

Prof. Pascale Vonaesch

Phage therapy to control human *Streptococcus salivarius* associated with inflammation in the intestinal tract of stunted children

Lead

To date, almost 150 million children suffer from chronic malnutrition, which results in stunted child growth and cognitive delays. This condition is associated with chronic inflammation of the small intestine caused by small intestinal bacterial overgrowth by oral bacteria (SIOBO). The control of the bacterial load of ectopically colonizing bacteria in the small intestinal tract could be key to reduce the inflammation and re-balance the intestinal tract microbiota, thus decreasing the pathophysiologic consequences of undernutrition. Indeed, to date, no therapeutic solutions exist to treat stunted child growth in an efficient way, and it is thus crucial to find better treatment for this devastating syndrome affecting almost a fourth of all children worldwide. Phage therapy is an attractive possible solution, as phages are strain-specific and could thus target only the taxa really contributing to disease. Further, combined in cocktails of several phages, phage therapy is often very efficient and rarely leads to resistance in the targeted bacteria.

Aims of the proposed PhD thesis

The overarching goal of this PhD is to identify, isolate and test phages and phage cocktails targeting oral taxa which have been previously shown to contribute to the pathophysiology in the small intestinal tract of stunted children. The specific aims of this PhD thesis are thus to identify potential active phages using bioinformatic tools, induce and isolate them and finally validate them in experimental models for their ability to suppress unwanted taxa, rebalance the microbiota and eventually ameliorate the pathophysiology, including low grade inflammation and finally child growth. To this purpose, a phage bank will be established, characterized, and tested on relevant clinical strains, faecal explants, and mouse models.

Rough project outline

The project explores the possible utilization of bacteriophages as therapeutic tools to reduce the bacterial load of pro-inflammatory oral strains in the small intestine of stunted children. To this purpose, the successful candidate will first search and characterize prophage sequences in the genome of multiple oral bacteria using bioinformatic tools, then generate a phage biobank using clinical samples as well as a strain biobank and finally characterize the phages for their potential to infect a set of oral bacteria isolated from the small intestinal tract of stunted children (pre-existing strain bank from the Vonaesch lab). The subsequent years will be used to assess for the potential of different phage cocktails to reduce the load of given oral bacteria, remodel community composition and eventually normalize the pathophysiological consequences associated with SIOBO. This validation will be first performed in vitro and later confirmed in rodent models. In parallel, we will also engineer phages and phage-derived particles as an alternative approach to the phage biobank. The successful candidate will use a combination of bioinformatic analyses tools and wet-lab experiments, including cloning, work under anaerobic conditions, using human patient material, an in-house strain bank of clinical isolates as well as rodent models. The successful candidate is also expected to develop in subsequent years his own ideas and to expand the initial project idea to further areas of interest.

Description of the research group

In the Vonaesch group, we are interested in the dysbiosis underlying nutrition-related diseases, especially in the first 1000 days of life, which are a critical window for subsequent health and well-being. To this purpose, we combine clinical/translational studies with in vivo and in vitro models. We further also work on developing better microbial identification tools to work with the microbiota and we develop microbiota-targeted interventions for such dysbiotic diseases. In the longer term, with our collaborators, we also aim to perform clinical trials to assess these microbiota targeted interventions in affected populations. The group is currently composed of three postdoctoral fellows, three PhD students, a Research Associate as well as Master and Bachelor students.

Supervision

This thesis will be jointly supervised by Prof. Pascale Vonaesch and Dr. Julian Garneau, senior postdoctoral fellow in the Vonaesch lab.

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