THE GLOBAL GRANTS FOR GUT HEALTH

ADVERTISEMENT FEATURE

Helping push the boundaries of microbiome research

July 2020

Hunting for novel bioactives, examining protists, and cataloging antibody–antigen interactions.

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THE GLOBAL GRANTS FOR GUT HEALTH

2020 Call for Applications

Application deadline: 30 September 2020

A growing body of evidence has emerged in the last decade supporting the major role the human microbiota plays in health and disease. To encourage the development of this promising field, Yakult and Nature Research have established a multi-year competitive grant programme for research into the human microbiota.

In 2020 The Global Grants for Gut Health will consider proposals for research projects — whether laboratory investigations or clinical studies — that advance our understanding of the impact of the small intestine microbiome on human health.

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IN SEARCH OF NOVEL INSIGHTS

Introducing the projects that aim to elucidate the role of protists in food sensitivity, identify novel bioactives to prevent or reduce inflammatory bowel disease (IBD), and look for antibody–antigen interactions in microbiome-related diseases

At the end of 2019, the Global Grants for Gut Health (GGGH) panel convened for only the second time to find the best proposals among the 132 project descriptions submitted. To use some terms appropriate for the field, both the load and the diversity of submitted applications were indeed large. This year, our focus was on seeking out bold and original proposals that will make important contributions to uncovering and understanding the mechanisms through which the microbiota exert an influence on human health.

With the GGGH, we hope to add to the generation of novel insights. As an adjective, novel means more than merely 'new'. Novelty implies originality, freshness, uniqueness. We were pleased that many of the applications contained highly novel aspects, and the three grantees were selected from a very competitive line-up. We are very happy to be able to congratulate the recipients of this year's GGGH:

Reinhard Hinterleitner, assistant professor at the University of Pittsburgh, United States, will use his grant to **unravel the role of gut commensal protists in immune-mediated food sensitivity**. His project tackles a huge need and deals with a poorly understood aspect of host-microbiome interaction. The panel found the proposal to be original and timely, highly mechanistic, and to have a high chance of bringing insightful outcomes. We are very excited to see the results.

Jakob Begun, senior lecturer and IBD group leader at the University of Queensland, Australia, sets out to use a very logical, stepwise approach to **identify bioactive strains within the gut microbiota**, and focus on their mechanisms of signalling to the host. The aim is to harness gut bioactives that suppress inflammation in IBD. The panel found the proposal to be original and clinically relevant, and to encompass the search for next-generation probiotics i.e. live strains from humans selected primarily for their bioactive potential.

Eran Segal, professor at the Weizmann Institute of Science, Israel, is a highly renowned player in the field of host-microbe interactions. His project involves **the development of a novel technique to screen thousands of microbial antigens for binding to human antibodies** in order to identify critical reactions that may be applied for prevention or mitigation of disease. This original and novel project has a clear mechanistic aspect, and builds on a multitude of existing data. The panel found that the downstream impact of this project might be huge, particularly when the results are made available to the scientific community.

The granted proposals reflect the GGGH's support of the global scientific community, since the three projects will be carried out on three continents. We very much look forward to seeing what these novel and interesting approaches will lead to, and how they might advance worldwide efforts to solve some of the many riddles related to the human microbiome.

Ending on this happy note, I warmly thank my fellow panelists; Eran Elinav, Paul W. O'Toole, Karen P. Scott, Kiyoshi Takeda and Liping Zhao for all their work and for making their excellent expertise available during the selection process.

Tine Rask Licht
Chair of the independent evaluation panel for the Global Grants for Gut Health

Meet the panel

The independent panel is made up of internationally renowned researchers in human microbiota from across the world.

Tine Rask Licht
National Food Institute, Technical University of Denmark (DTU Food), Denmark
Panel Chair

Eran Elinav
Department of Immunology, Weizmann Institute of Science, Israel

Paul W. O'Toole
School of Microbiology and APC Microbiome Ireland, University of Cork College, Ireland

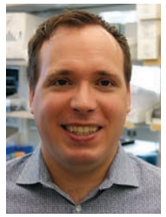
Karen P. Scott
Rowett Institute, University of Aberdeen, United Kingdom

Kiyoshi Takeda
Graduate School of Medicine, Osaka University, Japan

Liping Zhao
Chair of Applied Microbiology at Rutgers University, United States; Distinguished Professor of Microbiology at Shanghai Jiao Tong University, China

WHEN IT COMES TO FOOD ALLERGIES, SHOULD WE BE PRO-PROTIST?

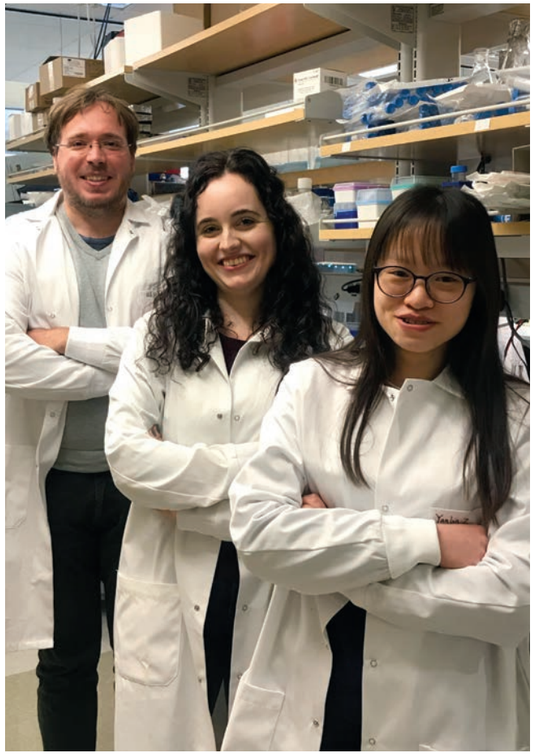
Immunologist Reinhard Hinterleitner will use his Global Grant for Gut Health to examine whether certain microbes, known as protists, have a protective role in food sensitivities.



Reinhard Hinterleitner is an assistant professor in the Department of Immunology at the University of Pittsburgh. He studied biotechnology at the University of Applied Sciences in Vienna and received his PhD from the Medical University of Innsbruck, Austria. Supported by an Erwin Schrödinger Postdoctoral Fellowship, Hinterleitner joined the laboratory of Bana Jabri at the University of Chicago where he studied the role of enteric viral infections on oral tolerance in the context of celiac disease. Hinterleitner's research focuses on the cross talk between gut microbes and the host mucosal immune system in the context of food sensitivities and intestinal inflammation.

What is the background to your research?
Incidences of immune-mediated food sensitivities, including celiac disease and various food allergies, are rising globally, and we need to understand why. At present, the only real treatment is to stop eating the food that causes symptoms. Food avoidance means that people with severe allergies have a restricted diet and risk a potentially lethal allergic reaction if there is any contamination. We know that gut microbes play an important role in food sensitivities. Dendritic cells constantly sample food antigens from the intestines and, through the induction of regulatory T cells, they help the immune system establish 'oral tolerance' to food antigens. There have been studies that show that imbalances in gut microbial communities ('dysbiosis'), lack of certain microbial products, and external factors, such as viral infections, can all trigger loss of oral tolerance. Dysbiosis can be caused by modern lifestyle practices, including high-fat low-fibre diets, antibiotic overuse, and urban living. If we can learn how to carefully modulate the gut microbial population using probiotics or other therapies, we might be able to quell the overreaction of the immune system and prevent inflammatory responses to certain foods.

How does your project differ from previous microbiome work?
Most previous research has investigated the associations and correlations between gut bacterial communities and disease. Bacteria are in the majority in the gut microbiome; other significant inhabitants — archaea, viruses, protists and fungi — have been studied far less. Our project will focus on protists: unicellular eukaryotic microbes that are actually quite large — you can see them swimming around under the microscope. Research has been mainly focused on disease-causing parasitic protists, and very little is known about commensal protists and their potentially beneficial role in our health. No-one has really studied protists in the context of food sensitivities. We will explore the function and mechanisms of gut protists in modulating immune responses in the context of food sensitivities. There are some interesting immune pathways we think that protists can induce, and we hope to pinpoint these.



Reinhard Hinterleitner with Magdalena Siller, who studied gut protists for her Masters thesis, and Yanlin Zeng, who continues the project.

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How will you examine the role of protists?
We will use different mouse models of celiac disease and food allergies to study how protists are modulating immune responses and whether the process is protective in these animal models. We are also using mice that are germ free — bred with sterile guts. They live in a bubble, effectively, until we come to work with them. This means we can control precisely what microbes we introduce to their gut and find out how the mice respond. It is a really powerful tool.

We hope to determine which immune cells and pathways are moderated by protists and whether the moderation is beneficial. We also want to know how protists are interacting with immune cells: are they producing a specific metabolite, for example? To visualize how the immune cells are behaving in response to the protist activity, we will stain different immune cells and use flow cytometry to monitor how they respond and interact with protists. We will also investigate whether protists can protect against viral-induced loss of oral tolerance, which we showed is linked to celiac disease development.

What will be the main application of your findings?
This grant will enable us to highlight the importance of the protective function of protists in the context of food sensitivities, and this will be the foundation of future projects. The hope is that we can show promise in the animal models, which will then facilitate collaborations to see if we can translate our findings to humans. There is also the possibility of commercializing some of our findings, and using protists in novel probiotic treatments.

What are your longer-term research goals?
My team and I will continue looking at the mechanisms by which gut microbes affect food sensitivities. Better understanding of the interactions between gut microbes and the immune system will give us the ability to fine-tune immune responses to prevent food sensitivities without causing side effects. Ideally, we want to accomplish that by either using probiotics or microbe-based products. These studies will also be helpful for us to unfurl the complexities of other bowel conditions, like inflammatory bowel disease, as well as for other extra-intestinal conditions influenced by the microbiome. Scientists have recently uncovered associations between gut microbes and autoimmune conditions, such as multiple sclerosis, and various cancers. The different populations of microbes in the gut help to train the immune system. If there are chronic microbial imbalances then your immune system is not fully charged, and it opens you up to all kinds of diseases and conditions.

NO-ONE HAS REALLY STUDIED PROTISTS IN THE CONTEXT OF FOOD SENSITIVITIES

Any advice for researchers who might apply for this grant in future?
It's important to be brave and follow your own ideas and not necessarily follow the lead of others; set your own trend and choose something that no-one else has looked into before.

What do you enjoy doing in your free time?
I play computer games and I like to think I'm honing my problem-solving skills! If you're too preoccupied with work, your ideas soon dry up and you become a bit robotic. My partner and I also love hiking in the mountains and visiting the beautiful national parks here in the United States. ■

BUGS AS DRUGS, AND DRUGS FROM BUGS

Biochemist and inflammatory bowel disease (IBD) specialist, Jakob Begun, will use his Global Grant for Gut Health to explore how microbial power could limit IBD progression.

Jakob Begun studied for his MPhil in biochemistry at the University of Cambridge, and his MD and PhD in genetics at Harvard Medical School. He completed his advanced training in gastroenterology and inflammatory bowel disease (IBD) at Massachusetts General Hospital. He moved to Australia in 2014 to research clinical and translational IBD and gut health. He is the Director of IBD at the Mater Hospital in Brisbane, IBD Group leader at the Mater Research Institute, and an Associate Professor at the School of Medicine, The University of Queensland. He leads a laboratory at the Australian Translational Research Institute, investigating the interaction between the innate immune system and the gut microbiome, as well as genetic contributions to disease.

© J. Begun

What inspired your grant application?
Globally, the number of cases of inflammatory bowel disease (IBD) is around 30 per 100,000 people — similar to the incidence of type 1 diabetes. IBD is a chronic, debilitating disease that is often diagnosed in the second or third decade of life, and consists of two main conditions: ulcerative colitis and Crohn's disease. About 30% of patients do not respond to existing therapies, so many people need surgery and there is high morbidity. There is also growing recognition of the role of gut bacteria and how they interact with the immune system. This interaction probably contributes to IBD, and to immune mediated diseases in general, such as rheumatoid arthritis, as well as autoimmune conditions, like lupus or thyroid disease.

What is the main goal of your project?
In IBD, there is an inappropriate immune response directed towards resident bacteria in the gut. It appears there is a breakdown in the innate immune system, and how it responds to gut bacteria. Our multidisciplinary team have been looking at the proteins and other metabolic products from bacteria, and examining how these molecules interact with and modulate the immune system, and how the immune system responds. This allows us to probe how gut microbiota can set the tone of the immune system, and how it might break down and end up with

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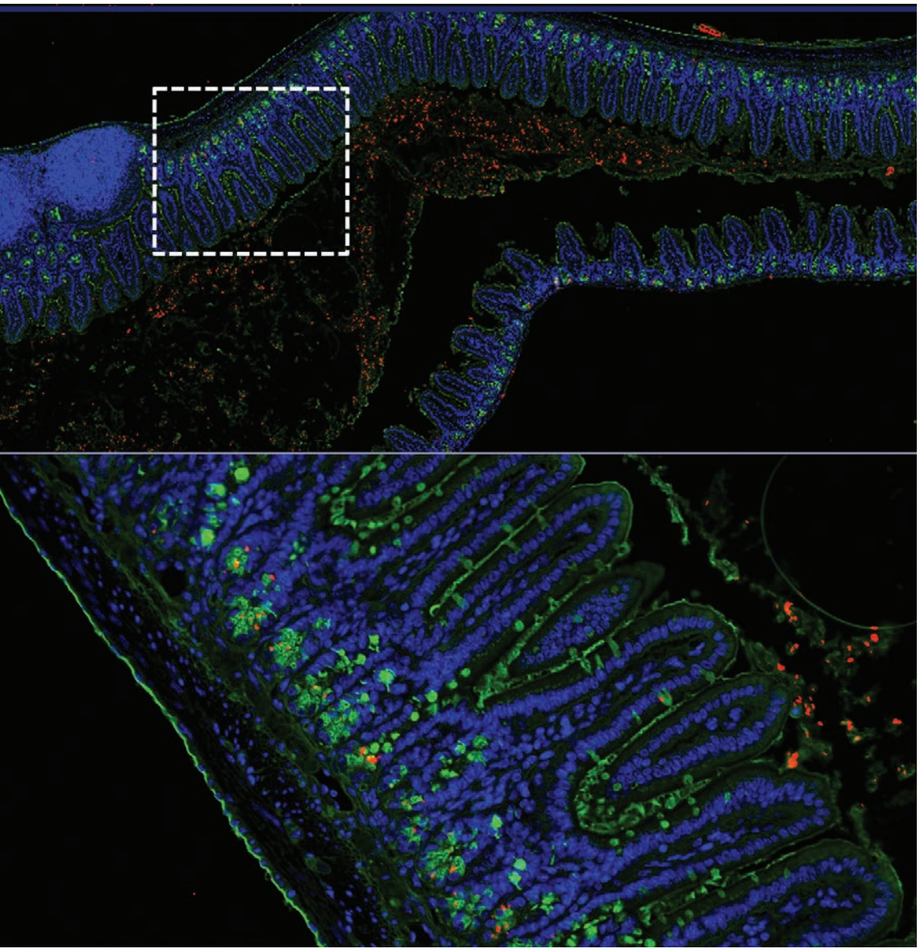


Some gut bacteria (red) are anable to penetrate the mucus barrier (green) to access the epithelial cells (blue).

© J. Begun

inflammatory conditions like IBD.

In this specific project, we will explore how bacteria in the gut can produce immunomodulatory molecules that affect a specific inflammatory pathway: the IL-23 pathway. We hope to identify how gut bacteria target that pathway and how the status quo might be disturbed in Crohn's disease and ulcerative colitis. We will look specifically at how the bacteria function, and whether we can enhance beneficial bacterial activity so that a patient's system returns to a more balanced, healthier state.

Why has this not been studied before?

One reason that these interactions have been overlooked is that they have been incredibly hard to study, largely because it has been difficult to culture and analyse gut bacteria at scale. The genomics revolution has given us unprecedented insights into the communities that exist inside the gut and the body as a whole. Now that we have newer techniques in bacterial culturing, including anaerobic growth chambers and specialized culture media, we can grow many more bacteria to study their function and discover how they modulate the host immune system. These technologies have revolutionized microbial research.

OUR DNA SHOWS WE ARE MORE MICROBIAL THAN HUMAN

What steps will your project take?

We already have a collection of bacteria isolated from stool samples from healthy individuals. We have selected bacteria of interest and cultured them. Using these monocultures, we can then use cell-based assays to examine how these bacteria interact with immune cells and, more specifically, the IL-23 pathway. We will use our high-tech metabolomics platform to isolate particular compounds the bacteria produce that are responsible for this immunological activity. We will then explore what aspects of the compounds we've identified actually trigger and modulate that activity, and that's the first step down the road towards novel drug development.

We will use animal models to validate that these bacterial components modulate immune responses. We will also investigate whether these bacterial products can affect immune signalling in human-derived samples from our IBD cohort. Within the timeframe of this project, I'm hoping to identify specific candidates from our library of bacteria that could be used to inform potential therapies.

What might be the practical applications of your project?

There are two overarching philosophies. One approach is 'bugs as drugs'— you take the bacteria that you have identified, and you develop them as super probiotics. We have the opportunity to personalize therapy here. A collection of, for example, 20 bacteria that can quell inflammatory activity might be tested on a patient's blood sample. The actual therapy would then consist of the six most effective bacterial strains for that person's immune system. We may soon be able to take a decision-based approach to probiotic therapy.

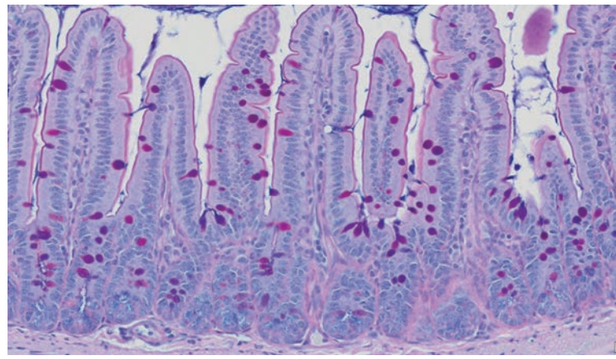
The second approach is 'drugs from bugs', where we would use the bacterial compounds we identify to design drugs with high affinity and activity against IL-23. Both approaches have the potential to reach beyond IBD, and might prove valuable for other immune-mediated health conditions.

What hobbies do you have?

I have an interest in sailing, which is an activity I often do with my parents. I am an avid skier; often conferences are close to ski areas and I enjoy getting together with colleagues on the slopes. I'm a keen cyclist and I'm involved in lots of activities with my children.

What advice would you give other researchers who might wish to apply for the Gut Health grant?

It is important to propose a project that is achievable within a short timescale, yet has the potential for big impacts in the field. Microbiome research as a whole is a vital focus, especially as we learn more about the 'holobiont' that is a human being, because it covers so much of how we function as organisms. After all, our DNA shows we are more microbial than human. ■



Goblet cells in the colon of a mouse with colitis after treatment with anti-inflammatory bacterial supernatant.

© E. Segal

NOVEL SCREENING APPROACH TO STUDY MICROBIOME-IMMUNE INTERACTIONS

Computational biologist Eran Segal will use his Global Grant for Gut Health to examine how the microbiome and immune system interact, and how it can go awry.

Eran Segal is a professor in the Department of Computer Science and Applied Mathematics at the Weizmann Institute of Science in Israel, heading a lab with a multi-disciplinary team of computational biologists and experimental scientists in computational and systems biology. His group has extensive experience in machine learning, computational biology, and analysis of heterogeneous high-throughput genomic data. His research focuses on the microbiome, nutrition and genetics, and their effect on health and disease. His aim is to develop personalized medicine based on big data from human cohorts.

When did you become interested in microbiome research?

I am a keen marathon runner, and as such I developed a strong interest in nutrition and how the microbiome responds to fitness diets. I originally started out in a different area of computational biology called gene regulation, but as my own interest in nutrition grew, I realised that the microbiome was a rapidly evolving area of new research in which I was keen to get involved. We had been working on a personalized nutrition project using our own novel immunology approach and this provided us with a ready-made collection of samples from our cohort, and the technological basis for this new study.

What is your project about?

We already know the importance of both the immune system and the microbiome to health. We know that the immune system and the microbiome interact; every day the human body produces around two grams of antibodies against gut microbes. Keeping the body in a healthy state requires a fine balance between the microbiome and immune responses. However, we have been largely blind to the scope of these immune-microbiome interactions because of our inability to perform measurements and analyse them at scale. Typically, a research project will study one particular gene from the immune system and examine its interaction with one specific bacterium. Our project will, for the first time, provide comprehensive mapping of immune-microbiome interactions in both healthy individuals and patients with autoimmune and auto-inflammatory conditions. We hope to determine which immune responses to gut-based antigens might trigger or exacerbate disease. We have created a pioneering high-throughput approach that can methodically identify hundreds of thousands of molecular interactions using a combination of machine learning, bacteriophage display technology, and robotic automation. It should provide detailed profiles of the way the immune system and microbiome interact under healthy and diseased states.

How does your novel screening approach work?

From 1,000 microbiome samples, taken from 250 patients with inflammatory bowel disease (IBD), 250 with multiple sclerosis (MS), and 500 healthy controls, we will select bacteria that are particularly abundant or interesting. We then select specific antigens within those bacteria; molecular regions that are likely to be recognized by the immune system, such as

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Segal's project will comprehensively map the interactions between the microbiota and the immune system.

secreted proteins and membrane proteins. Hundreds of thousands of these antigen designs are entered into a computer, and sent away to be synthesized. We use these synthesized antigens to create a bacteriophage library, wherein each phage displays a specific antigen and holds the DNA from which the antigen was produced. Next, we take blood samples from people, each of which contains that person's unique set of antibodies, and incubate each blood sample with the phage library. Any antibody that recognizes a specific antigen will bind to it. We can then extract all the bound antigen-antibody complexes, and subject the phage DNA to next-generation sequencing. This shows us which DNA elements are enriched compared to the initial library we started with. Enrichment tells us to what degree that particular antigen was selected by the antibodies of that person. We have worked very hard to calibrate our system carefully and increase the signal to noise ratio. The technology is very robust. It can test up to one million antigens against a given blood sample in one experiment, and it can run up to 100 samples simultaneously.

WE HAVE BEEN LARGELY BLIND TO THE SCOPE OF THESE IMMUNE-MICROBIOME INTERACTIONS

What insights will your results yield?

For each individual, the process will reveal which microbial antigens their immune system recognizes, and then we can then correlate that with other health data we hold on that individual. This will allow us to pinpoint direct relationships between IBD, MS and microbial activity, and hopefully highlight potential biomarkers for these conditions.

We are trying to answer broad questions. For example, is there a relationship between your current microbiome composition and what your immune system recognizes from these bacteria? Perhaps your immune system is actively excluding certain bacteria; it recognizes the bacteria as a danger or a source of intolerance, or it is taking note of which bacteria are safe and are part of your commensal microbiome.

To give a specific example, leaky gut is a process implicated in conditions such as obesity and diabetes. When a person suffers from a leaky gut, bacteria escape from the intestine and reach other parts of the body. With luck, they are stopped by the immune system. When that process does not fully stop, the infiltrated bacteria cause inflammation. If a person has, or has had, a leaky gut, we believe there will be a signature present in the immune system that our technology can find. It should also indicate the magnitude of the signal, providing information about the seriousness of the individual's condition.

What will be the long-term applications of your findings?

Firstly, our work will contribute to current scientific knowledge and advance our basic understanding of immune-microbiome interactions. Secondly, our study should identify biomarkers that could help develop valuable assays for diagnostics, prognostics and for measuring the efficacy of interventions in different diseases. The immune system signatures we find could be relevant for developing novel therapies. Ultimately, this platform could help with personalization of medicine, by highlighting antigens that individuals cannot tolerate with a simple, efficient test. The technology we have developed is very broad, it can test your immune response against any antigen. ■

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