Universität Basel

Research Project

Precision Microbiota Engineering for Child Health

Third-party funded project

Project title Precision Microbiota Engineering for Child Health
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Departement Biozentrum
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Intestinal microbiota composition correlates strongly with disease ranging from cancer to autoimmunity. A growing bank of data now demonstrates causal relationships and reveals mechanisms of host-microbiota crosstalk, indicating a major untapped therapeutic potential. However, a huge gap remains in therapeutic precision engineering of the microbiota.

Our key objectives are to develop two complimentary precision microbiota engineering tools to the point of human trial readiness. These complimentary approaches will be tested in gnotobiotic and humanized microbiota murine models for three serious childhood diseases with strong links to microbiota function and urgent need for better therapy/prophylaxis: 1) Urea cycle disorders, 2) Methylmalonic aciduria and 3) necrotizing enterocolitis.

REMoVE (Rational Engineering of the Microbiota by Vaccination-Exclusion) employs oral vaccine-induced or recombinant secretory immunoglobulin A (SIgA) to generate a selective pressure in the intestine. This drives replacement of the target bacterium, with a desirable niche competitor. REMoVE-driven compositional changes have proof-of-concept in mice and will here be expanded to human-relevant microbiota.

In situ genetic engineering employs broad host-range plasmids to deliver CRISPR interference arrays inhibiting gene expression in the microbiota, directly in the gut lumen.

Fundamental insight into microbiota-disease crosstalk, and quantitative preclinical insight of therapy efficacy will be generated with state-of-the art pathophysiology analysis (real-time metabolomics, single cell transcriptomics, novel medical imaging). Toxicity analyses, GMP and scale-up will be carried out for clinical trial readiness.

These diseases are prevalent in the developing world. Most of our tools can be produced, distributed and administered in low cost/low tech 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.

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