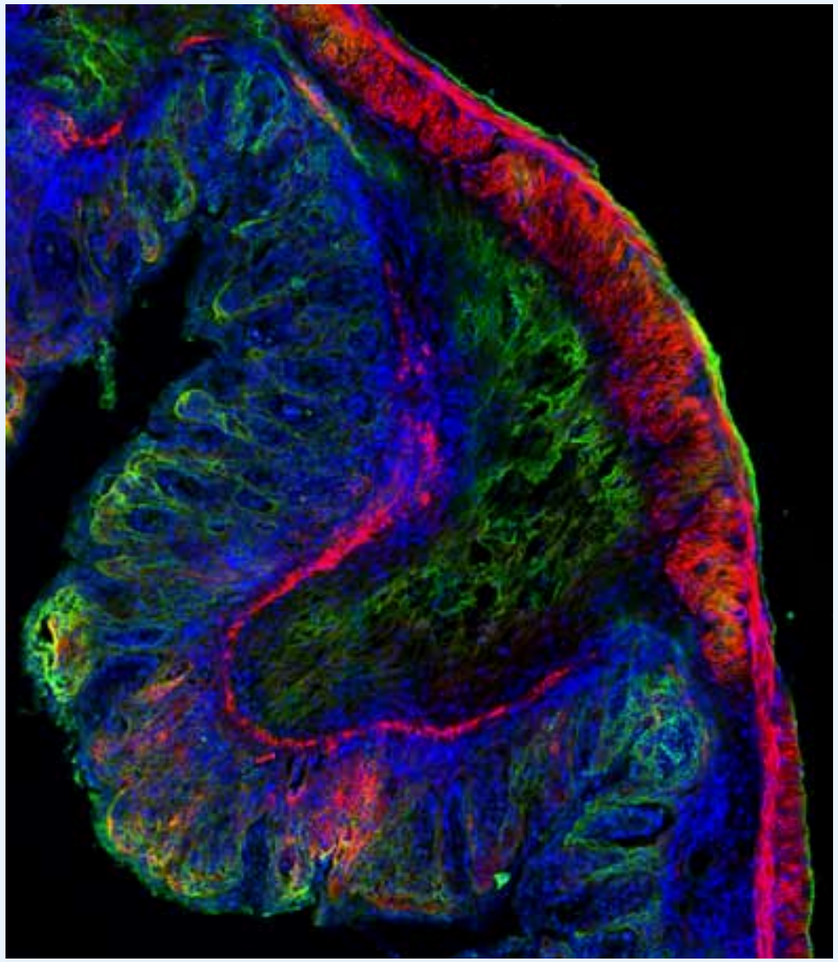
Precision Microbiota Engineering for Child Health



Staining of digestive tract tissue infected with *Salmonella typhimurium* shows extracellular matrix in green and red and cellular nuclei in blue.

Prof Emma Wetter Slack (ETH Zurich), Prof Médéric Diard (University of Basel), Prof Viola Vogel (ETH Zurich), Prof Ferdinand von Meyenn (ETH Zurich), Prof Johannes Bohacek (ETH Zurich) and Prof Shinichi Sunagawa (ETH Zurich) will develop novel intervention strategies for two very serious diseases of newborns, namely inborn errors of metabolism and necrotising enterocolitis. These conditions currently have high mortality rates, long-term consequences for child development and limited treatment options.

From shortly after birth, the large intestine is colonised by billions of bacteria, which make up the intestinal microbiota. Researchers have only recently begun to understand the extent and the mechanisms by which these bacteria influence child health and development. However, current studies support causal roles of bacteria in diseases as diverse as allergy and autism. The focus of this project is to develop novel tools to precisely engineer the microbiota of individuals with inborn errors of metabolism or necrotising enterocolitis. The project aims to replace individual species, either to remove a disease-driving organism or to alter the metabolism of the microbiota. This modification will be achieved by combining highly specific selective pressures exerted by intestinal antibodies, with the direct targeting of individual genes in intestine-resident bacteria using CRISPR-Cas9 methodology. Since microbiota engineering can be applied across a wide range of childhood diseases, this collaborative effort has far-reaching implications for the future of medicine.

The motivation of this highly collaborative project is to understand the mechanisms by which intestinal microbiota composition influences the development and prognosis of necrotising enterocolitis, neonatal sepsis and inborn errors of metabolism. Recent research by the consortium demonstrated strong associations between microbiota composition and disease severity and revealed mechanisms of host-microbiota crosstalk, indicating a major untapped therapeutic potential. However, a huge gap remains in therapeutic precision engineering of the microbiota. The consortium will further develop over the coming years two precision microbiota engineering tools to the point of human trial readiness. These complementary approaches will be tested in different murine models for four serious childhood diseases with strong links to microbiota function and the urgent need for better therapy/prophylaxis, namely urea cycle disorders, methylmalonic aciduria, neonatal sepsis and necrotising enterocolitis. These diseases are prevalent in many low- and middle-income countries.

The methods employed by the consortium range from the latest state-of-the-art molecular biology and antibody engineering technologies, to detailed analysis of tissue scarring, single-cell analysis of organ development and quantitative analysis of brain function. This range of expertise allows not only to develop microbiota engineering technologies, but also to develop detailed mechanistic insight into modification of the disease course, and biomarkers to assess efficacy in clinical trials. Secretory IgA, either delivered orally as a recombinant protein, naturally in breast milk or induced via oral vaccination, is used to generate a selective pressure on individual components of the microbiota. This permits replacement of the target bacterium with a desirable niche competitor. Additionally, the consortium will employ established CRISPR technology to genetically engineer a broad range of microbiota species directly in the gut lumen. Combining these techniques will allow antibiotic-independent selection of successfully modified bacteria, generating a robust and predictable change in microbiota function/composition. Fundamental insight into microbiota, and preclinical insight of therapy efficacy will be generated. Toxicity analyses, GMP and scale-up will be carried out for clinical trial readiness. Most of the tools can be produced, distributed and administered in low-cost and low-technology environments. As correction of pathological microbiota functions is relevant to a broad range of diseases, this represents a disruptive therapeutic approach with major consequences for medicine.

In addition to the principal investigators from ETH Zurich and the University of Basel, a number of local collaborators complete the consortium with their strong know-how in paediatrics and microbiology. Collaborators from the University Children's Hospital Zurich (Prof Matthias Baumgartner, Prof Johannes Häberle, Dr Sean Froese, Dr Johannes Trück), University Hospital Zurich (Prof Giancarlo Natalucci) and ETHZ (Prof Christian Wolfrum) strengthen the consortium by bringing expertise in clinical metabolism, paediatric immunology, murine models as well as the recruitment of paediatric cohorts. Researchers from the Paul Scherrer Institute (Dr Martin Behe) will investigate intestinal damage by novel imaging approaches and from the University Hospital Basel (Prof Adrian Egli) will focus on *E. coli* genome sequencing and its annotation in premature birth cohorts.

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