Awarded Projects – Transdisciplinary Research Prize TRA² 2024

Formalizing Proxy Failure Across Disciplines

Oliver Braganza (Institute for Experimental Epileptology and Cognition Research) & Wolfram Barfuss (Zentrum für Entwicklungsforschung)

“When a measure becomes a target, it ceases to be a good measure.” This adage, which we term proxy failure (PF), has been discovered and re-discovered across a staggering range of disparate contexts and scales. It has been invoked when corporations optimize profit as a proxy for value (or welfare) but undermine sustainability (i.e., long-term welfare) or when ‘reward systems’ in brains or artificial intelligence optimize internal proxies but end up undermining their original goals (e.g. reward-hacking or addiction). An emerging consensus suggests that PF represents a fundamental control-theoretic phenomenon in complex systems. However, despite substantial research within disciplines, we lack an understanding of why PF recurs across disciplinary contexts. Specifically, we lack a cross-disciplinary formal model of proxy failure, impeding knowledge transfer between specialities. Finding solutions to reduce PF in a domain-general model could unlock pathways to improvement in a wide range of disciplines. We propose to co-supervise two MSc projects anchored within the respective fields of the applicants (life- and sustainability systems science) but using the same formal framework to model PF. The long-term goal for the TRA² Prize project will be to use the generated results to apply for funding to develop a fully domain-general model.

Unravelling the Evolutionary Dynamics of the Human Oral Microbiome: A Multi-Temporal Metagenomic Analysis of Archaeological and Modern Dental Calculus and Modern Saliva Samples

Alice Toso (Bonn Center for Archaeoscience – Institute of Archaeology), Anna-Christin Konermann (Department of Orthodontics) & Marie-Christine Simon (Institut für Ernährungs- und Lebensmittelwissenschaften)

The human oral microbiome represents a dynamic ecosystem comprising a diverse array of microorganisms coexisting in symbiotic relationships, exerting profound influences on both oral and systemic health (Dewhirst et al. 2010). Recent advancements in metagenomic techniques have fundamentally reshaped our understanding of microbial communities, enabling comprehensive analysis of microbial diversity, composition and function. However, a significant knowledge gap persists in our understanding regarding the evolutionary dynamics of the oral microbiome and its adaption to changing dietary and lifestyle practices over time (Santonocito et al. 2022). This research proposal aims to bridge this gap by employing metagenomic approaches to investigate the human oral microbiome across multiple temporal scales, comparing archaeological and contemporary dental calculus as well as modern saliva samples. Additionally, the project seeks to study ancient microbial communities and the oral microbiome response to environmental stimuli across different historical epochs. Through these endeavors, we aspire to gain deeper insights into the influences of diet and lifestyle factors, particularly the impact of nutritional patterns throughout the course of evolution.

Breaking Mitoxantrone Resistance in Breast Cancer Cells and Increasing its Cytotoxic Activity by Side Chain Modification

Gerd Bendas (Pharmazeutisches Institut & Andreas Gansäuer (Kekulé Institut für Organische Chemie und Biochemie)

Malignant tumor diseases remain the most challenging task in biomedical sciences. Although tremendous progress has been achieved in the treatment of cancer, tumors are a leading cause of death in European countries. A major obstacle in clinical treatment of cancer patients is the development of tumor resistance, which is not limited to cytotoxic agents, such as mitoxantrone, but also covers other drugs or treatments.
Here, we will develop a strategy for improving the drug profile of mitoxantrone by chemical modification. Mitoxantrone is a highly important cytotoxic drug applied for the guideline-based therapy of breast and prostate cancer as well as various lymphoma diseases.
We propose to address these issues by modifying the side chain of mitoxantrone through introduction of more elaborate polyol side chains. In this manner, we will

1) modify the drug to achieve higher affinity in DNA-binding

2) overcome drug resistance by changing the binding profile to efflux transporters

3) improve the solubility properties of the drug to ease drug administration.

This is possible through a novel strategy for the preparation of the polyol chains developed by the Gansäuer group. In vitro-testing of the drug derivatives will be carried out in the Bendas group.