Laura Perna
Dr. sc. hum.

**Blood biomarkers of cognitive function and dementia**

Fach/Einrichtung: DKFZ (Deutsches Krebsforschungszentrum)
Doktorvater: Prof. Dr. med. Hermann Brenner

Blood-based biomarkers of cognitive impairment and dementia are ideal medical tools for early diagnosis and prevention as they are easy to obtain, minimally invasive, and inexpensive. Although several plasma and serum biomarkers have been proposed, the interaction of such biomarkers with other biological processes remains largely unexplored and, to date, there are no blood biomarkers of preclinical Alzheimer's disease (AD). In this work the interplay of known biomarkers of cognitive functioning (serum uric acid; SUA and apolipoprotein E e4 genetic polymorphism; *APOE* e4) with biological characteristics (sex) and hazardous exposures, including hypercholesterolemia and cardiovascular diseases (CVD), are presented. Furthermore, a novel blood biomarker specific for AD, the secondary structure distribution of the soluble Amyloid-β (Aβ) peptides, is introduced.

All analyses were conducted with subsamples from the ESTHER study, a prospective cohort of 9,949 participants recruited in 2000/2002 in Saarland, Germany. Analyses related to the *APOE* e4 polymorphism were replicated using the KAROLA study, a prospective German cohort of 1,206 patients with coronary heart disease recruited in 1999/2000. Cognitive functioning was assessed in both cohorts with the Cognitive Telephone Screening Instrument (COGTEL). Linear regression models with COGTEL total scores as outcome variable and restricted cubic spline functions were performed for analyses of SUA and *APOE* e4. The Aβ peptide was measured among167 cases (65 AD, 66 vascular dementia; VD, and 36 mixed dementia; MD) and 707 controls (247 AD, 311 VD, and 149 MD) included in a nested case-control study. An immuno-infrared-sensor was used to detect the β-sheet enriched secondary structures in baseline blood of ESTHER participants. Discrimination of

AD and all other groups (VD and MD cases, AD, VD and MD controls), which were merged to an overall disease control (DC) group, was evaluated by receiver operator characteristics (ROC) curve analysis and quantified by the area under the curve (AUC).

Results of regression models revealed that SUA levels and *APOE* e4 were inversely associated with cognitive performance and the association was much stronger among participants with CVD. Whilst SUA associations were not statistically significant among men, the reduction in cognition among women with CVD was equivalent to the effect of 6.6 years of age on cognition. Effects of *APOE* e4 on cognitive performance were especially detrimental among people with CVD and hypercholesterolemia in both independent cohorts with data suggesting that high total and low-density lipoprotein cholesterol might exert negative effects on cognition only among e4 carriers.

ROC curve analyses generated an AUC of 0.81 for AD-DC discrimination. A threshold of 1642 $cm^{-1}$ yielded an overall accuracy of 88% (sensitivity 71%, specificity 89%) for detecting AD years prior to clinical diagnosis. An AUC with 0.79 resulted for AD-VD differentiation indicating that β-folding of Aβ in preclinical dementia stages might be specific only to AD.

In conclusion, analyses concerning SUA and *APOE* e4 polymorphism showed that detrimental effects of SUA, but especially of *APOE* e4, on cognitive functioning depend on modifiable risk factors, and intervening on such factors could help to prevent or delay cognitive decline. Analyses conducted with the immuno-infrared-sensor showed that β-folding of Aβ might be a promising blood biomarker for detecting preclinical AD, and these findings, if validated in well-characterised AD cohorts, may pave eventually the way to new research avenues for the prevention and treatment of AD.