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Christophe Lacroix

NOVEL TECHNOLOGIES ARE KEY FOR THE DEVELOPMENT OF LIVE BACTERIAL THERAPEUTICS

Christophe Lacroix, ETH Zurich, Switzerland
christophe.lacroix@hest.ethz.ch

The potential of individual microbes, defined consortia or microbial communities to promote and restore health is an area of huge interest for medicine, for the treatment of chronic diseases associated with gut dysfunction. New therapeutic strategies may include administering living gut microbes - live biotherapeutic products (LBP) - that perform vital metabolic functions and confer homeostasis and resilience in the gastrointestinal tract and throughout the body.

The production of the current commercial probiotic strains, selected for oxygen-tolerance and technological ability, is carried out in batch fermentations of suspended (planktonic) cells. However, robust technologies for the production of single strains and consortia of gut strict anaerobes are currently lacking. In particular, the batch fermentation approach is not suited for GMP production of the functional consortia aimed for new LBPs.

In contrast to current technologies, intestinal microbes have evolved to grow continuously in the gut and comprise a major fraction of sessile (biofilm-associated) bacteria. In addition, their growth heavily relies on complex trophic networks with high level of cross-feeding. This presentation will focus on novel strategies accounting for the rational assembly of trophic network of gut microbes to support the manufacturing of functional consortia and standardized intestinal microbiota. , including: continuous fermentations, cell immobilization, high cell density fermentation, and microbial biomass stabilization. We assembled a minimal functional consortium of nine strains applying a bottom-up approach to recapitulate the main carbohydrate degradation pathways of the healthy human gut microbiota. This consortium allows the complete degradation of complex carbohydrates and the re-utilization of all key metabolites by cross-feeding, leading to final short chain fatty acid products. Applying physiological conditions of the large intestine including retention time, temperature, redox potential and pH in a bioreactor, we observed compositional and metabolic stability of the designed consortium during long-term continuous culture, and enhanced volumetric productivity in a GMP-designed simple medium. The consortium produced by co-cultivation showed increased functions on an acute colitis mouse model. We also investigated cell immobilization in highly porous gel beads for modeling colonic microbiota in continuously operated models closely mimicking the conditions of the host target. This technology was investigated for the controlled production of artificial gut microbiota, reproducing the high diversity, cell density and bacterial and metabolite composition akin to the donor gut microbiota; and high stability tested for up to 160 days. Our current research aims at combining the rational design of consortia with the flexibility and performance of immobilized cell technology to develop breakthrough technology for functional therapeutic consortia. New technological approaches with strong biology rational could substantially enlarge the range of LBPs, reduce the cost of manufacturing and enhance product efficacy.