. A. W. Beaudoin, K. S. Wise, C. Lerma-Ortiz, S. D. Bruner**, M. Breuer**, Z. Luthey-Schulten, J. Lin, M. A. Wilson, G. Brown, A. F. Yakunin, I. Kurilyak, J. Folz, O. Fiehn, J. I. Glass, A. D. Hanson, C. S. Henry, V. de Crécy-Lagard. **"Metabolite Damage and Damage Control in a Minimal Genome"** *mBio* (2022), 13:e01630-22. Citations (Web of Science): 5

3. C. Sarathy, **M. Breuer**, M. Kutmon, **M. E. Adriaens**, C. T. Evelo, I. **C. W. Arts**. **"Comparison of metabolic states using genome-scale metabolic models"** *PLoS Comput. Biol*. (2021), 17:e1009522. Citations (Web of Science): 1

4. P. Prickaerts*, **M. E. Adriaens***, T. van den Beucken*, E. Koch*, L. Dubois*, V. E. H. Dahlmans, C. Gits, C. T. A. Evelo, M. Chan-Seng-Yue, B. G. Wouters*, J. W. Voncken*. **"Hypoxia increases genome-wide bivalent epigenetic marking by specific gain of H3K27me3"**, *Epigenetics & Chromatin* (2016), 9:46. Citations (Web of Science): 47

5. X. Jiang, B. Burger, F. Gajdos, C. Bortolotti, Z. Futera, **M. Breuer**, J. Blumberger **"Kinetics of trifurcated electron flow in the decaheme bacterial proteins MtrC and MtrF"** *Proc. Natl. Acad. Sci. USA* (2019) 116:3425. Citations (Web of Science): 48