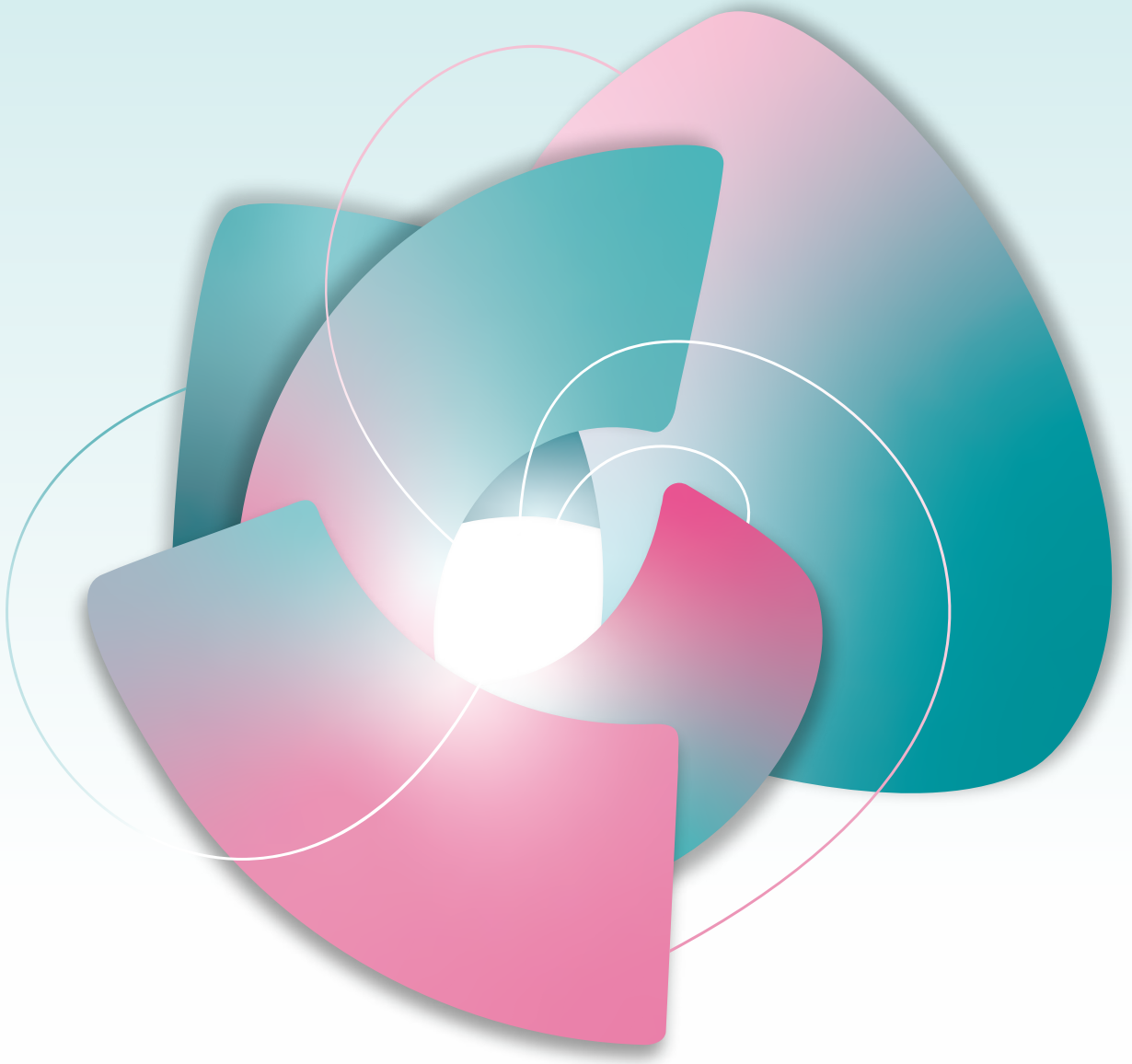
Beyond the gut bacteriome

Investigating the role of viruses and fungi in the gut microbiome



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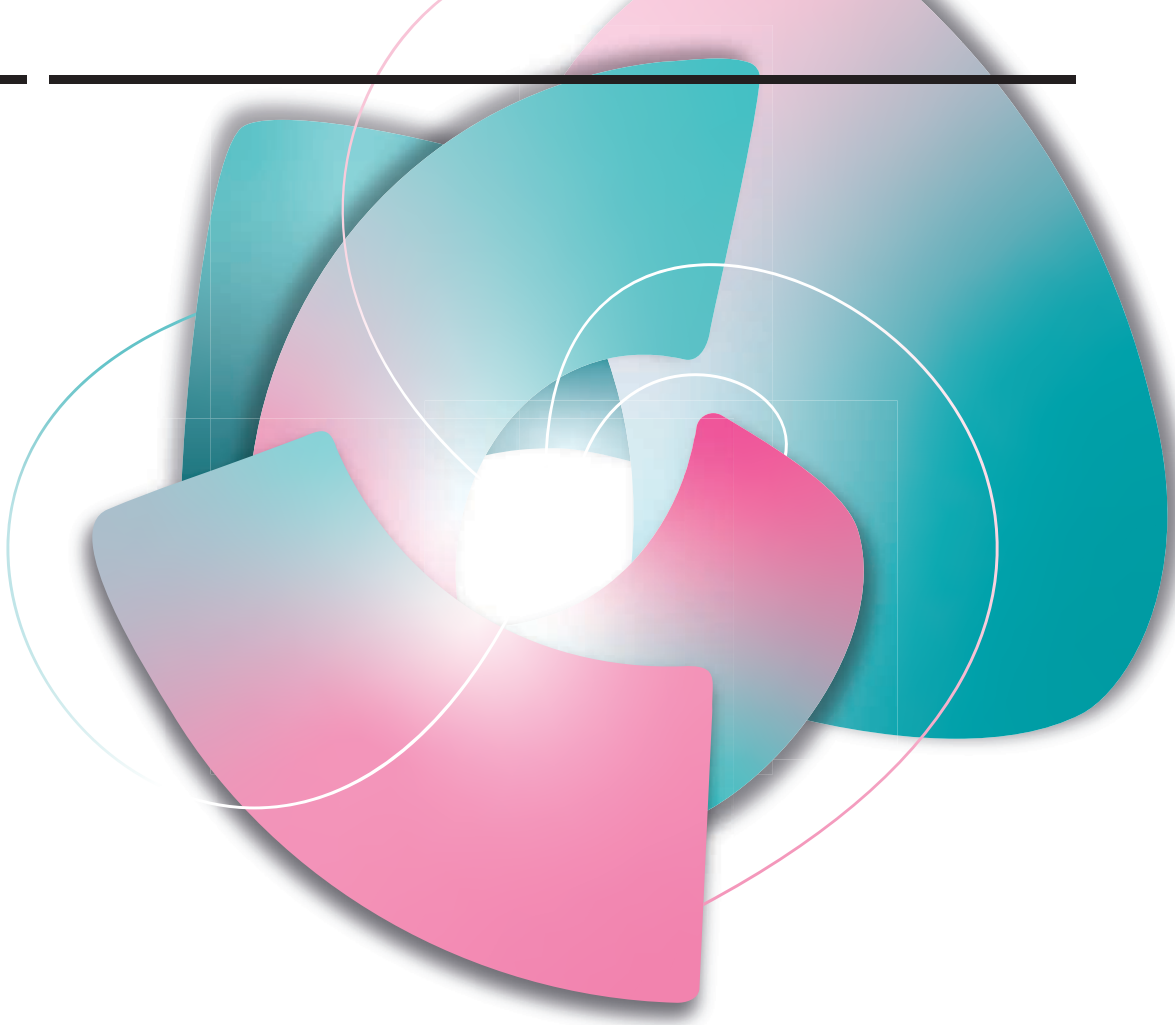

Call for Applications

The Global Grants for Gut Health program for 2025 invites innovative research proposals for projects that will explore how nutrition modulates the human gut microbiome and barrier function. We seek studies that could transform our understanding of this complex ecosystem by investigating the interplay between dietary components, microbial composition, and barrier homeostasis.

The program will provide up to three grants, each valued at up to US$100,000, per funding cycle to researchers investigating diet–microbiome interactions.

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Applications are accepted until September 9, 2025.
Discover more at guthealth-grants.com

LOOKING BEYOND THE GUT BACTERIOME

The Global Grants for Gut Health (GGGH) programme continues to support research investigating new ways to maintain human health through elucidating novel mechanisms of microbiota–host interactions.

We warmly congratulate the three recipients of the 2024 GGGH, which supports studies looking beyond the bacterial microbiome. Many gut-microbiome studies focus solely on the gut bacteriome. By contrast, the 2024 GGGH encouraged research investigating interactions between the host and other constituents of the gut microbiome. We're proud to present the three successful applicants and their projects.

Megan Baldridge (Washington University, St. Louis, United States) will focus on the potential role of viruses in inflammatory bowel disease (IBD). Specific interactions between bacteriophages and human proteins in the gut will be examined to determine how they may impact the inflammation characteristic of IBD. Uptake of bacteriophages by gut epithelial cells can trigger inflammatory responses, which could underlie the inflammatory flareups associated with IBD cycles. Cell-surface proteins expected to be involved in the uptake of bacteriophage will be investigated using a novel approach based on CRISPR screening to identify proteins involved in binding specific bacteriophages. The expression of such proteins can then be regulated to see the impact on bacteriophage binding and inflammatory markers. Limiting phage binding to human cells could be a new therapeutic route to reduce IBD-associated inflammation.

Souhaila Al Khodor (Sidra Medicine Women and Children's Hospital in Doha, Qatar) will also examine the role of the gut virome and its interaction with other members of the microbiome in children with IBD. Children tend to develop a more severe, debilitating, form of IBD than adults. The researchers have collected samples from a longitudinal cohort of paediatric patients. They aim to add the missing piece of the puzzle — the virome — to their existing datasets of the bacteriome and the fungal microbiome (the mycobiome). Investigating the changing compositions over time and disease state, and comparing the inter-kingdom relationships between the different microbes, and with the host, will provide crucial information and a route to identify key causative factors.

Virginia Pedicord (University of Cambridge, United Kingdom) aims to explore whether the mycobiome plays a role in the development of neurodegenerative diseases such as dementia. Gut-derived fungal components circulate in the body and can cross the blood–brain barrier, where they could cause neuroinflammation, potentially triggering cognitive decline. Imbalances between fungal and bacterial populations could alter the amount and type of such circulating molecules. This project will mine existing repositories of patient data, searching for associations between the mycobiome and neurodegeneration. To identify important correlations, the researchers will use AI tools to filter and analyse the data. This research could help to identify new early biomarkers for neurodegeneration.

Together with the rest of the panel, I'm confident these excellent projects will expand our knowledge of how interactions between all members of the gut microbiome, beyond the bacteriome, contribute to the development of disease, within and beyond the gut. I wish the three recipients the best of luck with their crucial work! Finally, I'd like to say a heartfelt thank you to fellow panellists Ami Bhatt, Sarah Lebeer, Kiyoshi Takeda and Gabriela Vinderola for their excellent and essential contributions to the evaluation process.

Karen P. Scott, Panel Chair

Meet the panel

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

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

Ami Bhatt
Departments of Medicine (Hematology & BMT) and Genetics, Stanford University, United States of America.

Sarah Lebeer
Department of Bioscience Engineering, University of Antwerp, Belgium

Kiyoshi Takeda
Graduate School of Medicine, Osaka University, Japan

Gabriela Vinderola
Biotechnology and Food Technology Department, National University of Litoral, Santa Fe, Argentina; Dairy Products Institute

EXPLORING HOW CELLS INTERACT WITH BACTERIOPHAGES IN THE GUT

Megan Baldridge and her co-workers will use their Global Grant for Gut Health (GGGH) to examine which human proteins interact with bacteriophage viruses in the gut, and how this might trigger inflammation in inflammatory bowel disease.

Megan Baldridge is an associate professor in the Division of Infectious Diseases in the Department of Medicine at Washington University in St. Louis, US. She completed her MD/PhD training at Baylor College of Medicine in Houston, Texas, in 2011, and then for her postdoctoral work, she joined Dr. Skip Virgin's laboratory to begin defining how intestinal viruses such as noroviruses interact with the bacterial microbiota. In 2016, she started her own laboratory at Washington University, and she currently oversees a research program exploring how gut microbiota, including bacterial and bacteriophage components, regulate virus infections and immune responses in the intestines.

What originally drew you to virology?
I've long been interested in viruses that infect humans and how they interact with the bacteria in our guts. During my postdoctoral training, I began to examine viruses that cause diarrhoea after infecting human cells, such as norovirus. I became intrigued by the idea that the bacterial microbiota can suppress or promote viral infections. When I started my own independent research programme, I decided that a key focus for my lab would be viruses that infect or reside in the gut, including bacteriophages.

What are bacteriophages?
Bacteriophages are viruses that infect bacteria. Different species have different lifecycles. Some infect a bacterium and kill it after replicating, whereas others become integrated into the bacterial genome and influence a bacteria's activity in that way. Because these viruses don't directly infect human cells, potential interactions between bacteriophages and human cells have mostly been ignored. However, we're convinced that it's important to understand not only how bacteriophages and gut bacteria interact, but also how bacteriophages affect human gut cells.

We know that bacteriophages are present in the human gut — and we also know that human epithelial cells, which line the intestine, can both sense and take up bacteriophages. This process can then trigger inflammatory immune responses to specific bacteriophages. We don't yet understand how this happens or what role this process plays in health and disease.

What role do they play in inflammatory bowel disease?
People with inflammatory bowel disease experience periods of calm and periods when their condition flares up, sometimes in a dramatic and life-altering way. It seems feasible that there could be a viral or infectious trigger that drives inflammation and flares.

Previous studies have shown that people with inflammatory bowel disease tend to have richer and more abundant bacteriophage populations in their bodies than healthy people. This also coincides with a reduction in bacterial species that boost gut health. It's possible that the bacteriophages are killing off health-associated bacteria, facilitating gut disease. But phages have also been shown to directly induce inflammatory cytokine pathways in human cells, so they might be driving immune responses and inflammation directly. It's critical to gain a better understanding of the direct and indirect effects of these altered bacteriophage populations on the human gut

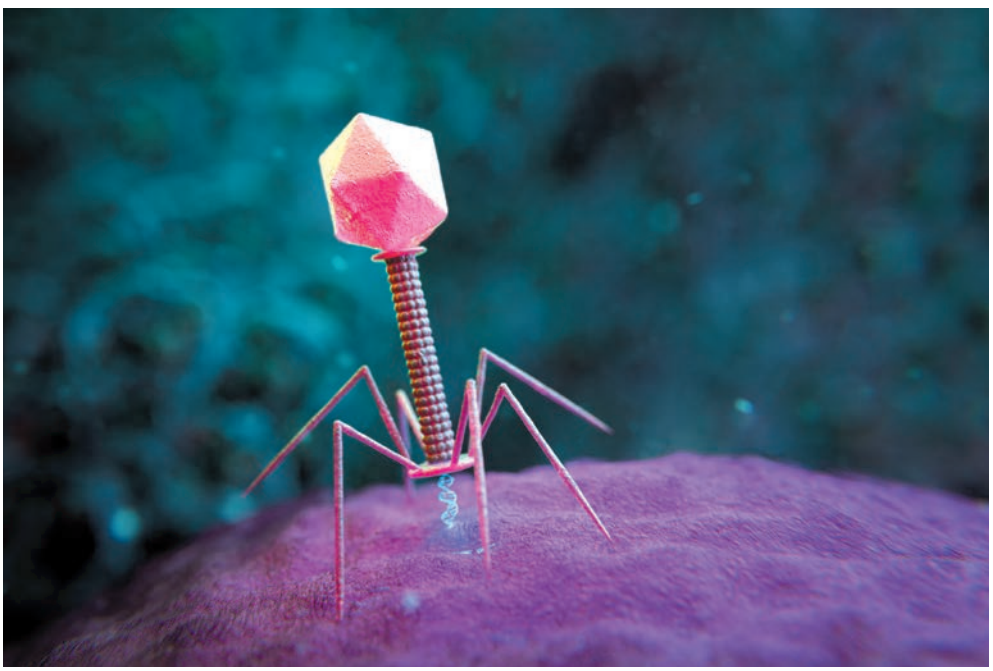


Illustration depicting a bacteriophage transferring its DNA into a bacterial host cell.

Thom Leach/Science Photo Library/Getty

in order to understand how they contribute to inflammatory bowel disease.

What are the aims of your GGGH project?
We're interested in finding out exactly which human factors or proteins are involved in the sensing and uptake of bacteriophages in the gut. We have developed a novel CRISPR screening library and we have human intestinal epithelial cell lines that overexpress a collection of known cell-surface molecules. We will use this collection to identify candidate molecules that interact with phages. We will look at bacteriophage isolates and communities of phages from both healthy participants and people with inflammatory bowel disease. We will then select several cell-surface proteins that we believe aid in the initial uptake of different phages into human cells and carefully examine them.

With luck, this will help us identify interesting human proteins that are involved in the uptake of phages into human cells. We will manipulate those proteins in cell lines to confirm that they facilitate phage binding. We will then characterize how those factors interact with the phages in more detail.


Researchers in Megan Baldridge's lab are studying viruses and bacteriophages.

How does your CRISPR screening library work?
It's pretty cool technology. In each cell of the library, there is an activating enzyme and a guide RNA that targets a particular cell-surface molecule. This combination enables us to over-express that specific surface molecule on the cell. We then use fluorescence-activated cell sorting to separate cells with enhanced phage binding — this will help us identify which of our library of cells preferentially binds to each specific bacteriophage. Subsequent sequencing will allow us to identify the specific activated human cell-surface proteins that are involved in bacteriophage binding and uptake.

Because we can control these cell-surface proteins, we can then turn them off or turn them up to see how different levels of expression either promote or limit phage binding. We can assess whether those factors are important just for initial binding or for the complete uptake process. We will then examine the downstream immune pathways from these binding molecules to find out how the body responds when faced with different phage populations.

What practical applications might your results have?
The viruses and bacteriophages in the gut are still something of a black box for scientists at this point. Interest is growing in bacteriophage-related therapies, but it's vital that we fully understand these viruses and how they influence human cells when considering them in new therapeutic approaches.

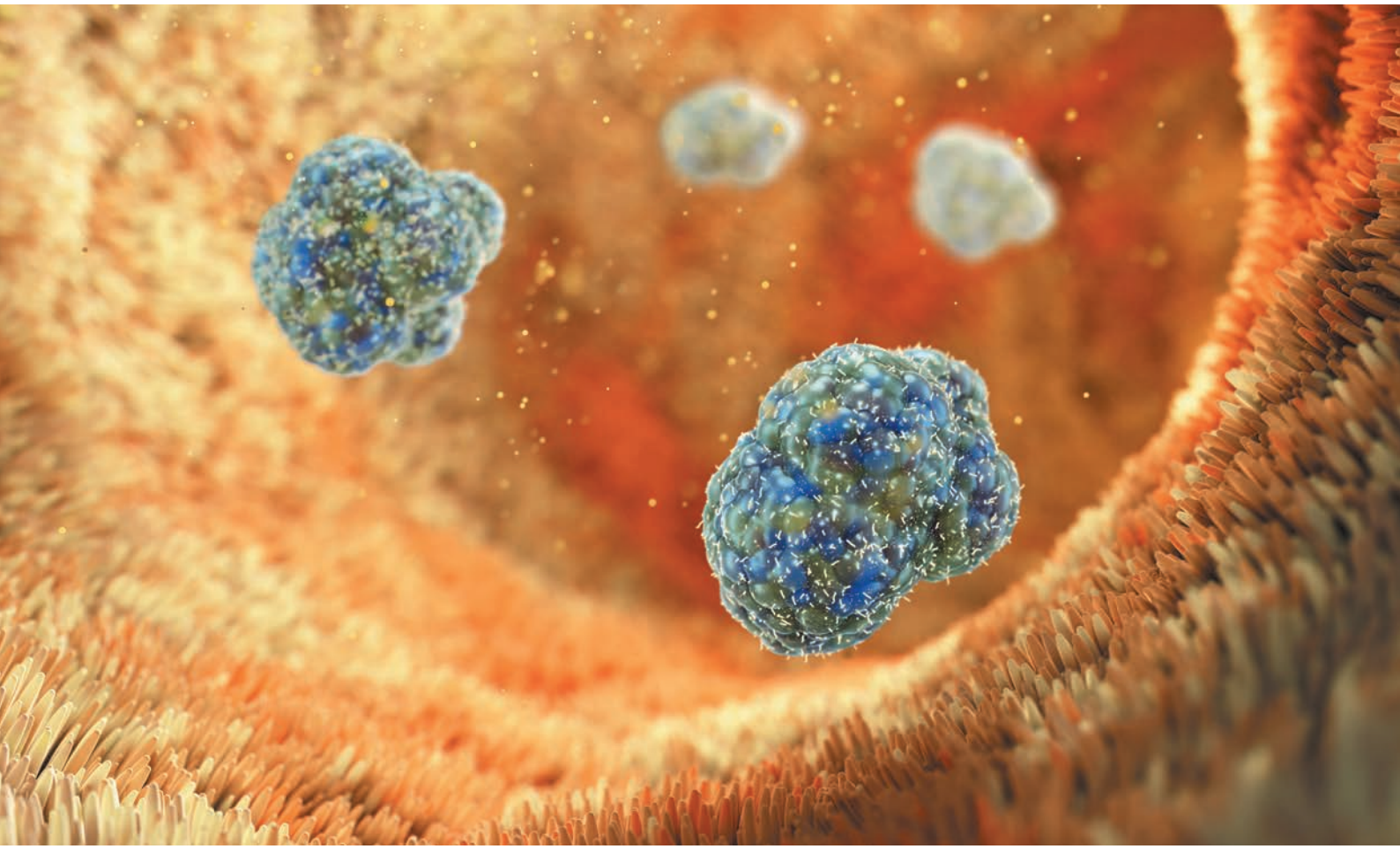
We hope that this project will contribute new basic scientific knowledge to the field, thereby facilitating further research into phage-related therapies for inflammatory bowel disease and other gut-related diseases. It would be ideal if we could learn how to target and then limit inflammatory processes before they begin. This would vastly improve patient quality of life. ■

VIRAL GUT COMPONENTS COULD INFLUENCE IBD FLARE-UPS IN CHILDREN

A team led by Souhaila Al Khodor will use a Global Grant for Gut Health (GGGH) to examine the role of the gut virome in children with inflammatory bowel diseases.

Souhaila Al Khodor is the director of the Reproductive and Perinatal Health Division and the head of the Microbiome and Biomarkers Discovery Lab at Sidra Medicine, a women and children's Hospital in Doha, Qatar. Al Khodor's laboratory focuses on using multi-omics (metagenomics, transcriptomics, proteomics) and computational biology tools to understand the molecular mechanisms underlying various diseases and identify early biomarkers for disease prediction. Her team conducts leading research on pregnancy complications and complex paediatric disorders including inflammatory bowel disease.

Why is researching IBD in children so important?
The incidence of inflammatory bowel disease (IBD) is rising globally, and this is becoming particularly stark in the Middle East and North Africa. The causes of IBD are still unclear, but they likely include a combination of genetic and environmental factors with immune system dysfunction. For reasons that are not yet clear, younger patients tend to experience more severe versions of IBD that require aggressive treatment. So the earlier we diagnose IBD and intervene, the better it is for their long-term health. I firmly believe



A conceptual illustration showing viruses in the intestines. A neglected component of the gut microbiome, viruses may play an important role in inflammatory bowel disease.

Alllex/E+/Getty

that we cannot fully understand disease pathophysiology without looking at the microbiome and its composition.

What encouraged you to apply for the GGGH this year?

I attended the International Human Microbiome conference in Rome in June 2024, where our initial cohort data was presented, and our work received an award for the best poster. I heard that the GGGH focus for this year was moving beyond gut bacteria into other aspects of the microbiome, including the mycobiome (fungal components) and the virome (viral components).

Our gut is an ecosystem comprised of bacteria, viruses and fungi that are all interacting with each other and with host cells. The bacteria do not work alone — they function in consortiums with each other, and with viruses and fungi. How these organisms work together probably impacts the progression of IBD, phases of relapse, and responses to treatment. The virome is the last piece of the puzzle that we have been missing in our paediatric IBD research. We already have an established longitudinal cohort with hundreds of samples to work with. From there, I felt encouraged to write the grant application, and I'm delighted that it was successful.

Tell us more about your longitudinal cohort.

IBD can be a truly debilitating condition, especially during periods of severe relapse. Children may miss school because of the pain, and sometimes they need to be admitted to hospital. In 2017, I received a grant from Qatar National Research Fund to build the first biorepository of paediatric IBD in Qatar. I designed the study so that, rather than taking a single snapshot of one patient at a specific point during their illness, we would take multiple samples from the same patients over time. We collected blood, stool and saliva samples from our young patients, and we followed them up every three months or every time they felt unwell. We were keen to limit the invasiveness of tests and sample taking, and so we also collected saliva samples from our patients. Blood samples allowed us to assess the transcriptome and understand how the immune system interacts with various microbial stimulations in IBD patients, while stool samples gave us insights into the composition of the gut microbiome.

What are the aims of your GGGH project?

Understanding the gut virome of paediatric patients will provide us with a more holistic and improved understanding of paediatric IBD and its causes. We already have an extensive data set collected from our paediatric cohort, which includes 46 patients with Crohn's disease, 21 patients with ulcerative colitis, 8 patients with unclassified IBD, and 8 patients with very early onset IBD, together with 58 age- and gender-matched healthy controls. Each patient has a specific trajectory of disease, and we have collected samples from them both during remission and disease relapse over time.

We have existing bacterial and mycobiome data, and we want to add the virome into this to assess inter-kingdom networks within the gut. We will analyse the networks between these different types of gut microbes and assess how they influence both health and disease states within the gut.

What analytical techniques will you use?

Firstly, we'll conduct in-depth sequencing of the viral component of the microbiome using an established protocol and bioinformatics pipeline. We will then model the networks between viruses, fungi and bacteria in the gut to examine the associations between different microbes. Imagine a series of nodes, some larger and more significant than others, but all interacting, both with one another and with smaller, secondary nodes. Next, we will analyse how this crosstalk between organisms differs between healthy guts and the guts of our IBD patients, and within individual patients when they are in relapse or remission.

Souhaila Al Khodor (right) working with samples (left) from patients with inflammatory bowel disease.

Finally, we hope to highlight the key players causing the imbalances in the gut microbiome that we see in children with IBD. Of course, all of these interactions between viruses, fungi and the gut microbiome will generate a huge amount of complex data to disentangle. My team will use various analysis strategies to ensure that we have a high signal-to-noise ratio within each dataset, so that we gather meaningful, targeted information.

What practical applications will this study have?

The gut virome is a relatively new field of research, and so contributing to basic science is a key part of our project. Understanding crosstalk and how the microbial kingdoms are interacting in patients versus healthy subjects is a unique approach, and scientists need to identify the correct intruders before attempting to take aim at them.

I'm hopeful that our findings will reveal patterns and potential targets for treatments in patients at different stages of disease. I envisage a future where we use personalized, precision medicine to diagnose and treat the disease early, and where we can move away from invasive sampling and treatment techniques, particularly for children. ■

THE HIDDEN ROLE OF GUT FUNGI IN NEURODEGENERATIVE DISEASES

Immunologist Virginia Pedicord and co-workers will use their Global Grant for Gut Health to explore how fungal components of the gut microbiome may play a role in the early stages of neurodegenerative diseases and dementia.

Virginia Pedicord is a group leader at the Cambridge Institute of Therapeutic Immunology and Infectious Disease (CITIID) at the University of Cambridge in the UK. She performed her doctoral studies with Jim Allison at Memorial Sloan Kettering Cancer Center in New York City, US, and her postdoctoral training at the Rockefeller University in New York City. Using functional metagenomics, *in vivo* models, cellular immunology, transcriptomics and proteomics, her research group identifies the cellular and molecular mechanisms by which resident gut microbes modify biological processes in their hosts. This allows them to characterize the complex interactions between the commensal microbial community and their environment during host development, homeostasis and the perturbations of disease.

How does the brain interact with the gut microbiome?

The microbiome, together with the metabolites it generates, educates and trains the immune system in ways that affect the entire body. We are in effect a 'holobiont' — an ecosystem hosting the microbial inhabitants that we have co-evolved with. We have evolved to respond to cues from these microbes, and they have evolved to respond to cues from us.

Some cues from the microbiome support the healthy functioning of the central nervous system. When signals from the gut microbiome are disrupted, this

can interfere with the integrity of various components of the central nervous system, potentially triggering harmful neuroinflammation and neurodegeneration.

How might changes to the gut's fungal components affect the brain?

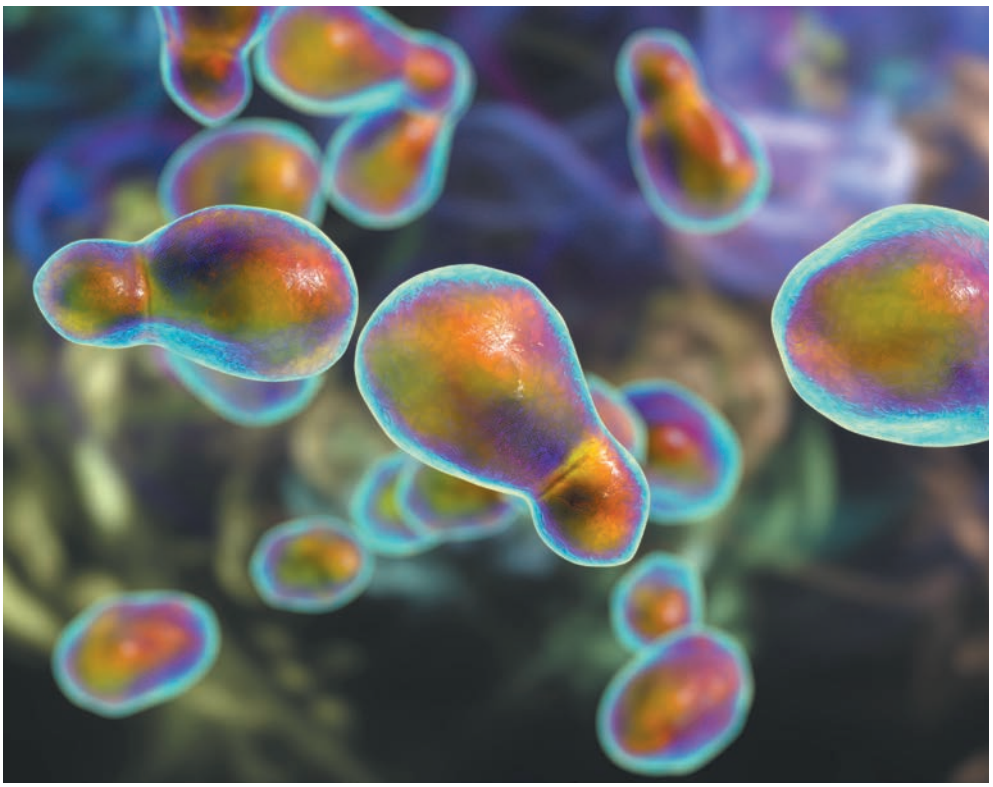
This is an area that we are only beginning to understand. The resident fungi, or the mycobiome, remain an understudied component of the human gut ecosystem.

Scientists have long studied host cell responses to fungal, bacterial and viral pathogens. For example, we know quite a bit about fungal meningitis. But we know far less about general health states with regard to fungal metabolites from the microbiome that may disseminate throughout the body, how our body responds to them, and what happens when these patterns are altered or disrupted. The severe neuroinflammatory response in fungal meningitis gives us an indication of how bad things can get in a pathogenic setting. But how might 'normal' fungal metabolites contribute to neurodegeneration?

For example, we know that dysregulation of the integrity of the blood–brain barrier is associated with dementia and Alzheimer's disease. We believe that there are cues coming from resident fungal microbes that could be modulating barriers in the host. In our GGGH project, we hope to explore how and why this might affect neurodegenerative diseases.

What are the goals of your GGGH project?

We will optimize existing bioinformatics tools to exploit the vast public repositories of patient metagenomic data that already exist, avoiding the need to sequence new samples. We will use these tools to mine these databases and extract information about the fungal component of the gut microbiome. We will then search for important associations between the mycobiome and neurodegeneration and dementia, and any potential triggers within these interactions. Imbalances between the bacteria and the fungi in the gut may indicate a predisposition to neurodegeneration. If we can pinpoint specific interactions or imbalances, we can then test these hypotheses in germ-free mouse models — mice bred without any commensal microbes in their bodies. We can add different microbes of interest to their guts to test how different combinations of bacteria and fungi affect the brain and ultimately memory and cognition.



Kateryna Kon/Shutterstock

Fungi have the potential to cause damaging neuroinflammation.

How do antibiotics affect the fungal components of the gut?

Within any healthy human gut ecosystem, there needs to be an ecological balance between the bacteria, viruses and fungi present. All these microbes interact and regulate each other's activity. If antibiotics, for example, diminish the bacterial component, the fungal and viral communities will also be affected. When bacteria are killed off, it results in a skewed ratio of different fungal members of the community, and this could contribute to more fungal-induced neuroinflammation in certain patients, perhaps due to fungal overgrowth. We plan to explore this.

How will AI help you to examine the mycobiome?

Even just two years ago, the scope of this project was just a pipe dream. It has been amazing to see how fast this technology has progressed. The algorithms we are developing will specifically seek out fungal DNA in the databases. AI forms part of this — we are using AI to help optimize data filtering and analyses, and it could help us identify false positive associations, for instance. Incorporating AI allows us to look at the data in a more holistic way, enabling us to observe the wider picture. For example, take our co-evolution alongside the microbes that live inside us: it would be fascinating to understand how different evolutionary pressures have shaped our development, our responses to our resident microbes, and how they respond to us.

What are the potential applications of your results?

Firstly, we hope to contribute new knowledge to the basic science of how neurodegenerative disorders might first develop, because that remains a key challenge in our field. Anything we learn in this regard will intrinsically reshape how we think about these diseases and how they are triggered. Our project may open up new possibilities for how these conditions could be treated or even prevented. It would be great if we could identify biomarkers for early diagnosis and early treatments in neurodegenerative diseases, including Alzheimer's disease. ■

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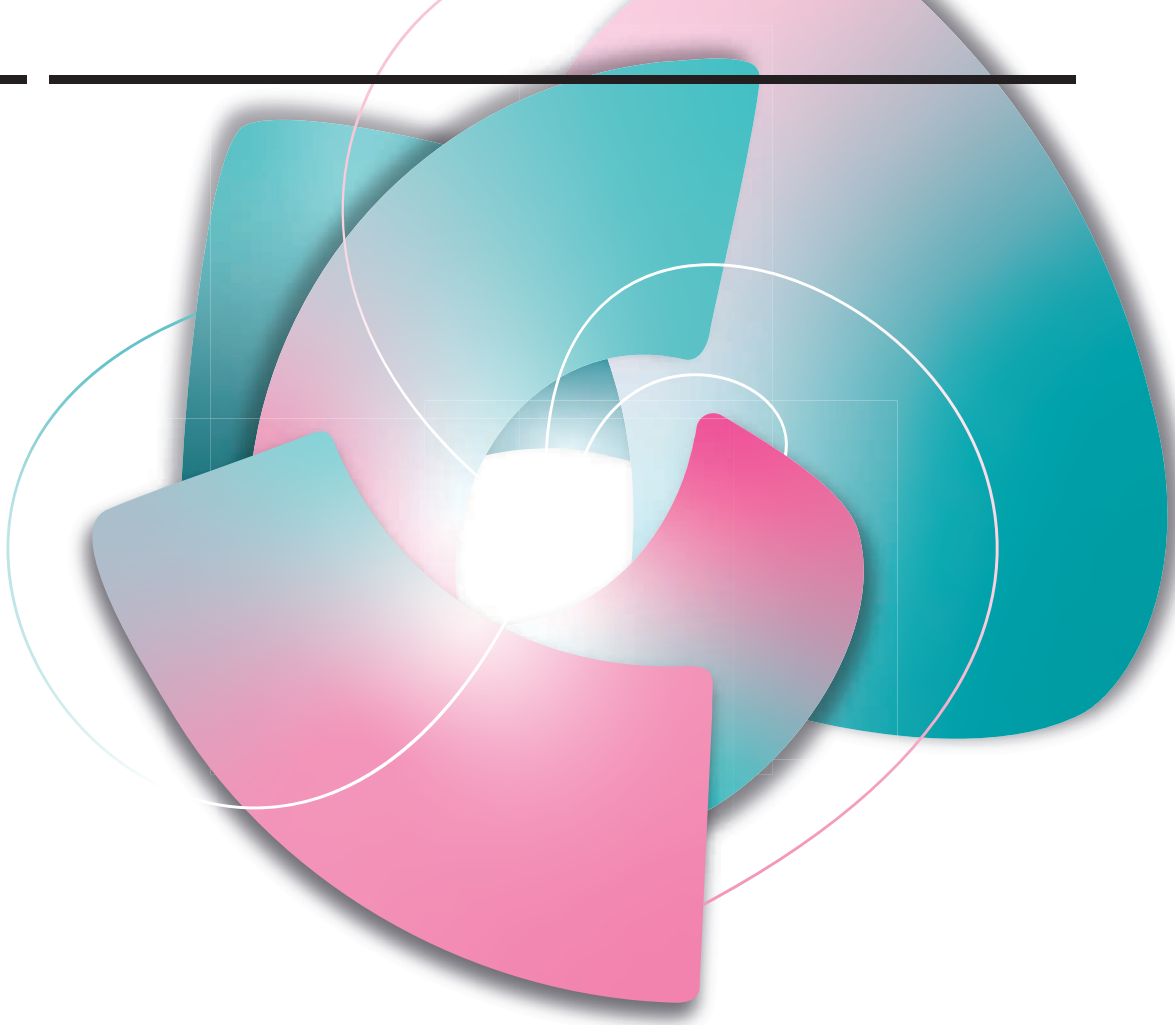

Investigating the gut microbiota and its role in human health

The Global Grants for Gut Health program funds investigator-initiated research on gut microbiota, supporting one-year projects that advance our understanding of its impact on human health. With funding of up to US$100,000, recipients can pursue their research goals while gaining visibility through featured placement on the Nature Portfolio platform. Each annual funding cycle makes up to three grants available for innovative research projects, creating opportunities for meaningful contributions to this expanding field.

2025 Key Dates

Application deadline: **September 9, 2025**

Assessment: **November 2025**

Notification: **December 2025**

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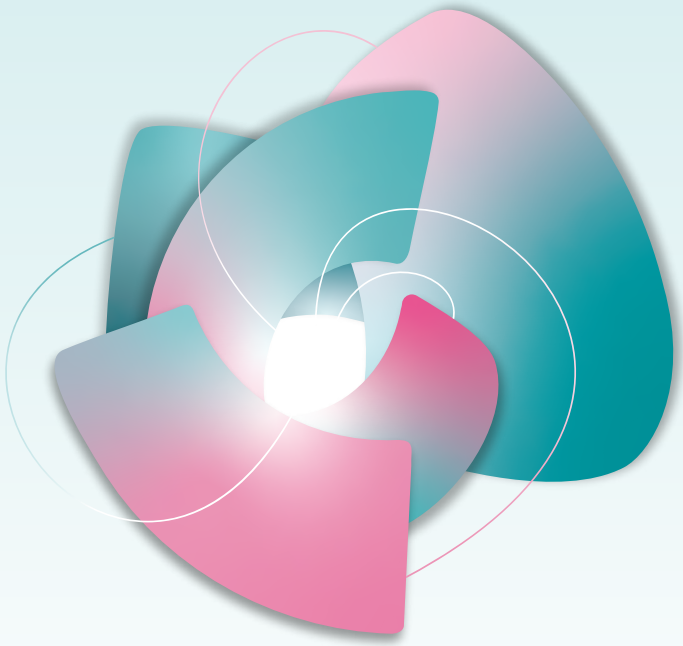

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