Gut-in-a-lab research

Our world is a microbial world and the evolution of life over millions of years took place in a constant backdrop of microbes. Several biogeochemical processes on planet Earth are driven by microbes and unsurprisingly, all living creatures on this planet have developed mechanisms to either cope with microbes, or adopt strategies to tolerate, harbour or even rely on endogenous microbes for maintaining an optimal health status.

The Center for Microbial Ecology and Technology (CMET)



© CMET- Prof. Dr. MSE. Tom Van de Wiele

The Center for Microbial Ecology and Technology (CMET) is part of the Faculty of Bioscience Engineering at Ghent University. CMET is specialized in the study of microbial ecosystems in their natural environments or in human-engineered reactor technologies. Within CMET, Prof. Tom Van de Wiele heads the Host Microbe Interaction (HMI) Technology group. Referring to the trillions of microorganisms that can be found in and on different sites of our bodies, the human microbiome has become an important field of study over the last 2-3 decades. The finding of clear associations between the microbiome and health status is indicative of a dynamic and intricate microbe-host interplay.

Dynamic gut models

“The difficult accessibility of certain body sites, the lack of control over microbiome-modulatory parameters within the body or the ethical constraints of (frequent) sampling of in vivo body locations are limiting us from getting a mechanistic understanding of how the microbiome operates within our body. We have therefore designed in vitro technology platforms, such as SHIME (Simulator of the Human Intestinal Microbial Ecosystem) that enable us to mimic the different stages of the human gastrointestinal tract.

Our most important developments include the study of the mucosal microbiome – the microbiota that colonizes the slime layer in the human gut. Our technology allows us to monitor the microbiome in its response to changes in the gut, to dietary shifts or to disease phenomena and it helps us understand how the microbiome modulates human health, either through the production of specific metabolites, establishing colonization resistance against pathogens, modulating immunity or triggering local inflammation. Such dynamic human gut models also allow the screening of a wide variety of candidate drugs, functional foods and/or feeds before a narrower selection enters the stage of in vivo trials,” Van de Wiele explains.

Complementary to in vivo research

Van de Wiele’s in vitro technology platform does not operate on its own. “The base of all of our research projects starts from human in vivo observations. Unfortunately, as human microbiome research often relies on stool samples or – occasionally – on gut biopsies, it is nearly impossible to capture health and disease-processes that are characterized by local and dynamic differences in the various intestinal environments.

The use of laboratory animals, such as mice, rats and pigs, is neither painting a fully representative picture of the human situation as significant differences exist in terms of gastrointestinal physiology, dietary composition and microbe-host interactions. In addition, the ethical concerns make that Europe is striving as much as possible to refine, replace and reduce animal testing. This is where our in vitro technology platforms come in,” says Van de Wiele.

“We usually start from complex human microbiota samples – saliva and/or feces – to inoculate our reactors with. Using a multi-parametric control, we can mimic the different physiological, enzymatic and biochemical gradients that prevail in the different gut regions, and after a certain adaptation time this results in microbial communities that are representative in composition and function for each of these human gut regions.

The experimental setup is very versatile and can be adapted to mimic different

individuals ranging from newborns to elderly and from healthy persons to patients. Following a careful validation of our in vitro model against human in vivo observations, we can use our model systems to conduct mode-of-action research and support clinicians, nutritionists and pharmaceutical scientists in better understanding diet-microbe or drug-microbe interactions with the host interphase."

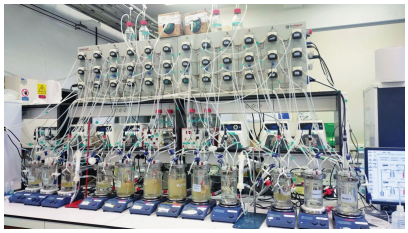
Broad range of applications

The possible applications of the technology platform are numerous and range from nutritional and pharmaceutical to translational clinical research. "We have been using the in vitro technology platform to unravel that there is a differential colonization and function of gut mucosal microbiota in patients with inflammatory bowel disease, chronic inflammation of the joints and of children that are malnourished. We also demonstrated that the microbiome is involved in the etiology and aggravation of cancer therapy-induced mucositis, while other projects led to the identification of microbes with specific metabolic properties that support gut barrier integrity.

With respect to nutritional research, we showed that the presence of wheat bran as an insoluble dietary fibre is an important driver of microbiome function and colonization. Other findings include a more accurate characterization of new classes of probiotics and live biotherapeutics. A study with *Akkermansia muciniphila* in the SHIME for example showed that this promising bacterium combines its preference for mucin degradation with the potential to strengthen the gut epithelial barrier, a finding that nicely confirms in vivo research.

In addition, we can investigate to what extent an active pharmaceutical ingredient (API) is released from its matrix and becomes available for intestinal absorption. This delivers important insights for drug dissolution and drug bioavailability research.

But the applications extend beyond human health research. "Because of the multi-parametric control, we even succeed in mimicking the digestion of certain animals. This can be important for studies on pets such as cats and dogs, and for production animals such as chickens or pigs. It can also be a lot more exotic: together with scientists from the Faculty of Veterinary Sciences at UGent, an in vitro model for the cheetah was developed."



© CMET - The Human Intestinal Microbial Ecosystem Simulator (SHIME)

Human personalized research

More recent developments include the use of the model in personalized nutrition and personalized drug research. The group showed that the unique features of a person's microbiome can be a determining factor of the health benefits that can be obtained from consuming fruits or vegetables or from specific drug treatments.

"For instance, the blood pressure lowering effect from pomegranate consumption is primarily driven by the ability of a person's microbiome to convert elagitannins (a compound in pomegranate) towards the bioactive urolithin type A," says Van de Wiele. "This knowledge on the interindividual variability of the microbiome's metabolic potential allows to screen patients and stratify them to offer a personalised and hence more efficient nutritional or pharmaceutical therapy."

Future outlook

The technology platform is in constant development. The etiopathology of many gastrointestinal diseases can often be located in the small intestine, a highly dynamic region of the gastrointestinal tract where food digestion and nutrient absorption takes place, but also a place of immense immune interactions and a possible site of several enteropathogenic infections.

"Our most recent developments therefore include the study of duodenal, jejunal and ileal microbiota and the role they potentially play in the occurrence and severity of small intestinal disorders such as small intestinal bowel overgrowth and short bowel syndrome," says Prof. Van de Wiele. More recently the group also succeeded in simulating the microbiome from other body sites such as the oral cavity, the upper respiratory tract and skin.

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