Inter-institutional projects for postdoctoral positions within the Heidelberg Mannheim Health and Life Science Alliance

Postdoctoral Project

Proposing parties:

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Project Title:

Family relationships as health-promoting factors in old age: Investigating markers of biological aging and health outcomes in a large cohort of older adults

Project outline:

Intimate social relationships improve individual health and longevity, an effect which is supposed to be mediated through epigenetic changes in stress-sensitive endocrine and immune mechanisms, with relevance for a broad range of diseases.

As part of the ongoing longitudinal ESTHER cohort study, originally 9,940 women and men aged 50-75 years were recruited in 2000-2002. Comprehensive sociodemographic, lifestyle, and health related data were obtained by questionnaires from the participants and their general practitioners at baseline and every 2-3 years since then. In three follow-up rounds (8, 11, and 14-year follow-up), these were expanded by home visits with comprehensive geriatric assessments. Biospecimen, in particular blood samples, were collected at baseline and each follow-up and have already been used for a wealth of genetic and epigenetic analyses based on genome-wide genetic and epigenetic profiling of the entire cohort. In an earlier satellite project, 200 partners of ESTHER participants were enrolled using identical instruments of data and biospecimen collection.

In the planned project - a joint effort of the groups from DKFZ, Heidelberg University Hospital and EMBL - the postdoc will be advised and supervised in the analysis and publication of data with a focus on immune-relevant epigenetic changes in the examined persons and couples of the ESTHER cohort.

Researchers from medicine, biosciences, epidemiology, computational biology, neurobiology, or psychology with a background and interest in the analysis of genetic and epigenetic data are invited to apply.

General Research Group description 1:

Research at Heidelberg University Hospital's Institute of Medical Psychology headed by Beate Ditzen is focused on the effects of social interactions on health parameters and – vice versa – on the influence of individual health on close social relationship functioning.

Within this focus, one central aspect is the role of neural circuitry and peripheral dynamics involving stress-sensitive endogenous neurosteroids and neuromodulators such as reproductive hormones, cortisol, and oxytocin affecting immune functioning in close family relations, and couple relationships in particular (Ditzen et al., 2009). Above this, we interpret genetic and epigenetic data in association with social relationships and test, how behavioral interventions aimed at improving social interactions can alter epigenetic factors.

Recently, we could e.g. show that mindfulness-based stress prevention training can improve everyday life dynamics in stress-sensitive hormones and enzymes (Aguilar-Raab et al., 2021) and alter serotonin-related epigenetic dynamics (Stoffel et al., 2019). In the cooperation within Heidelberg-Mannheim Health Alliance, we plan to be involved based on our expertise in the study of close relationships and social interaction in relation to health-relevant epigenetic changes in older adults.

References (max. 3, please use JCB format):

Aguilar-Raab, C., Stoffel, M., Hernandez, C., Rahn, S., Moessner, M., Steinhilber, B., & **Ditzen, B.** (2021). Effects of a mindfulness-based intervention on mindfulness, stress, salivary alpha-amylase and cortisol in everyday life. *Psychophysiology*, e13937. doi:10.1111/psyp.13937

Ditzen, B., Schaer, M., Bodenmann, G., Gabriel, B., Ehlert, U., & Heinrichs, M. (2009). Intranasal oxytocin increases positive communication and reduces cortisol levels during couple conflict. *Biological Psychiatry, 65*(9), 728-731.

Stoffel, M., Aguilar-Raab, C., Rahn, S., Steinhilber, B., Witt, S. H., Alexander, N., & **Ditzen, B.** (2019). Effects of Mindfulness-Based Stress Prevention on Serotonin Transporter Gene Methylation. *Psychotherapy and Psychosomatics, 88*(5), 317-319. doi:10.1159/000501646

General Research Group description 2 (max. 250 words):

The Division of Clinical Epidemiology & Aging Research at the German Cancer Research Center (DKFZ) headed by Hermann Brenner conducts large scale epidemiological studies with a particular focus on cancer and other aging related diseases, such as the ESTHER study described above.

The Division coordinates and is involved in multiple national and international consortia in clinical, epigenetic and genetic epidemiology. It is internationally renowned for pioneering work in the epidemiology and prevention of colorectal cancer (Brenner et al., 2014), and epigenetic and molecular epidemiology of aging related diseases and mortality (e.g. Stocker et al., 2020; Zhang et al., 2017). In particular, the research group has derived, by an epigenome-wide methylation study, the so far most predictive and concise blood-based epigenetic predictor of a range of health outcomes including mortality at old age (Zhang et al., 2017).

In collaboration with national and international partners, we demonstrated the potential of identifying increased risks of major aging-related diseases, such as Alzheimer's disease, by blood-based molecular signatures many years prior to disease onset which opens novel promising approaches for early detection and prevention (Stocker et al., 2020).

References (max. 3, please use JCB format):

Brenner H, Kloor M, Pox CP. 2014. Colorectal cancer. *Lancet 383*(9927):1490-1502. doi: 10.1016/S0140-6736(13)61649-9.

Stocker H, Nabers A, Perna L, Möllers T, Rujescu D, Hartmann A, Holleczek B, Schöttker B, Gerwert K, **Brenner H**. 2020. Prediction of Alzheimer's disease diagnosis within 14 years through Aβ misfolding in blood plasma compared to APOE4 status, and other risk factors. *Alzheimers Dement 16*(2):283-291. doi: 10.1016/j.jalz.2019.08.189.

Zhang Y, Wilson R, Heiss J, Breitling LP, Saum KU, Schöttker B, Holleczek B, Waldenberger M, Peters A, **Brenner H**. 2017. DNA methylation signatures in peripheral blood strongly predict all-cause mortality. *Nat Commun 8*:14617. doi: 10.1038/ncomms14617.

General Research Group description 3 (max. 250 words):

The Zaugg group aims at understanding the causes underlying phenotypic variation (including ageing) across individuals, with the goal of pushing the boundaries of precision medicine. We believe a crucial part of precision medicine is to quantitatively understand the interplay of genetics, epigenetics and environmental factors, including cellular interactions within their microenvironment. We have pioneered several approaches to investigate gene regulatory mechanisms in disease (e.g. Reyes-Palomares, Nature Communications 2020). Most recently this has culminated in a framework that employs enhancer-mediated gene regulatory networks to predict the importance of transcription factors for cellular response to perturbation (Kamal, bioRxiv 2021).

We are interested in expanding our framework to study genetic and epigenetic determinants of healthy ageing at cohort-level. In our most recent work, we have studied ageing on bone marrow-derived mesenchymal stem/stromal cells (MSC), which can differentiate into osteoblasts and adipocytes, revealed enhancer-mediated priming towards adipogenic processes in the elderly (Lai, bioRxiv 2021). This was specifically prominent in enhancers that were associated with traits linked to immune system function and points towards a mechanism whereby ageing of mesenchymal stem/stromal cells in the bone marrow may contribute to the known decline of the immune system with age.

References (max. 3, please use JCB format):

Lai MC, Ruiz-Velasco M, Arnold C, Sigalova O, Bunina D, Berest I, Ding X, Hennrich ML, Poisa-Beiro L, Claringbould A, Mathioudaki A, Pabst C, Ho AD, Gavin A-C, **Zaugg JB**. 2021. Enhancer-priming in ageing human bone marrow mesenchymal stromal cells contributes to immune traits. *BioRxiv.* https://doi.org/10.1101/2021.09.03.458728.

Kamal A, Arnold C, Claringbould A, Moussa R, Daga N, Nogina D, Kholmatov M, Servaas N, Mueller-Dott S, Reyes-Palomaresv A, Palla G, Sigalova O, Bunina D, Pabst C, **Zaugg JB**. 2021. GRaNIE and GRaNPA: Inference and evaluation of enhancer-mediated gene regulatory networks applied to study macrophages. *BioRxiv.* https://doi.org/10.1101/2021.12.18.473290.

Reyes-Palomares A, Gu M, Grubert F, Berest I, Sa S, Kasowski M, Arnold C, Shuai M, Srivas R, Miao S, Li D, Snyder MP, Rabinovitch M, **Zaugg JB**. 2020. Remodeling of active endothelial enhancers is associated with aberrant gene-regulatory networks in pulmonary arterial hypertension. *Nat Commun 11*(1):1673.