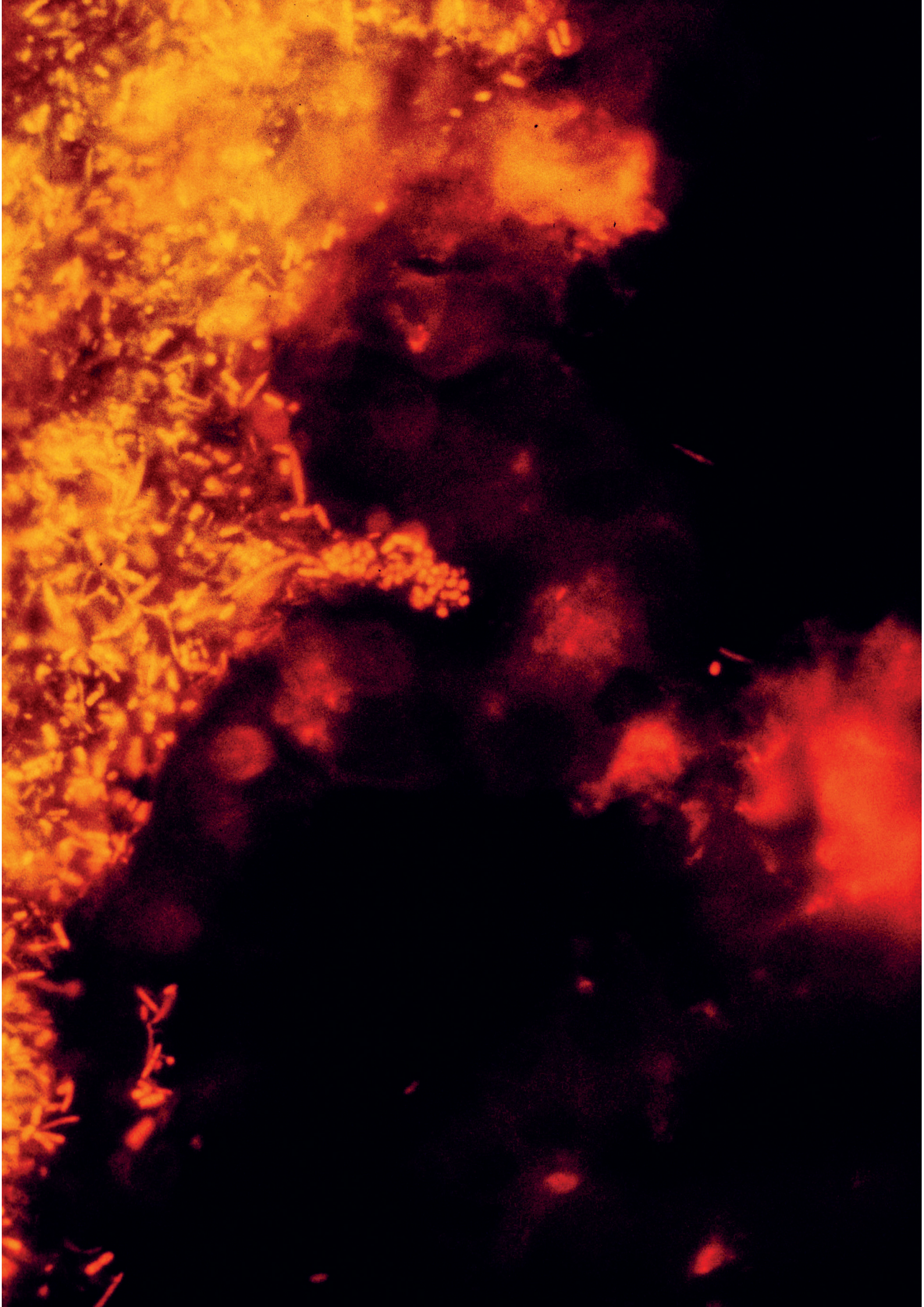
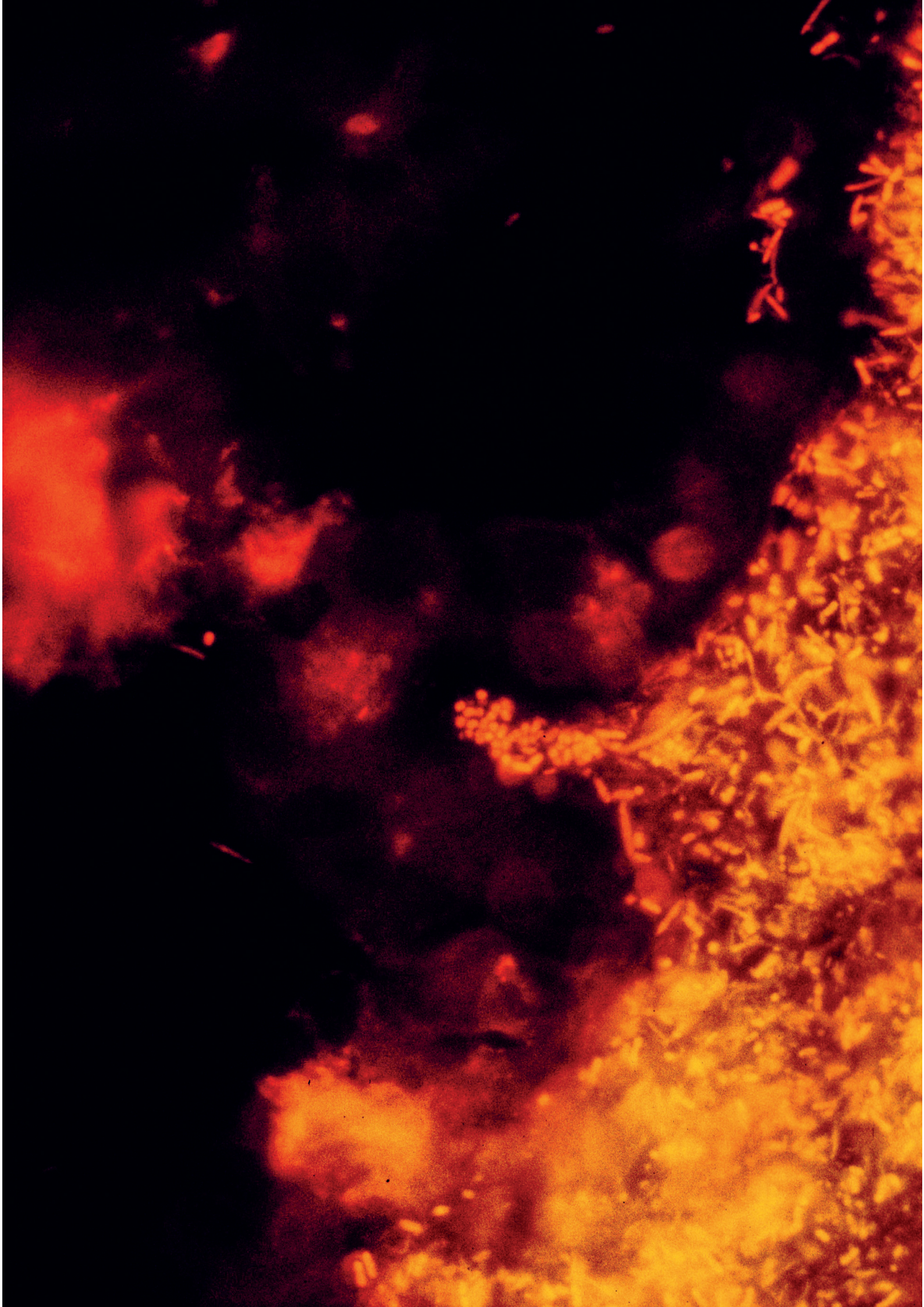


THE GUT MICROBIOTA OUR NEW HEALTH ALLY

Our body is home to ecosystems containing billions of microorganisms, known as microbiota. Initially studied in the rumen of cattle, the gut microbiota has emerged over the last 40 years as a key determinant of human health, causing a small revolution in our approach to medicine. Journey to the heart of our research to discover our new health ally.





The hidden world of the gut microbiota

The gut microbiota is the entire set of microorganisms living in our digestive tract. It is unique to each individual.



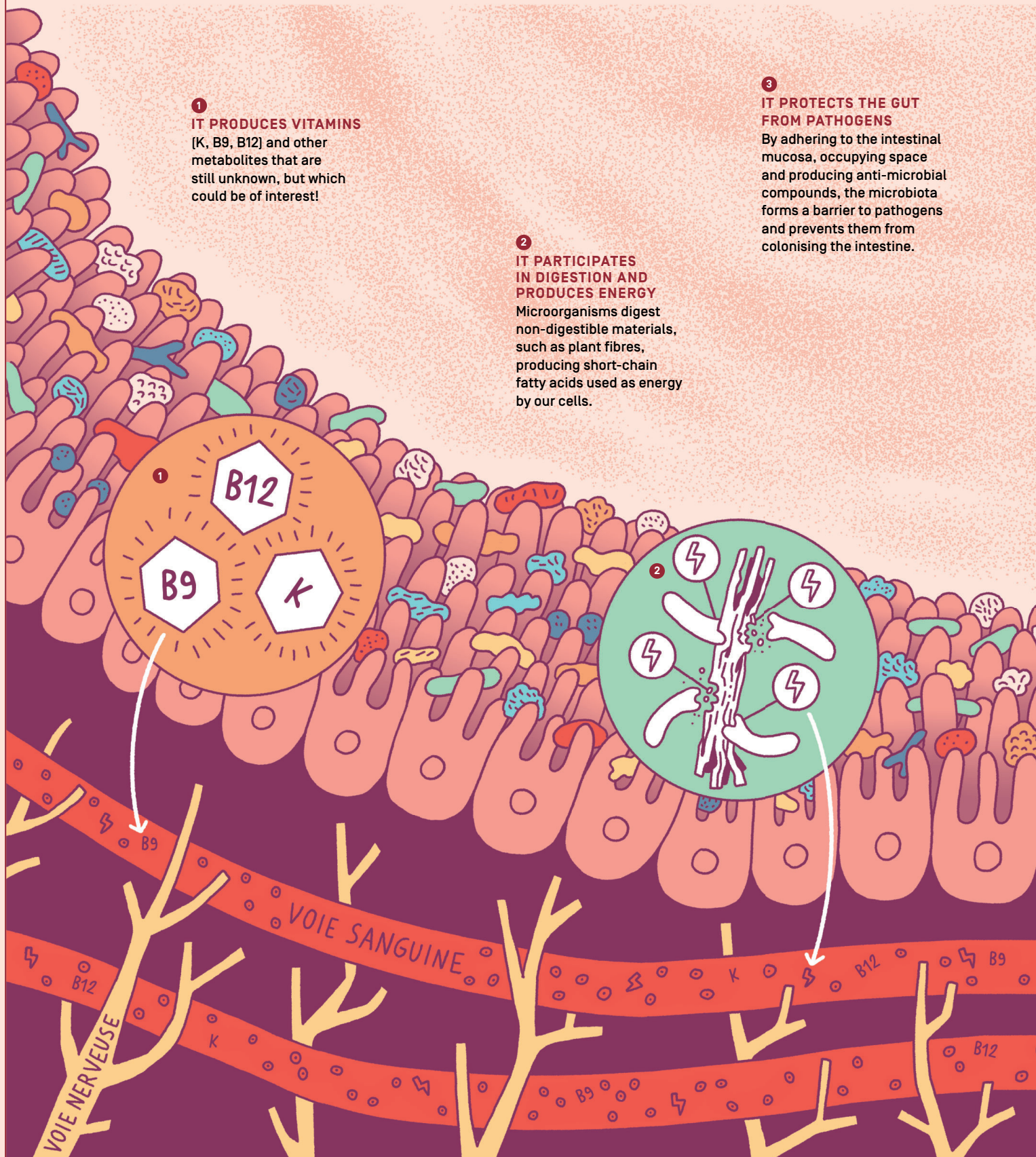
A LIFE IN SYMBIOSIS

Between the host [us] and its microbiota, there is a strong relationship of interdependence. We nourish it through our food and we offer it a living space, our intestine. In return, the microbiota provides us with many services.

1 IT PRODUCES VITAMINS
[K, B9, B12] and other metabolites that are still unknown, but which could be of interest!

2 IT PARTICIPATES IN DIGESTION AND PRODUCES ENERGY
Microorganisms digest non-digestible materials, such as plant fibres, producing short-chain fatty acids used as energy by our cells.

3 IT PROTECTS THE GUT FROM PATHOGENS
By adhering to the intestinal mucosa, occupying space and producing anti-microbial compounds, the microbiota forms a barrier to pathogens and prevents them from colonising the intestine.



50,000

billion microorganisms
for each human being,
as many as there are
human cells

300

different microbial
species in a healthy
individual

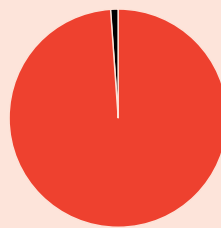
600,000

microbial genes...
25 times more
than human genes

1kg

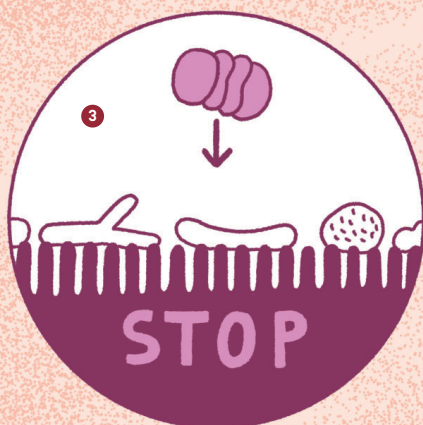
of bacteria (99%),
archaea, fungi, yeasts
and viruses

**COMPOSITION
OF THE MICROBIOTA**



● 99 %
bacteria and phages
(bacterial viruses)

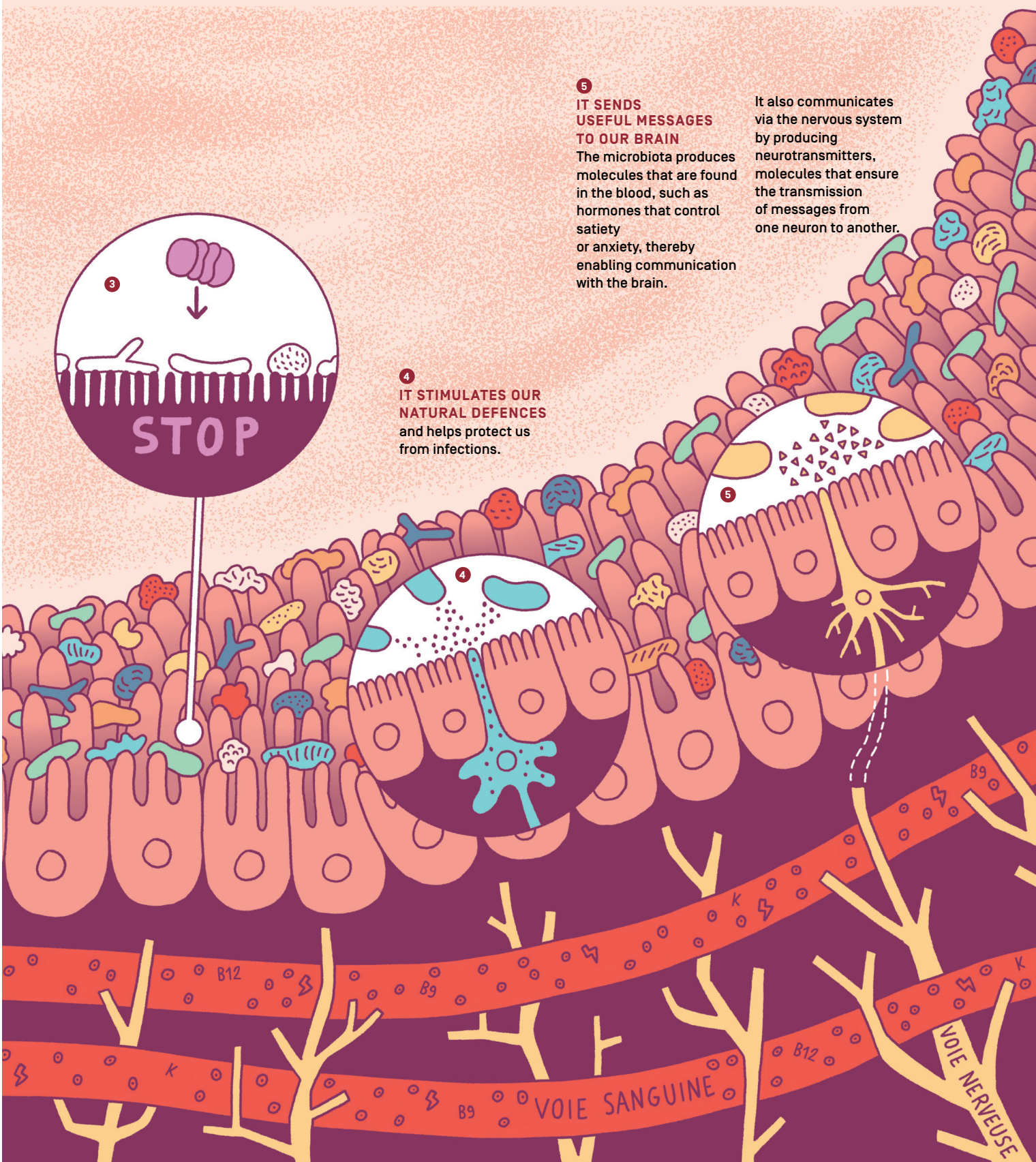
● 1%
archaea, fungi, yeasts,
viruses



4
**IT STIMULATES OUR
NATURAL DEFENCES**
and helps protect us
from infections.

5
**IT SENDS
USEFUL MESSAGES
TO OUR BRAIN**
The microbiota produces
molecules that are found
in the blood, such as
hormones that control
satiety
or anxiety, thereby
enabling communication
with the brain.

It also communicates
via the nervous system
by producing
neurotransmitters,
molecules that ensure
the transmission
of messages from
one neuron to another.



BACK TO THE FUTURE

Until recently, no one imagined that the microorganisms in our gut could play an important role in our health. Today, scientists are highlighting the links with many diseases, paving the way for a real revolution in our approach to health.

1940'S

The right method

The story began in the 1940s in the United States with a microbiology researcher, Robert Hungate, who developed a technique –still in use today– for cultivating bacteria from the rumen [the first digestive compartment of ruminants] of cattle, whose particularity is that they only grow in oxygen-free environments [strict anaerobic bacteria]. Until then, it was impossible to characterise them because it was impossible to cultivate them. With this method, the hitherto unknown world of anaerobic microorganisms that reside in the digestive ecosystems of animals and humans was opened to knowledge.

**The question was clear:
how do the microorganisms in
the rumen of cattle participate
in the digestion of fibres?**

1980'S

Microbiota and animal production

At INRA, the first work on what was then called “the rumen flora of animals” was carried out in 1980 in the microbiology laboratory of the Theix centre (Clermont-Ferrand). The question was clear: how do the microorganisms in the rumen of cattle participate in the digestion of fibre, the cellulolysis, a major function that was beginning to be described at the molecular and cellular level?

“We were the forerunners in the description of anaerobic fungi discovered in the rumen of herbivores, and then we were the first to demonstrate that protozoa produced enzymes that degraded fibres in the rumen”, recalls Évelyne Forano,

research director at the MEDIS joint research unit. At the same time, antibiotics were being used as growth promoters in livestock farming. Researchers therefore became interested in understanding the mechanisms of action of these antibiotics administered at low doses, but sufficient to limit the pathogen load,... in order to then do without them to meet a regulatory requirement! One of the approaches envisaged was to enrich the microbiota of farmed animals by feeding them live microorganisms, called probiotics, to reinforce the barrier effect against pathogens; this is how studies on probiotics used in the field of ruminant nutrition began.

What happened to the gut flora?

We all have in mind the term gut flora to represent the microorganisms of our digestive system. This term disappeared in the early 1990s when Carl Woese proposed a new classification of living organisms. Until then, bacteria were considered to be plants, and it was only natural that microorganisms were referred to as flora. But in 1990, Woese's new classification, distinguishing between bacteria, eukaryotes [including plants] and archaea, made the term “flora” for bacteria... inappropriate! It was then replaced by “the microbiota”.

1990'S

From animal to human

Impossible for scientists not to wonder about the human equivalent, known at the time as the gut flora. *“We applied all the methodologies acquired on animal microbiota to the study of human microbiota,”* explains Évelyne Forano, *and this accompanied the development of studies on human nutrition at INRA, following the creation of the scientific division NASA (Nutrition, Food and Food Safety).”*

Over the same period, new molecular techniques, including DNA sequencing, were being developed. A true revolution for science.

The contribution of DNA sequencing

Stanislav Dusko Ehrlich, then director of research at the Microbial Genetics Unit in Jouy-en-Josas, seized on these new technologies to gain a better –and much faster– understanding of the roles of lactic acid bacteria. Convinced that knowledge of the genome would make it possible to explain the biology of bacteria (growth, reproduction, feeding), Stanislav Dusko Ehrlich embarked on sequencing the genome of *Bacillus subtilis*, the complete sequence of which would be published in *Nature* in 1997. Numerous studies then ensued to characterise the animal and human microbiota by analysing its DNA: *“Thanks to DNA analysis, we can characterise the entire system, including bacteria that are difficult to cultivate (because they are sensitive to oxygen), which represent 70% of the microbiota”*, explains Joël Doré, Research Director at the Micalis¹ Institute and Scientific Director of the MetaGenoPolis unit.

1. Joint research unit associating INRAE, AgroParisTech and the University of Paris-Saclay.

2000'S

What is the use of the microbiota?

While DNA sequencing had made it possible to characterise the microorganisms of the microbiota, it remained to be seen –and understood in detail– what it is used for and how it functions. A little anecdote on great research: *“Joël and I were talking in a café on rue Claude-Bernard, the father of modern biology: you can’t make this up!”* recalls Hervé Blotot, then a biologist at the Micalis Institute. What can a microbiologist and a cell biologist have to say to each other? *“[...] We told ourselves that we had to study the dialogue between bacteria and cells!”* The circle was

complete, and a new approach was born, which consisted in analysing the interactions between the cells of our body and the microorganisms of our microbiota: functional metagenomics! The two researchers, with their teams from the Micalis Institute, then went on to develop a tool (MetaFun, a high-throughput cloning/phenotyping platform) allowing them to incorporate pieces of the genomes of intestinal microbes into the *Escherichia coli* bacterium. They obtained thousands of clones that they put in contact with human cells capable of emitting light or colour when a dialogue is established. This makes it then possible to find out which microbial gene is responsible for the functional changes observed in human cells.

Microbiota and health

By combining quantitative and functional metagenomic techniques, scientists are opening up new research perspectives: understanding the link between microbiota and health. In quantitative metagenomics, the microbiota of patients and of healthy subjects are compared, obtaining a characterisation typical of the “sick microbiota”; this allows to make a possible diagnosis and sometimes even to predict the occurrence of the disease or its aggravation in a patient.

In functional metagenomics, the aim is to identify the mechanisms of interaction between cells and microorganisms, as well as their

consequences, assumed to be responsible for the disease. The aim is then, among other things, to develop drugs to re-establish a good functional microbiota-host dialogue, and subsequently the patient’s state of health. Another method for establishing the link between microbiota and pathologies is to use axenic animals, which are raised in a sterile environment and therefore have no microbiota. By implanting them with the microbiota of a sick patient, one sometimes observes that they in turn develop the symptoms of the disease. Naturally, scientists first turned their attention to inflammatory bowel diseases, including Crohn’s disease, for which a direct link with the state of the microbiota was established in 2006.



2010'S

The decoding of the microbiota genome, a major advance for medicine

If there was a major step forward in the understanding of the microbiota, it was definitely this one. "Our other genome", was the title of the prestigious journal *Nature* in March 2010. After several years of work, and as part of the MetaHIT project coordinated by Stanislav Dusko Ehrlich, the genome of billions of microorganisms was deciphered! An initial catalogue of 3.3 million genes was published in 2010, completed in 2014 to reach 10 million genes. The question that then drove the scientific community: do we all have the same microbiota? The hypothesis was that there is an "average human microbiota" with a relatively identical composition of

microorganisms.

Wonderous world of science, "*we had two surprises with this work*", recalls Joël Doré enthusiastically, *the first is that there is no such thing as an average microbiota, but at least three major types of microbiota!*" Or rather enterotypes, i.e. three ecological organisations each dominated by a particular bacterial genus: *Bacteroides*, *Ruminococcus* and *Prevotella*. "The second surprise was that we observed rich and poor microbiota in terms of gene diversity, and therefore of microorganisms." As you might expect, the next step in this train of thought was: is there a link between enterotypes, the richness of the microbiota and the onset of chronic diseases? Joël Doré's answer is clear: "*Yes, a microbiota that is poor and of the Bacteroides enterotype is associated with a higher risk of cardiometabolic diseases. These are the first results, and there is still a long way to go!*" In parallel with these major discoveries, links between microbiota and various pathologies were continuously being brought to light: in 2012, scientists established a link between microbiota and

type 2 diabetes, in 2013 with obesity, in 2014 with cirrhosis and with fatty liver syndrome. In 2018, scientists discovered that certain bacteria in the microbiota could facilitate cancer treatments. Even more surprisingly, links were established between the microbiota and neurodegenerative diseases (multiple sclerosis, Parkinson's and Alzheimer's) as well as neuropsychiatric disorders (autism, bipolarity, schizophrenia, depression). Although the link between the state of the microbiota and this type of pathology was observed in animals in the early 1980s, the mechanisms governing this association have only recently been discovered: an alteration in the microbiota leads to inflammation in the intestine, which favours permeability of the blood-brain barrier. The role of the barrier is to prevent the passage of potentially toxic substances or pathogens into the brain and spinal cord. This permeability leads to inflammation in the brain, which is thought to promote the development of neurodegenerative and neuropsychiatric diseases. →

MAAT PHARMA

The start-up developing new therapies thanks to the microbiota

Created in 2014 based on INRA's know-how and more broadly on the work of Micalis and MetaGenoPolis, the start-up MaaT Pharma develops and standardises technologies to secure the therapeutic use of microbiota transfer. Its initial work consisted of developing a process for

conditioning intestinal content, making it possible to freeze-dry it in order to encapsulate it. Today, the research centres on the transfer of healthy microbiota via these capsules for therapeutic purposes in the treatment of cancer. Indeed, this transferred microbiota makes it possible to rebuild the host-microbiota symbiosis and thus to restore immune homeostasis.

In 2016, their clinical trials made it possible, thanks to the transfer of microbiota, to rebuild a normal symbiosis in 90% of patients with

acute myeloid leukaemia who had undergone chemotherapy. In 2021, they showed that microbiota transfer improves the survival rate of patients with graft-versus-host disease, a severe complication that sometimes occurs following bone marrow transplantation in the treatment of blood cancer. Currently, they are developing drug candidates that exploit the potential of microbial ecosystems throughout the care path of cancer patients.

maatpharma.com

In 2017, a strong link between the microbiota and autism spectrum disorders was confirmed. Research is ongoing within the framework of the European Gemma project (2019-2025) to study the role of the gut microbiota in these disorders. Also in the 2010s, MetaGenoPolis was created. It is a pre-industrial demonstrator with state-of-the-art equipment to go further and faster in understanding the microbiota and to develop innovations for society (see photo report on p. 11).

A life in symbiosis

As discoveries were made about the links between health and the microbiota, a new way of looking at them emerged. It is not enough to act directly on the microbiota, but rather to take into account the “microbiota and host” as a whole and therefore to also care for its environment (the host), our body. The results showed that it is indeed the way we take care of ourselves that allows our microbiota to be well-balanced and, in turn, contributes to our good health. At this point, the concept of symbiosis between the microbiota and the host gained a foothold and gave rise to the concept of dysbiosis, which occurs when the symbiosis is altered! Dysbiosis can occur in the event of oxidative stress, a decrease in bacterial diversity, an increase in the permeability of the intestinal barrier or an inflammatory state, all of which explain the link with the many pathologies mentioned above. Once the balance is altered, these parameters maintain a vicious circle creating a context favourable to certain chronic diseases that are at present incurable.

Transfer of microbiota

If the links between microbiota and certain pathologies are so obvious, why not transfer a healthy microbiota to a sick individual in order to treat them? This is the idea that led to the creation of the start-up MaaT Pharma (see p. 8) in 2014, of which Joël Doré is still the scientific advisor. INRA and MaaT Pharma then jointly developed a microbiota transfer technique that consisted of administering a suspension of stool from healthy donors into the digestive system of a sick recipient in order to restore the richness of his or her microbiota and provide a health benefit. The results obtained in 2016 are promising. Although there are still risks in transferring microorganisms from one individual to another, this work opens up new approaches to the treatment of severe diseases for which medicine sometimes has no solution left.

Almost 2,000 species of microorganisms have been identified. Each human being is home to about 300.

Microbiota and Covid-19

3 questions to Philippe Langella, Director of Research at the Micalis Institute

Is there a link between Covid and microbiota? Analyses of the gut microbiota of patients with Covid-19 show a dysbiosis, i.e. an imbalance of the microbiota, which is characterised by a decrease in bacteria with anti-inflammatory activity, a decrease that is all the more significant the more severe the form of Covid-19.

Is there any way to avoid such dysbiosis in the case of Covid? For many years, our laboratory has been developing prevention and therapeutic strategies based on new-generation probiotic bacteria to combat intestinal inflammation. The idea is to evaluate whether they could be used additionally in Covid patients to avoid the intestinal damage that is observed in 20% of them.

What are new generation probiotics? Probiotics are live microorganisms that are ingested with the aim of restoring or maintaining our host-microbiota symbiosis. Until now, the probiotics used were either derived from the consumption of fermented foods or from food supplements, but always obtained from natural ferments. The new generation of probiotics is now directly derived from the gut microbiota.

2020'S

The revival of preventive medicine

Work on host/microbiota symbiosis is continuing and expanding. A new project, The French Gut, began in September 2022 and aims to characterise the microbiota of the French population by collecting stool samples from 100,000 volunteers. For Joël Doré, this work offers in addition to new research perspectives a new way of thinking about health, moving towards preventive nutrition and using the microbiota as a lever.

Diagnosis and medication

As far as diagnosis is concerned, one day it will undoubtedly be possible to carry out a microbiota analysis in the same way as a blood test to assess the state of the symbiosis and help in the management of pathologies. Regarding medication: *"According to our initial results, acting simultaneously on the microbiota, the permeability of the intestinal barrier, inflammation and oxidative stress could be just as effective as standard drugs"*, explains Joël Doré. Indeed, an experiment on mice shows that a combination of a probiotic (which protects the intestinal barrier and has anti-inflammatory properties), glutamine (an amino acid that also protects the intestinal barrier) and curcumin (a polyphenol, anti-inflammatory and antioxidant), acts on the four factors of dysbiosis and gives results that are just as effective in treating depression as the antidepressant clomipramine, but without the side effects. In other words, the microbiota revolution has only just begun!

THE FRENCH GUT

Mapping the microbiota of the French

In September 2022, INRAE launched an ambitious project, The French Gut, to gain further knowledge of the microbiota and its links with health. The aim is to collect the stools of 100,000 volunteers as well as the associated nutritional and clinical data, and to analyse them in order to better understand what a healthy gut microbiota is and what alterations are observed in the case of disease. Led by INRAE,

The French Gut project is conducted in partnership with public and private institutions involved in microbiota knowledge. The ultimate goal is to open the way to innovative therapies to treat chronic diseases (such as diabetes, obesity and cancer) and neurodevelopmental disorders. The French Gut is part of the worldwide Million Microbiome of Humans Project (MMHP) which aims to analyse one million microbial samples from the intestines, mouth, skin and reproductive system.

<http://mgps.eu/projects>

THE MICROORGANISMS

A VAST WORLD

The gut microbiota is not the only one in our body, but to date it is the most documented. We have a microbiota on the skin, in the mouth, the vagina, the lungs, the eye and so on. All these microorganisms form a microbiome which itself forms, together with its host, a holobiont. But there are also microorganisms in our environment, in the earth, in the air, in plants, on and in animals.

All these microbiomes can interact and these interactions, on a more global scale, are still a little-known area of research. One example is antibiotic resistance. By dint of using antibiotics for our health and that of animals, we are encouraging the emergence of

antibiotic-resistant bacteria. This is becoming a global problem affecting our health, that of animals and of the environment. In 2020, INRAE launched a research metaprogramme called HOLOFLUX, "Holobionts and microbial flux within agrifood systems".

Its objective is to gain a better understanding, on the one hand, of the interactions within holobionts (between microbiota and hosts) and on the other hand, of the flows of microorganisms between holobionts and the agrifood system as a whole. This knowledge would make it possible to use them as levers for performance, sustainability and the preservation of human, animal and plant health.



①

Inside the labs

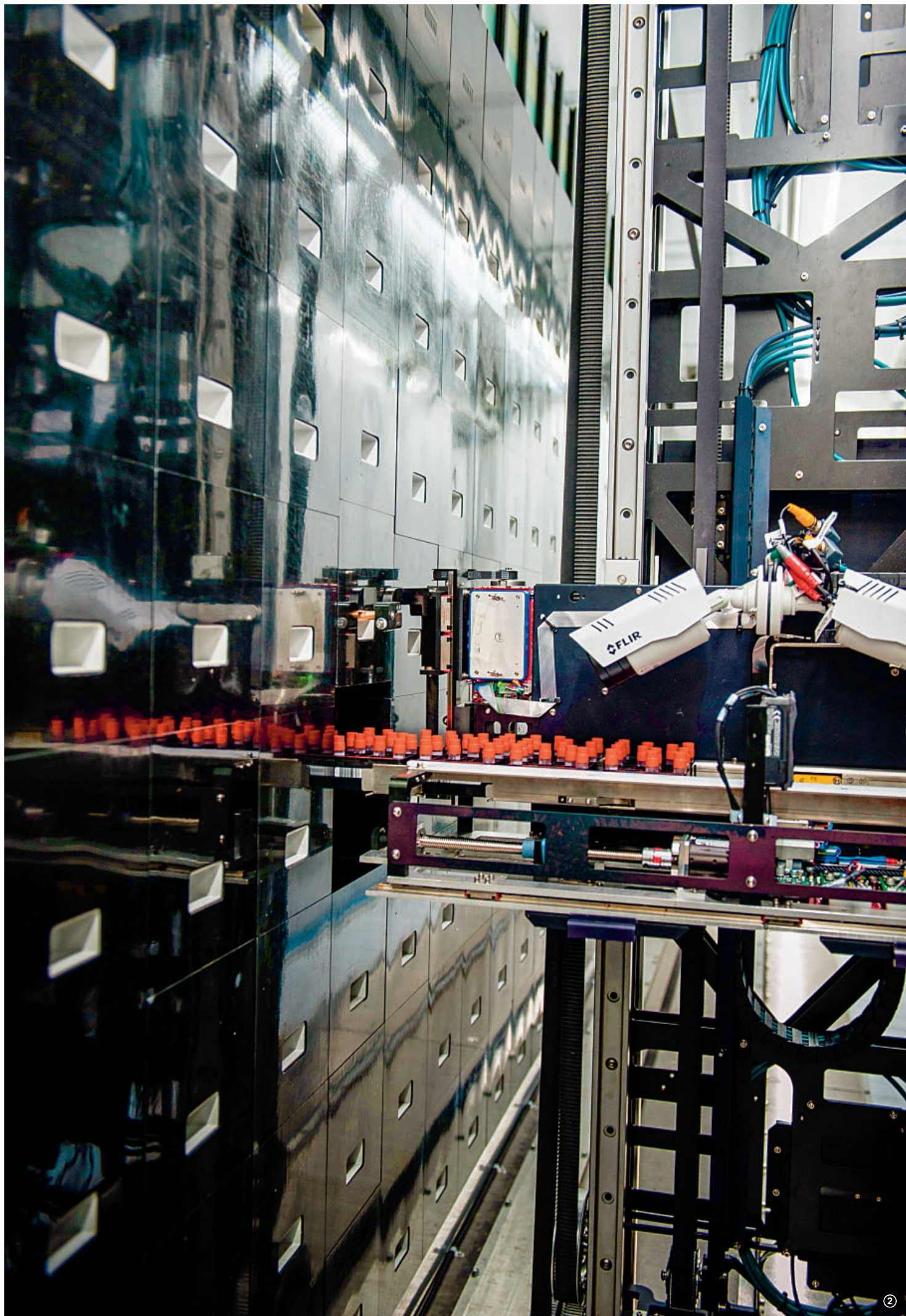
MetaGenoPolis, a unique place dedicated to knowledge on microbiota

Let us take a look inside the laboratories of MetaGenoPolis, a pre-industrial demonstrator located in Jouy-en-Josas (Yvelines, France), which explores the gut microbiota both quantitatively and functionally, thanks to state-of-the-art

equipment.

From sample collection to bioinformatics analysis and the generation of scientific knowledge, MetaGenoPolis is a key international player in microbiota science.

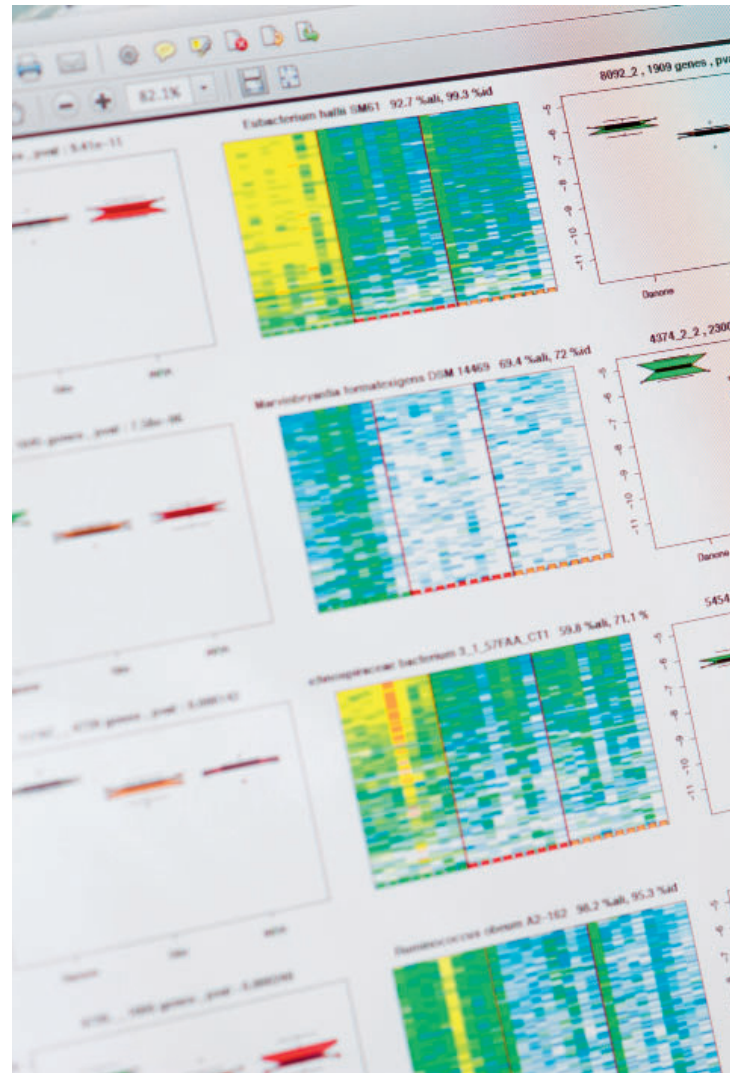
© INRAE – Bertrand Nicolas







④



⑤

① Sample collection and management

Whether in the context of clinical trials or research projects, the first step is the collection of stool samples from cohorts or individual volunteers. For this purpose, and as part of the International Human Microbiome Standards (IHMS) project that it coordinates, MetaGenoPolis has developed standard procedures that are a global reference for the preparation of stool samples, aimed at guaranteeing their integrity and that of their extracted DNA for a robust analysis of the microbiota.

② The biobank, management and storage facility for faecal samples

Once the samples have been obtained,

aliquots are generated, each with a barcode to identify them. These aliquots are then stored securely in the biobank. Fully automated, it can store up to 600,000 aliquots and DNA extracts at -80°C . A robotic arm deposits or retrieves the tubes for each analysis or experiment.

③ Preparation of DNA extracted from samples for sequencing

Before the DNA of the microorganisms present in the samples can be sequenced and thus characterised, it is necessary to extract this DNA by separating it from other cellular components and residues present in the samples. This involves physical and chemical disruption steps as well

as proven and standardised separation techniques.

④ High-throughput sequencing of DNA from microorganisms

High-throughput sequencing of the DNA of microorganisms (mainly bacteria) living in the digestive tract allows the characterisation of the gut microbiota. MetaGenoPolis uses the whole genome sequencing method called “shotgun metagenomics”, which focuses on all the genes of the accessible microorganisms. Using a reference gene database, the DNA fragments read by the sequencer identify the genes of the microorganisms present in the aliquot and their proportion. A considerable volume of



⑥

computer data is thus generated and analysed.

⑤ **Computational and biostatistical analysis**

After sequencing the DNA, scientists obtain a large amount of data which is then analysed to answer different questions: for example, to study the impact of the consumption of a product, of a diet or of a probiotic on the gut microbiota. Cross-referencing data from individuals in the same cohort can help identify the role of the microbiota in diseases such as obesity, diabetes, inflammatory diseases or liver cirrhosis.

⑥ **Screening platform for functional metagenomic analysis**

This automated high-throughput screening platform makes it possible to analyse interactions between microorganisms and epithelial or immune cell lines. Functional metagenomics thus allows a better understanding of the function of each of the bacteria in the gut microbiota, to decode host-microbiota interactions and to identify new target molecules of therapeutic interest. ●

To find out more
→ youtu.be/rxuvV0-pC0k

140

scientific publications, many of them in high impact journals. 15 of these publications are among the most cited in the world.

82

research projects with more than 100 public partners (including 8 European projects and 5 international projects) for a total budget of 18 million euros.

154

research projects for innovation with 69 private partners in the agrifood and health sectors, for a total budget of 24 million euros.

36

patents, 10 licences.



Scientific excellence and innovation

3 questions to Alexandre Cavezza,
Executive Director of MetaGenoPolis

Created in 2012 through funding from the French Investments for the Future programme (*Programme d'Investissement d'Avenir* PIA1) and backed by INRAE, MetaGenoPolis is a pre-industrial demonstrator whose mission is to understand the links between microbiota, health and food. At the interface between scientific excellence and innovation with companies, MetaGenoPolis is an expert in the analysis of human and animal gut microbiota.

What are the assets of MetaGenoPolis?

We have unique equipment at the cutting edge of technology and ISO 9001 certified processes. This is the case, for example, with the biobank and its barcode and automation system, which allows us to store nearly 600,000 faecal samples in a standardised and secure manner. We also have several robotic platforms for high-throughput metagenomic analysis. This involves both quantitative analysis of the microbiota to determine its composi-

tion as well as functional metagenomics to understand the interactions between the microorganisms and their host. These are very powerful technologies that allow a large quantity of samples to be analysed in a very short time.

What are your ties with industry?

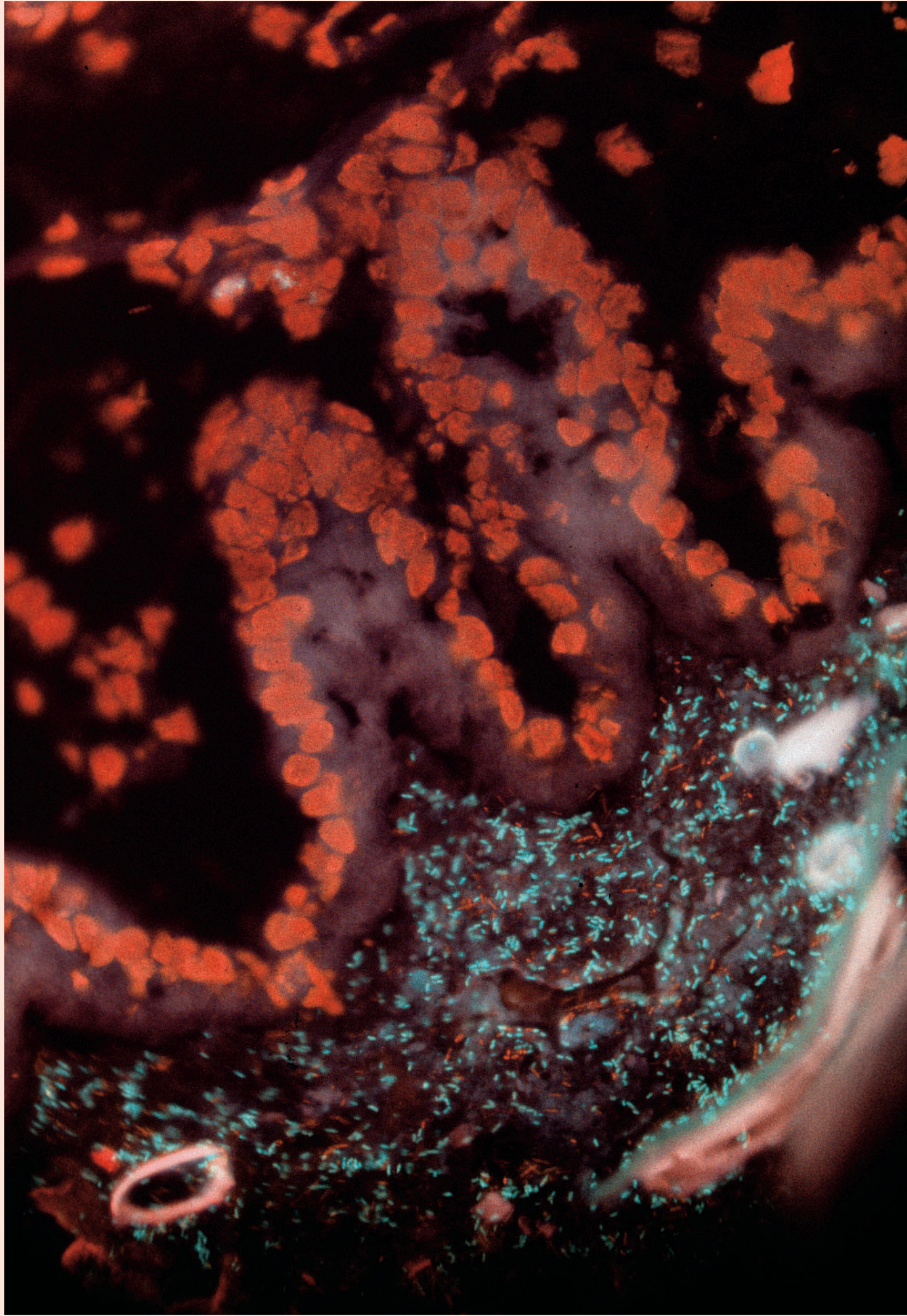
There are many, and this is what the pre-industrial demonstrator is all about. We work with private and public partners mainly through research collaborations. MetaGenoPolis is at the interface between public research and private players. MetaGenoPolis conducts outstanding research, with nearly 150 scientific publications in top-ranking journals since its creation. We capitalise on this scientific knowledge by working with industrial partners, in particular concerning the proof of concept, a key stage in the transition from fundamental research to industrial development. This is a delicate and costly stage that our structure makes possible. One example is the design of the Amibiote baguette, a bread enriched with plant fibres, which is proper food for the bacteria in our microbiota and has been marketed since 2019. Our results are also being exploited through the creation of start-ups: MaaT Pharma (see p. 8), Enterome, which develops new drugs that interact with the microbiota, and Novobiome, which develops drugs containing living microorganisms that

have a positive influence on the health and physiology of the host.

What are your prospects?

We have two major structuring projects that are at the centre of our activity. The first, The French Gut, consists of characterising the gut microbiota of a cohort of 100,000 people living in metropolitan France (see p. 10). This will enable us to create knowledge and develop partnerships with both public partners such as Inserm, the Paris Public Hospital Authority (AP-HP) and the CEA as well as with industrial partners through a consortium and thus create common value.

The aim in particular is to gain a better understanding of the heterogeneity of healthy French gut microbiota, the environmental and lifestyle factors that impact them, and their deviations in chronic diseases. The other project to which we will contribute is the "Ferments of the Future Grand Challenge", of the "Sustainable food for health" acceleration strategy of the French Investments for the Future programme (PIA4), whose objective is to understand the impact of ferments on our health and on the microbiota in order to give them their rightful place in the healthy and sustainable food of tomorrow.



Recent discoveries show that the links between microbiota and health are numerous. The good news is that there are ways to take care of our microbiota and preserve our interactions with it. **A look at the key factors for a life in symbiosis.**

TAKING CARE OF OUR SYMBIOSIS

With the microorganisms in our gut, when all goes well, we are in a symbiotic, win-win relationship. We give our microbiota room and board, and in return it provides us with many services: it digests plant fibres and produces energy, it stimulates our immune system, it produces vitamins, it protects the intestinal barrier and sends important messages to the brain. This balance contributes to our general good health. It is therefore necessary to take good care of our microorganisms via their host, our body, in order to preserve the symbiosis. Because when this is not the case, we run the risk of being in a state of dysbiosis, which is associated with numerous pathologies: obesity, type 2 diabetes, irritable bowel syndrome, autism spectrum disorders, anxiety, depression,

1,000
first days of life
to develop our
immune capacities

cirrhosis, multiple sclerosis, allergies and Crohn's disease. The list is long. On the other hand, symbiosis also has some “collateral” benefits. For example, it can limit the effect of food contaminants or prevent the risks of muscle wasting that seniors often suffer from as they age.

What does it take to be in symbiosis? The answer is simple (or almost): to have a rich microbiota, both in terms of the number of microorganisms and the number of different species, and a host that provides what the microbiota needs to maintain this diversity. So how do we maintain the richness of our microbiota? How do we give our microbiota everything it needs to maintain its diversity? In other words, how do we take care of our symbiosis? A four-step guide. →

01

By feeding it a varied, high-fibre diet

Our microbiota is composed of microorganisms that do not all feed on the same thing. A varied diet, especially with fruit and vegetables rich in fibre and polyphenols, ensures the maintenance of bacterial diversity. Fibre is not digestible by human enzymes, but the bacteria of the microbiota love it. Is there an ideal diet for our symbiosis? Studies show that the Mediterranean diet is a good candidate: rich in fruit and vegetables, and therefore in fibre, with little red meat and the use of olive oil, which provides good quality fatty acids. Scientists also show that the “fast food and ultra-processed foods” diet has an indirectly deleterious effect on the microbiota because when fibre intake is reduced, the microorganisms are deprived of an important source of carbon and energy, and the microbiota then attacks the mucus of the intestinal wall to feed itself, weakening it and making it permeable to molecules and pathogens.

“25 different fruits and vegetables per week is what we should be eating.”

Joël Doré

02

By stimulating it during the first 1,000 days of life

The microbiota is established at birth. In utero, the baby is in a sterile environment, but as soon as the waters break, the baby's body (and not just its intestine) is colonised by the microorganisms it encounters, mainly those of its mother. *“The development of the baby's microbiota during the first few years of its life is completely parallel to the maturation of its immune system”*, explains Hervé Blottière, a microbiologist at the PhAN unit (Physiopathology of Nutritional Adaptations).

“If this maturation goes well, the baby will be in symbiosis between its cells and its microorganisms, but if the symbiosis is disturbed, there is a risk of infectious disease and immune disorders leading to the development of chronic diseases.”

So how do we take care of our symbiosis from birth? Through the food we eat, of course, in particular breast milk which itself contains a microbiota, and then through a varied diet. But also by exposure to microorganisms from an early age, those of the mother, during a vaginal delivery, and then those of the environment: playing in the dirt, having pets, all these factors play a role in the composition of our microbiota and the maturation of our natural defences.

Conversely, taking antibiotics in the early years can delay or modify the maturation of the microbiota and the immune system by reducing bacterial diversity, reducing beneficial bacteria, and even increasing resistant bacteria. While normality usually returns, there are some cases where a persistent change in the microbiota can be observed and which increases the risk of developing certain diseases.

03

By having a healthy lifestyle

Because taking care of our symbiosis also means taking care of the host... To avoid dysbiosis, we need to take care of our intestinal barrier, and limit what could lead to inflammatory states or oxidative stress, and consequently increase the risk of colorectal cancer... For example, limiting the consumption of alcohol or meat products as it induces intestinal permeability: the cells of the intestinal barrier move apart and allow molecules to pass that would not be able to do so

under normal circumstances.

Similarly, there is a release of cortisol into the bloodstream when we are stressed or anxious which also has an effect on the permeability of the intestinal barrier. The environment in which we live and exposure to various contaminants (in the air, water) also seem to influence the state of our symbiosis.

As for physical activity, it appears to be beneficial to the diversity of the microbiota and is therefore highly recommended!

04

By supplying it with probiotics

Diversity of the microorganisms is the key factor in symbiosis. One possible way is to ingest them. This is the principle of probiotics. These are living microorganisms (bacteria or yeast) that are naturally found in fermented products, such as cheese, yoghurt, raw sauerkraut and bread. They can be added to certain food products, yoghurts in particular, or consumed as a food supplement. Probiotics benefit our microbiota for two reasons. The first is that they naturally provide living microorganisms that increase the diversity of our microbiota. The second is that the fermentation process carried out by the enzymes of the microorganisms adds metabolites to the diet that are of multiple interest for the microbiota and more widely for our health. Studies furthermore show that probiotics, depending on the strain used, help digest lactose, can prevent or reduce diarrhoea linked to antibiotics or certain viral infections, and strengthen the intestinal barrier.

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Dysbiosis

It is caused by external factors (like certain medications and alcohol consumption) or when the microbiota-host relationship is altered, resulting in a loss of bacterial diversity, an increase in pathogenic bacteria, an increase in the permeability of the intestinal barrier and, subsequently, a weakening of the organism and its immune function.

Amibiote baguette

With a little help from science, researchers at the Micalis Institute have designed a bread, the Amibiote baguette, enriched with plant fibres, whose health effects have been demonstrated: control of cholesterol levels and improvement of insulin sensitivity in subjects at metabolic risk.

THE ISSUE

The great challenge of fermented foods

Yoghurt, cheese, bread, sauerkraut, olives, wine, kefir, tofu, kombucha, kimchi..., will fermented foods take up more space on our plates? It is in any case a serious approach for obtaining health benefits from food.

Consumers are already getting started on it: "More and more people are fermenting their vegetables themselves", but micro-trends aside, Marie-Christine Champomier-Vergès, Director of Research at the Micalis Institute, reminds us that there is a real challenge in developing fermented foods and in fully understanding the role of ferments in the health of our microbiota and our health in general: fermentation leads to the production of bioactive compounds, which, combined with the presence of probiotic bacteria in some of these products, can make them beneficial to health. Many questions arise: What are the interactions between food and microorganisms? What fermentation methods are there? With which strains? For what taste? For what nutritional effect? What are the interactions between the

microorganisms in the food and our gut microbiota? And what about regulations? "Introducing microorganisms into our food, sometimes strains that are not usually consumed, is new and not harmless. In parallel with our research, we need to consider the regulations that will accompany these new products." Science is taking on these questions.

A participatory science project, FLEGME, is calling on citizens in order to study fermented vegetables from artisanal production. A European network, PIMENTO, is gathering around these issues. Furthermore, and as part of the French Investments for the Future programme (PIA4), the "Ferments of the Future Grand Challenge" has been proposed by INRAE and ANIA (The French National Association of Food and Drink Industries) to maintain France's international leadership in fermented products.