Microbiome

Spotlight on ERC projects

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Set up in 2007, the European Research Council (ERC) is the first pan-European funding body designed to support investigator-driven frontier research and to stimulate scientific excellence across Europe. It aims to support the best and most creative scientists to identify and explore new directions in any field of research (Physical Sciences and Engineering, Life Sciences and Social Sciences and Humanities) with no thematic priorities and the only evaluation criterion being excellence. To date, the ERC has awarded over 9 000 long-term grants to individual researchers of any nationality and age who wish to carry out their research projects in Europe. With a budget of over EUR 13 billion from 2014 to 2020, the ERC is part of the EU Research and Innovation framework programme, Horizon 2020.

Introduction

‘Microbiome’ is a term used to describe the community of microorganisms and their genetic information that inhabit a confined environmental niche, such as a host organism, soil or the ocean. The microbiome composition varies substantially depending on the environmental niche and can include different bacteria, archaea, fungi and viruses. Research has shown that these communities of microbes play crucial roles in host physiology and development, ecology and evolution.

The microbial life associated with the human body is extremely rich and diverse, with the number of microbial cells outnumbering that of human cells. The majority of these microorganisms reside in the gut, which is estimated to be colonised by approximately 1 000 different species of bacteria containing roughly 2 000 000 genes — that is to say a hundred times more than the 20 000 human genes. These gut microbes greatly influence the digestion and absorption of certain nutrients, the susceptibility to pathogens, and even human behaviour. It is known that the human microbiome composition can vary between individuals, and is associated with the development of diseases, such as cancer, obesity, inflammatory bowel disease and autism. Researchers are now studying how perturbations of the human microbiome composition — through antibiotics, diet and fecal transplantation — can play a role in the development and treatment of certain illnesses.

The advent of high-throughput DNA sequencing and metagenomics have allowed researchers to dissect not only the microbial diversity and dynamics in host organisms, but also in other environmental niches. For instance, the microbial life present in the soil is essential for nutrient cycling and carbon storage. Similarly, the marine microbiome plays a critical role in regulating carbon and nitrogen cycles, and the overall structure and function of the oceans. The composition and function of both of these microbiomes are known to be affected by environmental factors (like temperature), thus studying their dynamics is particularly important in the context of global climate change.

To date, the European Research Council has supported more than 150 projects on various aspects of the microbiome, for example exploring their composition and function in different habitats, and dissecting their role in the context of human health and diseases, such as metabolic, inflammatory and infectious diseases. This brochure highlights some examples of these projects.

Akkermansia, a friendly bacterium who cares

The abundant presence of a certain bacteria in our intestine, Akkermansia muciniphila, to give it its full name, is an excellent sign according to metabolism and nutrition specialist Patrice Cani. With his team, he discovered the role of these bacteria in reducing cardiometabolic risk factors - like insulin resistance or hypertension - that are leading causes in the development of cardiovascular diseases and type-2 diabetes.

The intestine is one of the most important organs in the human body. Also known as "the second brain", it hosts the majority of our immune cells. In the past decade, the occurrence of chronic diseases like type-2 diabetes or hypertension has dramatically increased. In Europe, an estimated 66 million people had diabetes in 2017, and 1.9 million European Union citizens died of cardiovascular diseases in 2016. These conditions are characterised by metabolic inflammation – the activation of the disease by a high concentration of chemicals produced by the immune system.

The causes of these metabolic alterations are still not fully understood. However, researchers at UCLouvain (Belgium) found that a specific type of bacteria plays a central role in regulating the host's energy metabolism. Naturally found in the human digestive tract, *A. muciniphila's* role was discovered serendipitously. Although first identified and isolated in 2004 by Prof. Willem de Vos from Wageningen University, Prof. Patrice Cani highlighted the bacteria's metabolic virtues only in 2007.

With the ERC support, he found that the abundance of *A. muciniphila* had the same beneficial impact of a caloric restriction diet on cardiometabolic risk factors. He designed a protocol for clinical trials on subjects at risk of developing metabolic disorders and started a pilot study in 2016. During this period, volunteers received the bacteria in the form of a nutritional complement for three months. The analysis of the data will be published in summer 2019, and if they are positive, *A. muciniphila* could be available on the market by the end of 2021 through the Belgian spin-off company "A-Mansia Biotech".

Researcher: Patrice Cani, UCLouvain (Belgium)

ERC project: Gut microbiota, innate immunity and endocannabinoid system interactions link metabolic inflammation with the hallmarks of obesity and type 2 diabetes (ENIGMO)

ERC funding: Starting Grant 2013, EUR 1.5 million (2013-2018)

Patrice Cani is a professor at the Université Catholique de Louvain (UCLouvain) in Brussels where he co-leads the Metabolism and Nutrition research group (MNUT). He holds a bachelor's degree in Dietetics, a master's degree in Health Sciences and a master's degree as well as a PhD in Biomedical Sciences. His field of interest lies in the interaction of gut microbiota with the host and specific biological systems, such as the endocannabinoid system and the innate immune system in the context of obesity, type-2 diabetes, metabolic inflammation and cancer.

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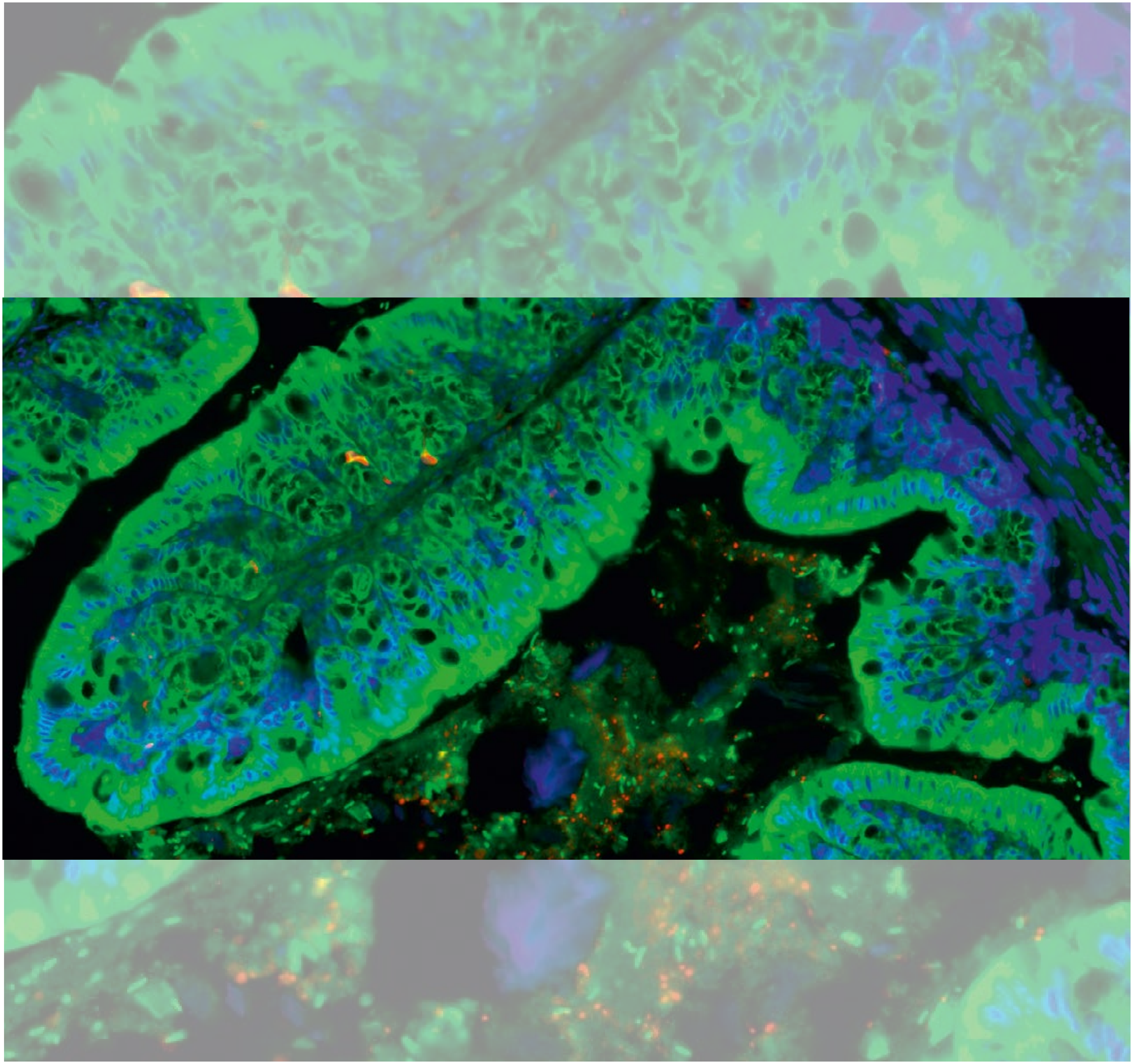

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Immunofluorescence image of enteroendocrine L cells in the epithelium and gut bacteria in the luminal content of the mouse proximal colon

Life in the deep – microbes of the abyss

The deep seafloor covers around 70% of our planet's surface and is home to a diverse community of microorganisms, mostly bacteria. These single-cell life forms inhabit some of the most extreme places in the world, with freezing waters, permanent darkness, high pressure and little food. ERC grantee Antje Boetius studies these microbes in the abyss and their important role for the Earth's nutrient cycles.

What's it like at the deepest depths of our seas? From a human perspective not very friendly. Special adaptations are needed to live in this extreme environment without sunlight and hence without plants. An exception are bacteria that thrive on the deep seafloor with billions of organisms per millilitre sediment. Their role in global nutrient cycles is pivotal: they convert most of the organic matter that sinks to the bottom of the oceans back into nutrients that can be used by other organisms. Others fix CO_2 and keep it in the deep ocean, removing carbon dioxide from the atmosphere on geological time scales.

Their functions in geochemical cycles are of great importance for other marine life and for our climate. Despite this, very little has been studied about what types of bacteria live in the depths of our oceans, how they make a living, and how they interact with each other and with other organisms in this remote ecosystem. Prof. Boetius and her team have completed the first global survey of abyssal bacteria, discovering thousands of species per tablespoon of sediment. They have identified what may be the most abundant microbes in the world's deep ocean, and used state-of-the-art genomic techniques to elucidate their key functions and community roles.

Her work combined microbiology, ecology, biogeochemistry, and marine biology, in a discipline she likes to call "discovery-driven research", to understand the diversity of this large and mysterious ecosystem. She pushed the boundaries of our knowledge, not only in terms of biology, but also in the development of new instruments for marine deep-sea exploration and sampling. How these organisms operate and will continue to operate under different environmental conditions is key to predicting realistic scenarios for the years to come, and to understand how our oceans will respond to climate change and other anthropogenic pressures.

Researcher: Antje Boetius, Alfred Wegener Institute - Helmholtz Centre for Polar and Marine Research (Germany)

ERC project: Assessment of bacterial life and matter cycling in deep-sea surface sediments (ABYSS)

ERC funding: Advanced Grant 2011, EUR 3.4 million (2012-2018)

Antje Boetius is the Director of Germany's Alfred Wegener Institute, Helmholtz Center for Polar and Marine Research. She is Professor of Geomicrobiology at the University Bremen, and leader of a joint research group on Deep Sea Ecology and Technology of the Alfred Wegener Institute and the Max Planck Institute of Marine Microbiology. She is an expert in marine biogeochemistry, biological oceanography, deep-sea biology. She has lead or participated in 50 expeditions, working on polar seas, on chemosynthetic ecosystems and other extreme habitats of the ocean.

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Your mother's microbes protect you

Maternal microbiota is crucial for the future health of a child. The transmission of microbes to offspring is a process that begins in the uterus and is influenced by the delivery method, breastfeeding and the mother's diet. However, the mechanisms behind the protective role of maternal microbes on the baby's health are not yet fully understood.

The mother's microbial environment during pregnancy and delivery may remarkably impact a new-born's immune development with short- and long-term consequences on children's health. Recent research shows that early microbial colonization - from the mother to the child - may contribute to reduce the risk of chronic diseases such as obesity, allergies and inflammatory conditions. Hence, the first days and months of life are extremely important and many factors are at play. For example, the type of delivery affects the composition of maternal milk and the mother's diet has an influence on the bacteria transmitted to the child.

Prof. Maria Carmen Collado studies early exposition to bacteria, focusing on breastfeeding. Breast milk carries a significant amount of bacteria that constitute an important source for the baby's intestinal microbiota. More specifically, she looks at the milk microorganisms transferred during breastfeeding and their effect on the child's well-being. "*We are seeing the great importance of bacteria in mother's food. What the mother eats seems to be key for the transfer of microbiota to the child and the development of an adequate immune system*" she says.

These results open up new possibilities for research and applications in the field of personalized nutrition and medicine. "*Pregnancy and early infancy are, to our current understanding, the most interesting critical stages and targets for dietary interventions aiming to reduce disease risk. This project could contribute to new dietary strategies, design of functional food, and further development of nutritional guidelines and recommendations*" concludes Prof. Collado.

Researcher: Maria Carmen Collado, Spanish National Research Council – CSIC, (Spain)

ERC project: The Power of Maternal Microbes on Infant Health (MAMI)

ERC funding: Starting Grant 2014, EUR 1.5 million (2015-2020)

Maria Carmen Collado holds a Research Scientist position at the Spanish National Research Council (CSIC) at the Institute of Agrochemistry and Food Technology (IATA-CSIC) in Valencia (Spain). Her research work is multidisciplinary and includes microbiology, food science, nutrition and human health. Her interests are focused on probiotics, microbiota and health and nutrition during pregnancy and early life period.

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Honey bees – what's in their guts?

Honey bees are an important species for ecology and economy, but their population has shrank worryingly. Prof. Philipp Engel focuses on gut microbiota, a critical factor for bee health, to understand how it evolved and diversified over time. His study addresses timely questions about evolution, ecology, microbiology and could eventually contribute to new strategies for managing bee colonies' health.

Research on animals' gut microbiota is one of the hottest topics in current biology. The gut harbour a great diversity of microorganisms that during millions of years have evolved and adapted and that have become essential for the animal's health. Despite its relevance, very little is known about early bacteria evolution and diversification in animals' guts.

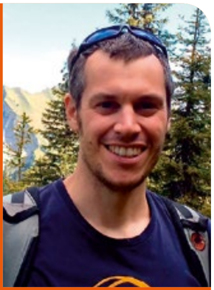
The relatively simple and easy-to-manipulate microbiome of honey bees could help shed some light on this issue. Bees are surprisingly similar to humans when it comes to their gut microbiome: both communities have their origin in only a few bacterial founders. However, those of mammals has evolved into complex and astoundingly diverse groups, while bacterial communities in bees' gut are much simpler and, therefore, easier to study. Bees' guts harbour specialized bacterial communities dominated by only eight different species. Therefore, honey bee microbiota is an excellent model that provides unique opportunities to study bacterial evolution in the gut. To this purpose, Prof. Engel and his team apply a truly multidisciplinary approach, using cutting-edge genetic techniques.

The results of this project will provide insights into microbial evolution, identifying causes and consequences of gut bacterial diversification and will reveal the genes and strategies that allow bacteria to interact with each other and with the host, advancing our understanding of how bacteria influence bee health, behaviour and biology. For example, finding that the gut microbiota influences the behaviour of bees could lead to the establishment of the honey bee as a novel model to investigate the gut-brain axis, i.e. how the gut microbiota communicates with the nervous system. The research will also be relevant from an applied point of view, because honey bees are pollinators of important ecological and economic value, whose numbers have declined over the years.

Researcher: Philipp Engel, University of Lausanne (Switzerland)

ERC project: Evolution of the honey bee gut microbiome through bacterial diversification (MicroBeeOme)

ERC funding: Starting Grant 2016, EUR 1.5 million (2017-2022)



© Philipp Engel

Philipp Engel carried out his doctoral research at the Biozentrum in Basel (Switzerland). Then he moved to Yale University (USA) to work on various aspects of the gut microbiota of honey bees. In 2014 he came back to Switzerland where he started his independent research group at the University of Lausanne, continuing his work on the bee gut microbiota.

Félix Imhof © UNIL

Bacterial wars

Bacteria fight big. When they meet competitors, they are as aggressive and bloodthirsty as they come. ERC grantee Kevin Foster studies how bacteria wage war against each other. His aim is to understand what led to the evolution of such extreme competitive behaviours, and how to exploit them for our own health.

Bacteria are often extremely aggressive towards one another. They release toxins into their environment, stab neighbours with poisoned molecular spears, even sacrifice themselves if it means delivering the final blow. This contrasts with animal contests, where a large body of work has sought to understand why species, from damselflies to deer, are so reluctant to fight one another.

Professor Kevin Foster, from the University of Oxford, uses bacteria's extreme aggression as a model to provide a new perspective on how organisms have evolved competitive behaviours. To be able to understand bacterial war tactics, his research team combines several tools: competition experiments, game theory, experimental evolution, and molecular genetics. The researchers develop techniques to provide images of bacterial battlegrounds at a molecular scale. Using fluorescent dyes that are produced when bacteria fight allows the lab to follow the action in real time, and has already exposed some interesting strategies. For example, that some strains respond as a collective to attacks, with some individuals literally acting as sentinels for the rest of the colony. While these behaviours are frequent in animals, for the first time they have been observed in these microorganisms.

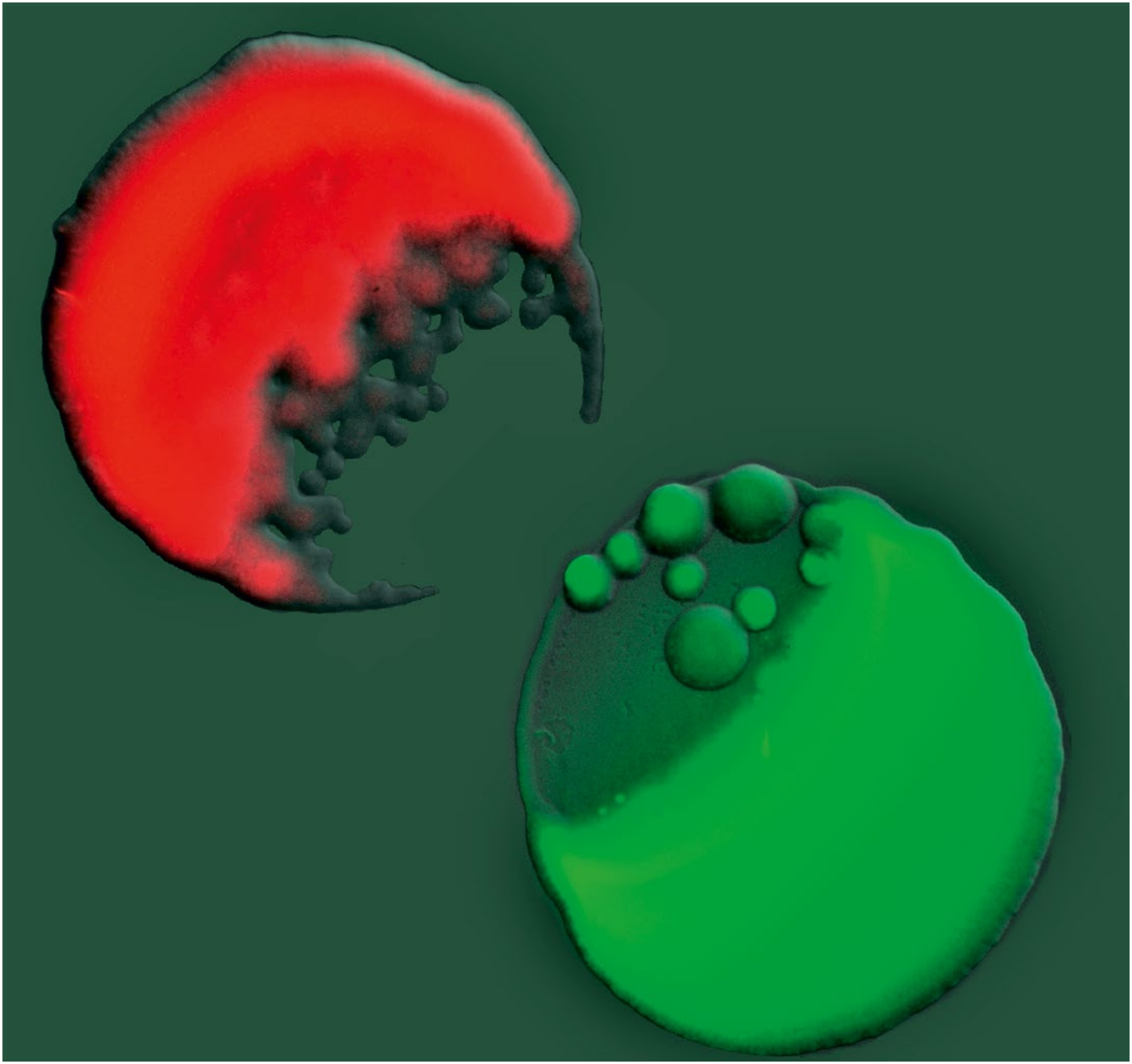
Understanding how bacteria fight can help us learn how they spread, why some species are more successful than others, and maybe how to stop them. Ultimately, Prof. Foster's goal is to be able to describe how different species compete with each other, and whether weaponised bacteria can be used to kill pathogens and fight infection.

Researcher: Kevin Foster, University of Oxford (UK)

ERC project: The Evolution of Bacterial Warfare (MicroWars)

ERC funding: Advanced Grant 2017, EUR 2.8 million (2018-2023)

After degrees in Cambridge and Sheffield (UK), **Kevin Foster** worked in Texas, Berlin and Helsinki before starting his group as a Bauer Fellow at Harvard in 2006. In 2010 he returned to Oxford with an ERC Starting Grant. Since 2011, he is Professor of Evolutionary Biology and now holds a joint appointment between the Department of Zoology and the Department of Biochemistry at Oxford.



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Two colonies of *E. coli* at war

Microbiota: a cure for obesity?

Effective treatment for obesity remains a challenge and the only intervention proven to maintain weight loss is bariatric surgery. Intrigued by the beneficial effect that this procedure has on the composition of gut microbiota, Dr Fredrik Bäckhed explores the possibility of mimicking these changes to develop a treatment for obesity that won't require going under the knife.

The adult gut microbiota consists of up to 100 trillion microorganisms. Its composition is observably altered in humans with cardiometabolic diseases. Researchers have suggested that this difference can be considered as an environmental factor increasing adiposity and influencing obesity-associated metabolic diseases such as type-2 diabetes.

Dr. Bäckhed, who has spent the past 15 years studying the microorganisms living in our digestive tract, developed the hypothesis that surgery changing gut physiology would affect the microbiota too. This was based on the observation that patients undergoing bariatric operations experience a dramatic improvement of metabolic parameters, like insulin resistance, independent of weight loss. The underlying mechanisms of these beneficial effects are still unclear.

Funded by the ERC, in 2015 Dr. Bäckhed presented data confirming his hypothesis. He realized that the more effective the surgery, gastric bypass, the more profound the effect on microbiota. By transferring the microbiota contained in the faeces of humans before and after surgery to mice, his team was able to see that mice with microbiota from post-surgery patients didn't gain as much fat mass.

The researchers are now trying to figure out what part of the operation induces these changes and are performing clinical trials. Ultimately, their analysis may reveal whether it is possible to induce those microbiotic alterations that lead to weight loss and improvements in metabolism without having surgery. '*We may find a new drug that could change the microbiota in a similar way as the surgery or we may identify bacteria that can have that effect*' says Dr Bäckhed.

Researcher: Fredrik Bäckhed, University of Gothenburg (Sweden)

ERC project: Metagenome and Bariatric Surgery - New Avenues to Treat Metabolic Disease (Metabase)

ERC funding: Consolidator Grant 2013, EUR 2 million (2014-2019)

Based at the University of Gothenburg, **Fredrik Bäckhed**, an expert in cellular microbiology and mouse physiology, combines clinical research with mouse models to address the role of the normal gut microbiota in metabolic diseases. He received a PhD from Karolinska Institutet (Sweden) and performed his postdoctoral training at Washington University, St Louis (USA), where he identified the gut microbiota as an environmental factor that regulates adiposity and obesity.

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Probiotic bacteria, normal intestinal microbiota

Wake-up call for soil microbes

Our soils are inhabited by millions of microorganisms; however, the majority of them lay dormant. In her ERC project, Prof. Dagmar Woebken explores the mechanisms that allow soil microorganisms to go into dormancy and thus survive unfavorable conditions. It is further the goal to reveal the environmental signals that lead to their resuscitation to perform important ecosystems functions.

Soils harbor the largest microbial diversity on planet Earth. Millions of microorganisms inhabit a single gram of soil, yet the vast majority remains asleep, only to awake after specific cues. These dormant microorganisms ensure the stability of ecosystem processes and thereby ecosystem function despite changes in the environment. Prof. Dagmar Woebken and her team from the University of Vienna explore the "wake-up calls" that allow these dormant microorganisms to resuscitate and the genetic mechanisms involved.

In microcosm experiments with samples from the Negev Desert (Israel), Prof. Woebken and her team simulate environmental conditions that lead to active and dormant phases of the inhabiting microorganisms, which are investigated using cutting-edge technologies in microbial ecology. Meta-omics technologies are applied to identify the microorganisms together with the mechanisms of their survival strategies. The activity status of single cells can be revealed using stable, heavy isotopes (such as in "heavy water") followed by high-resolution secondary ion mass spectrometry (NanoSIMS) analysis to detect the incorporation of the heavy isotopes.

The researchers uncovered a large diversity of previously unknown soil microorganisms with very different strategies to survive unfavorable conditions. Some microorganisms that follow a "feast-and-famine" strategy are equipped to react to sudden pulses of water and utilize a variety of energy-rich organic nutrients, but also need to spend resources to prepare themselves for long periods of inactivity. Other microorganisms do not encode such elaborate preservation mechanisms but rather run a more minimalistic and streamlined metabolism. They are enduring unfavorable conditions by scavenging atmospheric gases that keep them alive when nutrients or water are scarce.

This work provides novel insights into the survival strategies of soil microorganisms and will be essential in understanding the limits of microbial life.

Researcher: Dagmar Woebken, University of Vienna (Austria)

ERC project: Revealing the function of dormant soil microorganisms and the cues for their awakening (DormantMicrobes)

ERC funding: Starting Grant 2014, EUR 1.5 million (2015-2020)

Dagmar Woebken is a microbial ecologist and an Assistant Professor at the Centre for Microbiology and Environmental Systems Science (University of Vienna, Austria). Research in her group focuses on microbial participants in key processes within the terrestrial carbon- and nitrogen-cycles and on the survival strategies of soil microorganisms, including the principles of dormancy and resuscitation.

© Dagmar Woebken

Members of the Woebken group sampling soil in the Negev Desert (Israel)

Healthy lungs start from your toothbrush

Until recently, lungs were believed to be sterile, but today we know that they are inhabited by microbes migrating from the mouth. Dr Randi Bertelsen has been awarded an ERC grant to investigate the role played by the oral microbiome in lung disease.

The composition of bacteria in the mouth has a lot to do with lung health, but it could also influence the development of inflammation throughout the whole body. Research has shown that, in addition to asthma, inflammation in the gums increases the risk of diabetes and cardiovascular disease.

Dr Bertelsen's hypothesis is that oral microbiome communities dominated by bacteria with strong inflammatory effects, will have a negative effect on the respiratory tract. In this project she will test her hypothesis with in vivo and in vitro experiments to identify whether a specific bacterial composition in saliva samples predicts lung function and respiratory health over time. She will use data and samples from study centres in northern Europe, Spain and Australia, making it possible to compare populations from different geographical areas.

"If we show that improved oral health leads to fewer infections and lung and cardiovascular diseases, we will pave the way to new research in respiratory health and future studies to block bacteria without administering antibiotics. And we know how important it is to reduce the use of antibiotics to prevent the development of antibiotic resistant bacteria" says Dr Bertelsen.

Proving a causal link between the oral microbiome and lung health will also be important from the perspective of public health. Oral health could be a feasible target for intervention programs aimed at preventing respiratory conditions such as asthma and chronic obstructive pulmonary disease, whose prevalence is expected to increase, according to the World Health Organization.

Researcher: Randi Bertelsen, University of Bergen (Norway)

ERC project: Oral bacteria as determinants for respiratory health (BRuSH)

ERC funding: Starting Grant 2018, EUR 1.5 million (2019-2023)

Randi Bertelsen works at the University of Bergen (Norway). She has a MSc in Evolutionary Biology and Ecology and a PhD in Environmental Medicine and Epidemiology. In 2010 she received the Voksentoppen Research Award for her outstanding work in paediatric respiratory medicine and allergology, and in 2014 a young research talent grant from the Research Council of Norway. Her research interests focus on environmental exposure, microbiome, asthma and allergy.

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>
> Jean-Pierre Bourguignon
> ERC President and Chair of its Scientific Council

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