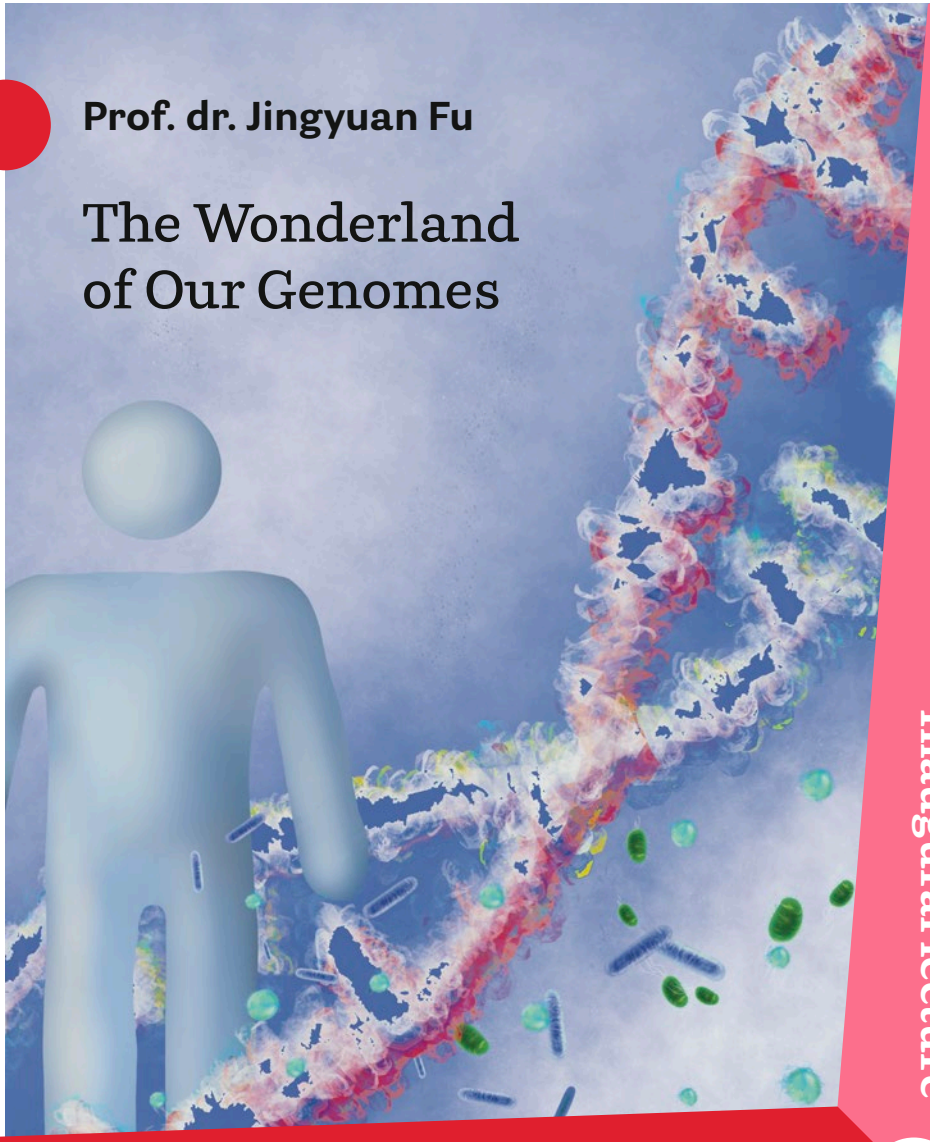
university of groningen

umcg



Prof. dr. Jingyuan Fu

The Wonderland of Our Genomes

Inaugural lecture

21 April 2023

The Wonderland of Our Genomes

Inaugural lecture by

Prof. dr. Jingyuan Fu

21 April 2023

On acceptance of the post of professor of

Systems Medicine

at the

Faculty of Medical Sciences

University of Groningen

university of groningen

Published by University of Groningen Press
Broerstraat 4
9712 CP Groningen
https://ugp.rug.nl/

Design: LINE UP boek en media bv | Riëtte van Zwol
Cover illustration: Jingyuan Fu
Photo author: Jingyuan Fu
Illustrations: Jingyuan Fu, Vivian Yang, Carlos Martinez Moreno, Isabel Tamargo-Rubio
Editing: Kate Mc Intyre

DOI: https://doi.org/10.21827/6422ddb18e087

Dear Rector Magnificus,
Members of the Board of the
University and the UMCG,
Colleagues, Students,
all my friends and family,
Ladies and Gentlemen,

thank you for coming.

2023 is a landmark year for human genome researchers worldwide. This year marks the 20th anniversary of the completion of the Human Genome Project, as well as the 10th anniversary of completion of the first phase of the Human Microbiome project. These projects have established the reference sequences of the human genome and the gut microbiome. Now, just as Alice entered a new wonderland when she chased the rabbit down the hole, a completely new horizon of human genomes research has opened up in front of us. Since we took this great leap into the unknown, we have witnessed a data explosion that has been driven by the rapid development of high-throughput sequencing and genomic data profiling. Population-level genomic research in the UMCG and University of Groningen has blossomed and become fruitful, and we are very proud that our work in the past decade has been recognized internationally and that some of our research has already been included in a biology textbook for Dutch high school students.

A major component of this success is due to the Lifelines cohort, the population-based biobank that makes large-scale genomics research possible. Based on Lifelines, several landmark genomics projects have been initiated, namely the UMCG Genetics Lifelines Initiative that focuses on the human genome, the Lifelines Dutch Microbiome Project that focuses on the human microbiome, and the Lifelines-DEEP project that

investigates the molecular routes from genotype to phenotype via multiple genomics data integration. I am very delighted to see most of the project founders here today. They include Prof. Cisca Wijmenga, who initiated all of these projects a number of years ago and who is now our Rector Magnificus, Prof. Sasha Zhernakova from the Department of Genetics, Prof. Rinse Weersma from the Department of Gastroenterology and Hepatology and Prof. Hermie Harmsen from the Department of Medical Microbiology. But I am also missing one very special and important person, Prof. Marten Hofker, who initiated the first nation-wide consortium to investigate the role of the gut microbiome in cardiovascular disease and who was the founder of the Dutch Microbiome Project. Sadly, Marten passed away a few years ago, and I would like to address special thanks to him today. My journey to the wonderland of human genomes could never have gone so far without these leaders, my collaborators, and all of my past and current team members, and the support of my family, most of whom are also sitting in this hall.

2023 is also an exciting year for researchers who believe that microbiome-based medicine may lead to a clinical revolution. In November 2022, the U.S. Food and Drug Administration approved the first-ever fecal microbiota product for the prevention of recurrent *C. difficile* infections. This marks a turning point for microbiome therapy. It has become clear that personal-

ized medicine needs to be re-conceptualized, and that we should take both the human genome and the gut microbiome into account simultaneously. Different from our genetics, which are already determined before birth and won't change over time, our gut microbiome is acquired and established after birth and can undergo dynamic changes during the whole course of our lives. More importantly, the gut microbiome can be modified, by diet, probiotics, prebiotics, medication, fecal microbiota transplantation and many other means, making it an attractive therapeutic target for disease prevention and treatment. To pave the way to the second-phase of personalized medicine, clinical translation needs us to come to understand causality and mechanisms of how the human genome, the gut microbiome and the environment interact with each other and affect human health and disease.

In answering that call, 2023 also marks the beginning of a new chapter for Groningen microbiome research. Microbiome research has become an important research pillar of the UMCG, and we will soon officially open the Groningen Microbiome Hub. This hub aims to facilitate microbiome-based research and clinical translation.

2023 also marks a milestone in my journey in pursuing fundamental understanding of host–microbe interactions in human health, as a newly appointed Professor of Systems Medicine. You may wonder which way I ought to go? This afternoon, I'd like to take this opportunity to outline several challenges that we are facing, as well as the opportunities I see. I would also like to share my vision of how to keep Groningen microbiome research at the forefront of technological development, scientific discoveries and clinical translation.

WHICH WAY TO GO?

Vivian Yang

Only time will tell

In our experience up to now, it actually seems more difficult to find a disease that does not associate with the gut microbiome than to find one that does. The causality behind genetic associations with human diseases is straightforward, as the effect can only go from genotype to phenotype. In contrast, microbial associations do not directly imply causality. They could be due to the confounding effects of environmental factors, such as diet, and the effects can also be bi-directional. The gut microbes can influence human health, but the physical status of the host can also influence the microbial community in the gut. So it is very difficult to find out what is "chicken" and what is "egg" here. Host genetic variants can be used as instrumental variables to make inferences about causality using a method called Mendelian randomization. However, as the effect of host genetics on the gut microbiome turns out to be small, the power of such an analysis is low. The causality of most cross-sectional associations thus remains to be solved. So how can we tell causality from association? One answer is "Time will tell".

Longitudinal, prospective cohorts will be of great value in causal inference. Since 2006, Lifelines has completed three rounds of screening, with 4–5 years between each round. We have also completed microbial sample collection at three timepoints. These include fecal microbiota collection from about 1,500 individuals of the Lifelines-DEEP cohort in 2012;

fecal, nasal and throat microbiome collection from 10,000 individuals of the Dutch Microbiome Project in 2016 and follow-up collection in over 4,000 individuals completed last year. With the 10-year follow-up data, we expect to answer many questions that cross-sectional studies cannot, particularly about temporal variation in the gut microbiome and its causal relationships with phenotypic developments in individuals. However, for most chronic disorders, the change within 10 years is still limited. It would therefore be very important to make fecal sample collection a part of regular protocols for Lifelines sample collection, in order to keep cohort-based microbiome research sustainable. This is unfortunately not yet the case, so it would be of great benefit if this could be organized centrally.

We have to recognize that time stops for no one. While we are enormously proud that we were among the first to carry out population-based microbiome research in the Netherlands, and even worldwide, other large studies that include thousands of individuals have now been initiated in Israel, France, Finland, the UK and many other countries. If we lose our current leading position, it will be almost impossible to get it back. We need to take action to secure our position before it is too late. Moreover, the population-wide microbiome data we generate also serves as a reference to study the microbiome in diseases. To facilitate genomics and microbiome research in disease cohorts, we are also very happy to share our genome and microbiome research

experience and protocols, for instance, via the help of the Cohort and Biobank Coordination Hub of the UMCG. This also fits well with the UMCG's ambition of the to become a "*cohort champion*".

TIME WILL TELL

Vivian Yang

The red queen and the white queen

Another challenge of gut microbiome research is the lack of an ecological view and of functional understanding of the microbial community. Microorganisms do not live separately; they interact with each other. Some species interact with many other members and play an important role in maintaining a niche community, and these central species are referred to as "*keystone species*". You can also think of them as a "*queen*" in the microbial community. However, even within the same species, there can be large genomic variations at strain level. Thus, just like the red and white queens in Wonderland, who are sisters but have completely different characteristics, two strains within the same bacterial species can behave very differently. One strain can be beneficial and maintain microbial homeostasis, while another can be pathogenic and lead to microbial dysbiosis. Thus, to truly understand microbial functionality, we need to zoom in on the differences in their genetic makeup and gene content.

My research group is among the first to have made this leap from microbial composition to microbial genetic makeup. By making use of bacterial genetic variants, we can now zoom in from species level to sub-species or strain level and distinguish the "*red queen*" from the "*white queen*" based on their gene contents. Moreover, building on the concept of genome-wide association study conducted in the human genetics field, my

research group is now developing approaches to carry out bacterial SNP-based metagenome-wide associations. In such a way, we hope to pinpoint functional bacterial genes that may play an important role in human health and determine how to turn the "*red queen*" into the "*white queen*". In the coming 5 years, my research group will devote efforts to this new level of discovery, thanks to support from my NWO-VICI grant.

RED QUEEN VS WHITE QUEEN


DALL-E2

Believe as many as six impossible things – the AI revolution

More than ever, I, probably like most of you, have suddenly realized that artificial intelligence is around the corner. The picture you see behind me was made using DALL.E[1], an AI system that can create realistic images and art from a description in natural language, in this case: "*A caterpillar sits on a magic mushroom and uses a computer, Alice in Wonderland*". Right now, everyone is talking about ChatGPT[2], which is a natural language processing tool based on AI technology that allows people to have a human-like conversation with a computer. ChatGPT might even have composed a better inaugural lecture than I have.

These are AI advances that are very much in the public eye. What most of you may not know is that AI advances have also been made in many scientific areas, such as structural biology. Traditionally, structural identification of individual proteins by X-ray crystallography or electron microscopy would take months or years. Recent AI breakthroughs like AlphaFold[3] and RoseTTAfold[4] now enable highly accurate protein structure prediction. Structure prediction can also be enhanced by leveraging large language models, as demonstrated by the Meta AI team who developed a new protein-folding approach, ESMfold[5],

1 https://openai.com/product/dall-e-2
2 https://chat.openai.com/chat
3 Jumper, J. et al. *Nature* 596, 583–589 (2021)
4 Humphreys, I. et al. *Science* 374, eabm4805 (2021).
5 https://esmatlas.com

to generate the structures of the metagenomic world at the scale of hundreds of millions of proteins. This AI-based structural biology advance, in combination with targeted experimental validations, opens up unprecedented opportunities for structure-based classification, annotation and novel metabolite discovery. My research group is currently taking this novel route and moving from sequence-based 1D prediction towards 3D- and 4D-based prediction of bacterial gene function.

Moreover, AI will be very powerful when it meets big data. The UMCG has now set up the Data Science Center in Health, referred to as DASH, to promote data-driven innovation and support research, education and implementation in the field of data science, AI and eHealth. I hope the coming years will bring a closer collaboration with AI experts and the chance to let our big data on genome, metagenome, exposome and omics meet AI in order to enable data-driven knowledge discovery, patient stratification and therapeutic decision-making.

BELIEVE AS MANY AS SIX IMPOSSIBLE THINGS

Carlos Martinez Moreno
Isabel Tamargo-Rubio

Metabolic alliance

To develop microbiome-directed strategies for disease prevention and treatment, we also need to understand the mechanisms of how gut microbes affect our health via their interactions with host genetics and environment, especially our diet. Microbes are believed to play an essential role in human immunity and metabolism. My research covers both areas, but with a greater focus on metabolism. Every living organism needs a continuous input of energy for its existence, including humans and the microorganisms living in the human gut. Small molecules used as building blocks and energy for cells are called metabolites, and the chemical processes to generate these metabolites are called metabolic processes. Our diet is the source for various substrates crucial to these metabolic processes. So, as you can imagine, we and our gut microbes share food, which means that you eat not only for yourself but also for your gut microbes.

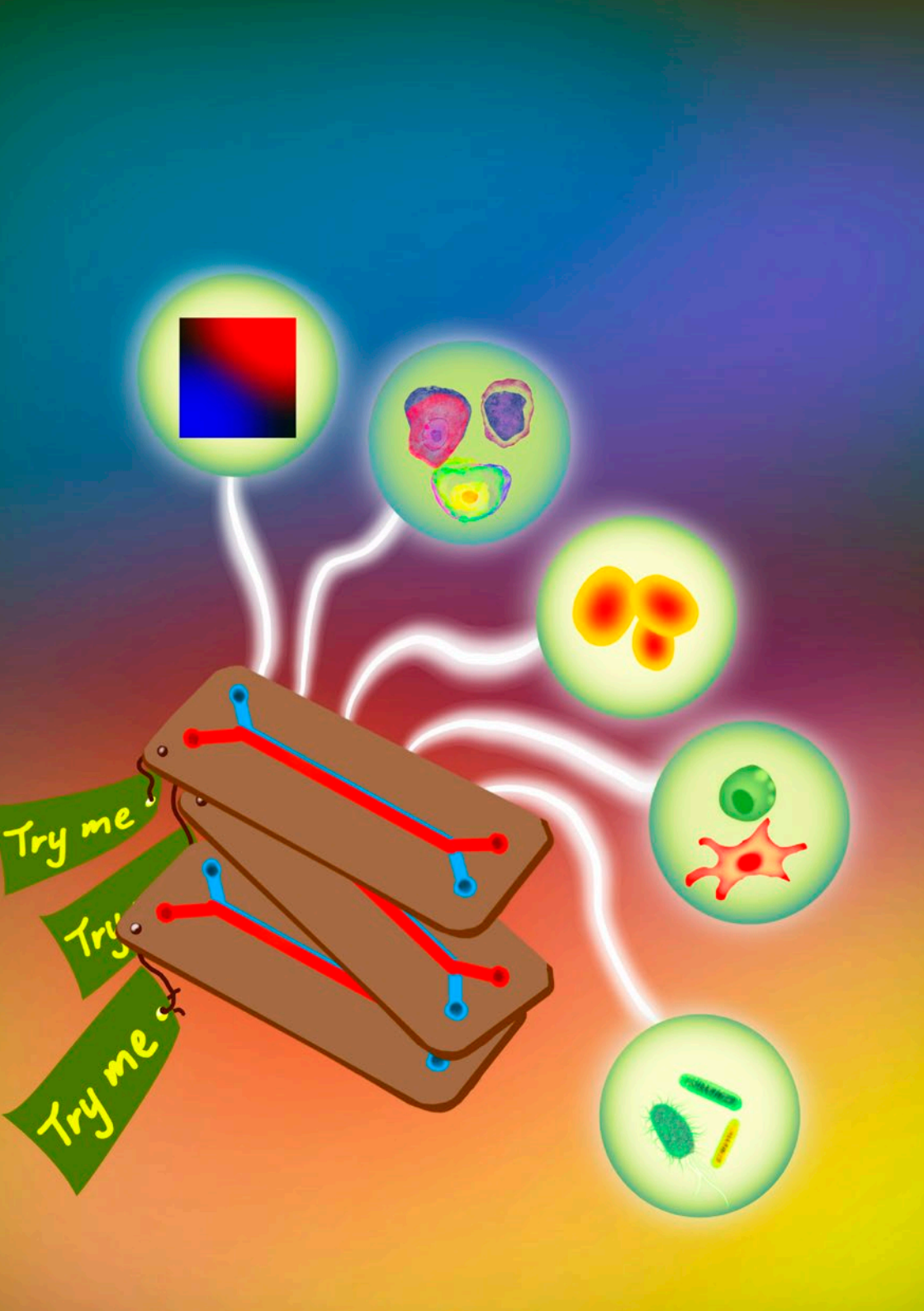
There are extensive metabolic interactions between a human host and their gut microbes, and together they form an alliance to maintain metabolic homeostasis of the human body. Diet–microbe–host interactions in metabolism are a complex process. Human metabolism analysis is still centered on blood. The study of fecal and urine metabolism lags far behind the study of plasma metabolism, and we still lack a comprehensive overview of the metabolic landscape in the human body.

Moreover, metabolic profiling in humans is often a static measurement, while metabolic processes are dynamic. Fluxomics is an emerging omics technique to assess the rate of metabolic fluxes and portray the whole picture of molecular interactions, with fluxomics using stable isotope labeling compounds or heavy water increasingly being used to monitor metabolic pathways. This technology has already been implemented in the Interfaculty Mass Spectrometry Center of the UMCG. Making use of it, I hope to obtain a more comprehensive overview of metabolic dynamics in host–microbe interactions. The Laboratory of Pediatrics has a mission to build the future of metabolic health from early childhood onwards, and I believe my expertise in host–microbe interaction in metabolism can make a substantial contribution to that goal.

In addition to metabolism in general, I have a special interest in drug metabolism. Nearly half the European adult population suffers from at least one chronic disorder, yet individual response rates to commonly prescribed drugs are typically in the range of 50–75%, with some patients showing adverse drug responses, which are the cause of about 3.5% of the hospital admissions in Europe. Genetics is one factor that determines an individual's drug response, and the Department of Genetics has launched a pharmacogenetics passport project to leverage genetic information for therapeutic decision-making. In line with this, I developed the pharmacomicrobiomics project BugDrug because the

gut microbiome can also contribute to drug metabolism and affect drug bioavailability, activity and toxicity. With the support of my ERC-Consolidator grant, I am working to combine genetics and the gut microbiome to better predict an individual's drug response. More importantly, we aim to modify the gut microbiome to lower drug toxicity and make drug non-responders into responders. To do so, I have set up a collaboration with the Department of Clinical Pharmacy and Pharmacology of the UMCG.

METABOLIC ALLIANCE


Try me
Try me

Magic cookie in organ-on-a-chip

However, mechanistic study of host–microbe interactions in metabolism and drug response faces some technical challenges. Experimental animals cannot recapitulate human physiology, and we currently lack a human-based, in vitro system that would allow us to study the human genome and metagenome simultaneously. The call in the European Union for non-animal, human-based tools and strategies for biomedical research is also getting louder and louder. In Wonderland, Alice drinks the "*Drink Me*" potion and eats the "*Eat Me*" cookies to change her size. In a sense, such magical cookies now exist for humans in the form of an "*organ-on-a-chip*". With this technology, we are able to create a physiological model of a human organ on a microfluidic platform that is approximately the size of a USB stick. Combining this together with the technological advance of human induced pluripotent stem cells (HIPSCs), which can be further differentiated to different tissue cell types, we can construct a personalized mini-organ-on-a-chip, like a mini-gut or mini-liver, with the same exact genetic background as you.

The Netherlands Organ-on-a-Chip Initiative and the Institute of Human Organ and Disease Model Technologies have a mission to develop cell culture models that mimic healthy and diseased human tissues based on organ-on-chip technology. For my research focus on host–microbe interactions in metabo-

lism, I will need to model the microbe–gut–liver axis in metabolism, and I am in a unique position at the UMCG to develop such a system. HiPSC-based gut-on-a-chip is already operational at the UMCG due to outstanding successful advances made by the research team of Prof. Sebo Withoff. Through collaboration with the Withoff team, my research group has already made significant advancements in hiPSC-based liver-on-a-chip.

My research team is also able to use bacterial culture tools to investigate the function of gut microbes thanks to a partnership with Prof. Hermie Harmsen, a specialist in anaerobic bacterial culture. Although the culturing of gut microbes and gut- and liver-on-a-chip are separate methods at the moment, I, together with many of my colleagues, have the ambition to make them physiologically connected in order to model the microbe–gut–liver axis for biomedical research. In that aspect, our chip system should be able to model physical and chemical gradients to mimic the in vivo cellular environment and enable co-culture of different cell types, which can be from different origins, such as organoids, hiPSCs or primary cells. Moreover, we aim to co-culture microbes with human cells to directly assess host–microbe interactions. This is one of the most important missions of the Groningen Microbiome Hub, which aims to create a platform where different technologies can converge, including functional genomics, bacterial culturomics, cellular biology, metabolism, organ-on-a-chip and big data.

ORGAN ON A CHIP

Vivian Yang

Curiouser and curiouser: mapping curiosity into student learning activities

This research line is relatively new and has quickly developed into a multi-disciplinary research area over the past decade. To ensure the sustainability of this research, there is no doubt that we need to foster tomorrow's scientists and train the next generation of leaders in this rapidly evolving field. This should be done at different levels.

First, we ought to continuously adapt our bachelor's and master's curricula and implement educational modules with current-state-of-the-art knowledge components. In the past decade, the University of Groningen has already paid special attention to this issue, and many new courses on genetics and genomics, big data and the microbiome have been set up, including the "*Big Data in Human Health*" course that I first organized in 2015.

Second, we need to break down the boundaries between faculties and promote interdisciplinary education. This is already happening. In line with the strategic plan of the University of Groningen to solve society's great challenges through connection and cooperation, four interdisciplinary schools have been set up where research, education and impact converge. These schools are the Wubbo Ockels School of Energy and Climate, the Aletta Jacobs School of Public Health, the Jantina Tammes

School of Digital Society, Technology and AI and the Rudolph Agricola School for Sustainable Development. Microbiome research and education can be linked to all of these schools due to its interdisciplinary nature and high potential for socio-economic impact.

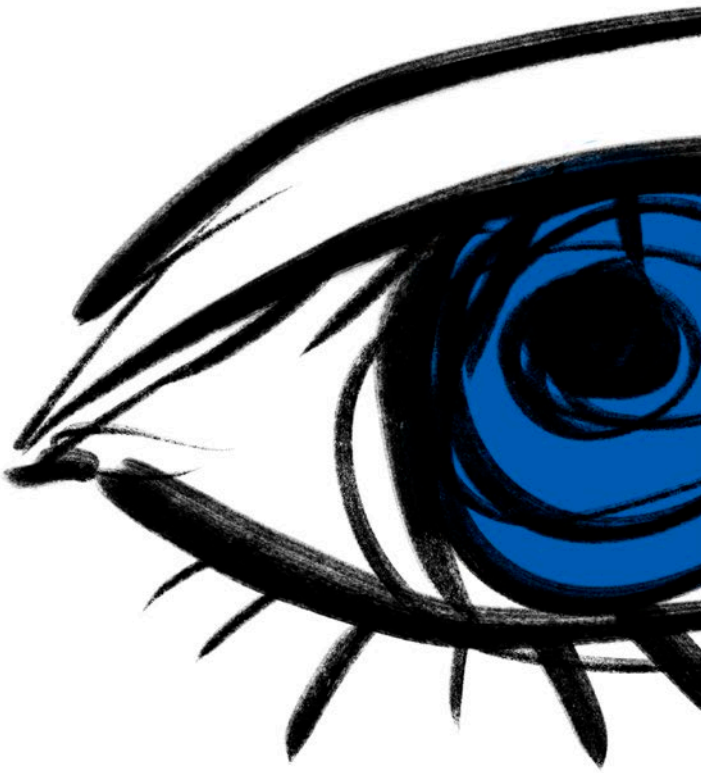
Third, in training Ph.D. students and postdocs, personal competencies are as important as scientific competencies, including, but not limited to, stress management, work-life balance and network-building. Many of you may have realized that it is getting more and more difficult to find and keep young talent in academia. We need to prioritize the health and sustainable growth of young researchers by providing a secure environment and career prospects. In addition to all of these, there is one thing, in my opinion, that is one of the most important elements in education: training students to become curiouser and curiouser! Curiosity is a driving force for learning, and we need to map curiosity into student learning activities. It is only when students become curious about something that we can turn passive education – passing facts from teacher to student – into active education in which students seek knowledge through interaction with teachers and other sources.

CURIOUSER & CURIOUSER

How can one possibly pay attention to a book with no pictures in it?

Communication in science is important. Albert Einstein said: "*The finest scientists are artists*". Or as Alice in Wonderland said: "*How can one possibly pay attention to a book with no pictures in it?*" I believe one good picture is better than a thousand words. We don't all have to become artists or develop our drawing skills, but I do believe that having a good sense of art can improve our scientific creativity, and vice versa. Making graphic illustrations for my research is my hobby, and I am very proud that many of my group members have also started to present their work using their "*artistic*" language. Nowadays, more and more journals are asking authors for graphical abstracts and potential cover art. Behind me, you can see some of the cover suggestions made by my group and its associated members. I am very proud that some of these have been featured as journal covers. This is an excellent way to increase the visibility of our research.

ART IN SCIENCE



Vivian Yang

Vivian Yang

Mad, we are all mad here!

In the past 30 minutes, it has been my pleasure to share my enthusiasm for science, education and art. I am excited because I believe the next phase of personalized medicine is coming, one that will include both an individual's genetics and their gut microbiome in developing personalized strategies to improve health.

One can imagine that, maybe in the near future, everyone will have a genetic passport made at birth, and every house will be equipped with a high-tech, smart toilet that analyzes your stools every day and provides a real-time monitor of your gut microbiome and metabolism. Computers with AI technology will integrate all of your data, monitor your health and provide personalized suggestions.

Have I gone mad? As the Mad Hatter said:
"*The best people usually are!*"

Ik heb gezegd.

SMART MEDICAL HOME

Acknowledgement

There are so many people whom I need to thank, and it is difficult for me to decide where to start.

Let's first begin with my supervisors and mentors, who have had a big influence on my career development, including Cisca Wijmenga, Marten Hofker, Ritsert Jansen, Folkert Kuipers, Nine Knoers, Eduard Verhagen and Dewei Zhu. I wanted to take a moment to express my deep gratitude for your support of my work over the past years. Your trust, support and encouragement have made all the difference to me.

Sasha Zhernakova and Rinse Weersma, there are no words to express how lucky I feel that I could work together with you on gut microbiome research over the past decade. A triangle is the strongest shape, and I think that also represents the strength of the collaborations between the three of us. Your passion for science, dedication to our projects and unwavering support have been truly inspiring, and I feel incredibly lucky to have had the opportunity to work with colleagues as talented and dedicated as both of you.

There are so many colleagues and collaborators whom I cherish. They include, but are not limited to, Jackie Senior, Kate Mc Intyre, Gerard te Meerman, Lude Franke, Sebo Withoff, Hermie Harmsen, Serena Sanna, Jackie Dekens, Daan Town,

Debby Koonen, Paula Maas, Hélène Lauvenberg, Mathieu Platteel, Hans Jonker, Mihai Netea, Andre van der Ven, Niels Riksen, Max Nieuwdorp, Marnix Medema, Ramnik Xavier, Hongwei Zhou and Jun Wang. Most of you have also become close friends. Your kindness and generosity have made our time together so enjoyable, and I cherish the memories we have made both inside and outside of work.

The success of the work is all due to my team. I would like to thank all my past and current team members, including Naishi Li, Biljana Atanasovska, Marijke R. van der Sijde, Lianmin Chen, Shixian Hu, Valerie Collij, Marwah Doestzada, Daoming Wang, Sergio Andreu-Sánchez, Yue Zhang, Angel J. Ruiz-Moreno, Joanne Hoogeland, Dasha Zhernakova, Jiafei Wu, Jiqiu Wu, Isabel Tamargo Rubio, Victoria Palasantzas, Gwen Weijer, Ángela del Castillo Izquierdo, Haoran Peng, Toon Scheurink, Nataliia Kuzub, Asier Fernandez Pato, Johanne Spreckels, Lei Liu, Wenqiang Shen, Sana Garmaeva and Trishla Sinha, as well as all the Ph.D. students, postdocs and technicians from the Groningen Microbiome group and the NOCI-OoC team, including Marc-Jan Bonder, Alexander Kurilshikov, Ranko Gacesa, Arnau Vich Vila, Anastasia Gulyaeva, Renée Moerkens, Joram Mooiweer, Floris Imhann, Jody Gelderloos-Arends, Soesma Medema-Jankipersadsing, Dianne Jansen, Arno Bourgonje, Yanni Li, Jelle Slager, Esteban Lopera-Maya, Siobhan Brushett, Milla Brandão Gois, Laura A. Bolte, J. Casper

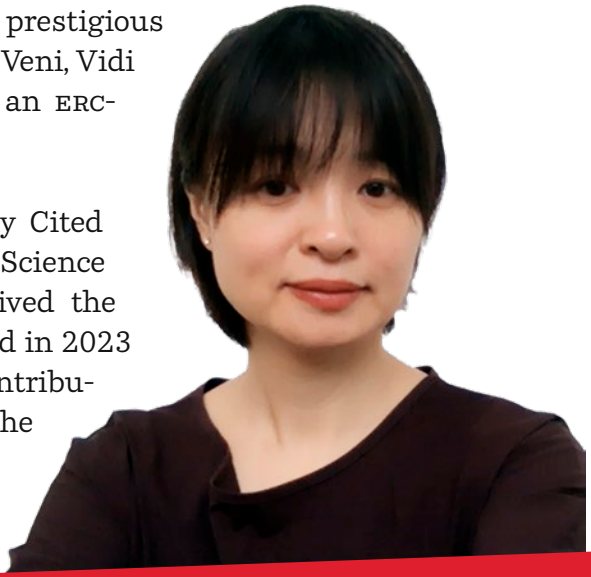
Swarte, Johannes R. Björk and so many others that I cannot list all of their names here.

Moreover, I would like to thank Marian Joels and Erik Boddeke for their support of the Groningen Microbiome Hub, the LifeLines organization for the fruitful collaboration and the Genomics Coordination Centre for providing data infrastructure. I also thank the funding institutes that have supported my research, in particular the Dutch Research Council (NWO), the European Research Council (ERC) and the Netherlands Heart Foundation (CVON).

Lastly, I would like to thank my parents (Shengqiao Fu and Weiyi Huang), my husband (Haifei Yang), my daughter (Vivian Yang), my brother and sister and their families (Yuanyuan Fu, Biyuan Fu, Yang Yu and Jing Huang) and all my relatives for their support and love.

Jingyuan Fu is Professor of Systems Medicine at the University Medical Center Groningen (UMCG). Her research aims to gain a better understanding of the interactions between the human genome and the gut microbiome in human health and disease in order to develop better ways to predict, prevent and treat diseases. To do so, her research employs large-scale genetics and genomics analysis of large numbers of people and functional understanding of the gut–liver axis in human metabolism developed using innovative technologies such as bacterial culturomics and organ-on-a-chip.

Fu studied Bioinformatics at the University of Groningen, where she obtained her Ph.D. with honours (*cum laude*) in 2007. She then joined the UMCG, where she started her own independent research group. Fu has received numerous prestigious grants, including NWO Veni, Vidi and Vici awards and an ERC-Consolidator award.



Fu has been a 'Highly Cited Researcher' on Web of Science since 2020. She received the AMMODO Science Award in 2023 for her outstanding contributions to research on the gut microbiome.