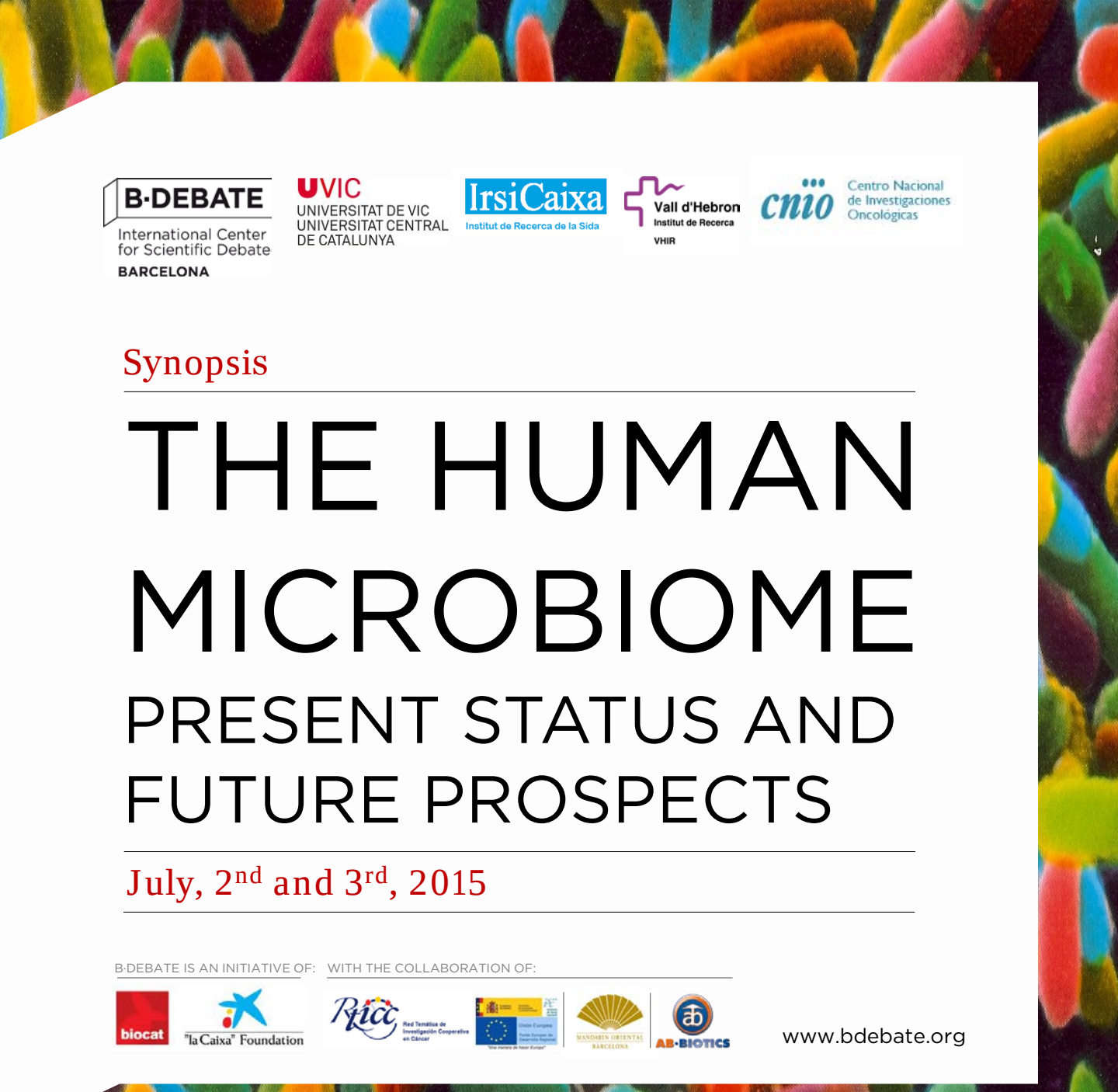

B·DEBATE International Center for Scientific Debate BARCELONA

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cnio Centro Nacional de Investigaciones Oncológicas

Synopsis

THE HUMAN MICROBIOME

PRESENT STATUS AND FUTURE PROSPECTS

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AB·BIOTICS

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MICROBIOME: FROM FORGOTTEN ORGAN TO A NEW FRONTIER

Each human being plays host to some 100 trillion bacteria, of some 10,000 different types, weighing an average of 2 kilograms. And while in the past we dreamed of being free of microorganisms, today we know that aspiration was misguided.

The bacteria we co-exist with are key to processes like digestion and educating the immune system. But their role goes much further, as variations or alterations in their composition have been associated with all sorts of diseases: obesity and diabetes, allergies, certain types of cancer. Recent studies suggest that they may also be linked to infection with the Human Immunodeficiency Virus (HIV) or even to behavioral disorders like autism. This is why the microbiome, the community of microorganisms that inhabit the human body —more than 90% of which are bacteria— is now known as the forgotten organ.

Some of the top international experts in the microbiome presented and commented on the latest work in this area at B·Debate, an initiative of Biocat and the "la Caixa" Foundation to promote scientific debate.

CONCLUSIONS:

- ✓ In terms of the microbiome, richer is better: greater bacterial diversity tends to correspond with better overall health.
- ✓ According to the hygiene hypothesis, increased asepsis in developed countries has reduced the diversity of beneficial microorganisms, contributing to the increase in allergies, obesity and diabetes.
- ✓ Some bacteria have been linked to certain types of cancer, like colon or pancreatic. With HIV, the intestinal damage caused by the virus allows bacteria to pass into the blood and accelerates cell ageing.
- ✓ The intestinal microbiome can even impact behavior and has been linked to cases of autism. Research is being done on the use of prebiotics, probiotics and even fecal transplants to treat this and other conditions.

FROM A BACTERIA-FREE WORLD TO THE 'MICROBIOME BOOM'

"We've known that microorganisms exist for some time now, but until recently they were contaminants. The dream was to be bacteria free," remembered Francisco Guarner, head of the IBD Section at Vall d'Hebron University Hospital and one of the scientific leaders of this B·Debate. But when scientists managed to breed mice without germs, "they didn't grow, had many allergies and died surprisingly easily": microorganisms are essential to a *normal* life.

"New DNA sequencing techniques have allowed us to study the genome"

M. Luz Calle

Director of the Bioinformatics and Medical Statistics Group at the University of Vic-Central University of Catalonia

Since World War II, there has been a rise in the number of cases of chronic non-communicable conditions like cancer, autism and allergies. This hasn't happened in developing countries. One possible explanation is referred to as the hygiene hypothesis: the use of antibiotics, increase in cesarean births, decrease in breastfeeding and, in general, increased asepsis in wealthy countries has limited our contact with certain microorganisms that are necessary to educate our defenses. This is why, according to Guarner, **"the immune system makes more mistakes and changes to the *traditional* microbiome may be the origin of this increase in disease."**

But why the relatively sudden interest in the microbiome? Because of technology. "New DNA sequencing techniques have allowed us to look at and study our other genome, that of all those microorganisms," said M. Luz Calle, director of the Bioinformatics and Medical Statistics Group at the University of Vic-Central University of Catalonia. This technology can not only identify the types of microorganisms but also the genes they contain.

In general, we have an average of 600,000 microbial genes in our gut alone and, in the words of Dusko Ehrlich, director emeritus of the French National Institute for Agricultural Research, **"with regard to the microbiome as well, it's better to be rich than poor."** The lower the diversity, the greater the tendency to accumulate fat, to develop diabetes and, in general, to be in poorer health.

FEEDING BACTERIA

A person whose microbiome is lacking in diversity can improve its wealth through their diet. A diet rich in fruit, vegetables and whole foods, many different sources of fiber, seems to be the healthiest option for us and our bacteria. However, as Professor of Genetics at the University of Valencia Andrés Moya pointed out, we don't yet know the level of diversity that correlates with health, "and if we aren't yet sure what a healthy microbiome is, it's more difficult to know what is unhealthy."

FROM BACTERIA TO OBESITY, DIABETES AND ULCERATIVE COLITIS

A good part of the studies on the microbiome are done on feces, as the gut is home to more than 90% of all the microorganisms in our bodies. In 2011, one of these studies divided the population into three groups according to the composition of the bacteria in their feces (enterotypes). Belonging to one group or another seems to be linked to a tendency towards obesity or to develop diabetes. One possible explanation for these results, however, could be that the accumulation of fat changes the bacteria and not that they play a role in causing obesity.

Nevertheless, during the B·Debate, Karine Clement, director of the Institute of Cardiometabolism and Nutrition in Paris, cited a famous study (see below) that suggests that certain microorganisms do in fact promote obesity.

Clement's own team has proven that the greater the microbial diversity, the more effective a diet will be in promoting weight loss. And that this may be due, in part, to a type of bacteria mentioned many times by the experts at this B·Debate: *Akkermansia muciniphila* (AKK). The hypothesis is that if there is inflammation (*irritation*) **"certain defense cells may enter the intestinal cells, altering their reaction to insulin and affecting nutrient absorption,"** explained Clement. AKK may protect intestinal cells by taking care of the mucosal barrier that protects them and reducing inflammation. The difficulties in cultivating this type of bacteria explain why it hasn't yet been studied as a treatment.

Changes in the intestinal microbiome may also explain the origin of ulcerative colitis, an illness, Francisco Guarner recognizes, **"we don't know the origin of."** However we do know that "the number of cases has increased in recent years, that genetics doesn't seem to be very important and that there isn't a therapy to treat it yet." At the B·Debate, Guarner showed how patients with this type of colitis have lower microbial diversity than healthy people –especially those who tend to have more episodes- while four strains of bacteria are missing nearly entirely in these patients, among them, AKK.

MICROORGANISMS THAT MAKE YOU GAIN WEIGHT: THE EXPERIMENT IN MICE

A famous study by the team led by Karine Clement, director of the Institute of Cardiometabolism and Nutrition in Paris, suggests that certain microorganisms may cause obesity. In the study, they transplanted feces from a set of twins, one obese and one thin, into mice. The mice with the feces from the obese twin gained a lot more weight than the ones with the feces from the thin twin. And if they were put together for some time, the thinner mouse was able to pass those bacteria to the obese one and protect it (as long as their diet was somewhat under control).

BACTERIA, CANCER AND AIDS

"Some types of cancer tend to be seen more in certain families but don't appear to be genetic," said Núria Malats, principal investigator in the Genetic and Molecular Epidemiology Group at the CNIO. The microbiome may be responsible for some of those cases, like colon cancer. At the B·Debate, Peer Bork, head of Bioinformatics at the EMBL in Germany, explained that there are 22 strains of bacteria that are particularly abundant both in the gut and in the tumors of patients with this type of cancer. He highlighted one of these, *Fusobacterium nucleatum,* which has already been proven to promote cancer in the laboratory. Bork said that this data could be used to detect colon cancer early, as it increases the effectiveness of the test currently in use, which consists in detecting blood hidden in feces. However, he warned, "certain factors like a change in diet or some treatments may affect the results."

Another type of cancer that has been linked to the microbiome is pancreatic cancer, which has a high mortality rate as it is often diagnosed quite late. Dominique S. Michaud, professor in the Department of Public Health and Community Medicine at Tufts University Medical School in Boston, showed how the mouths of sick people tend to have bacteria that are not normally found in healthy people. Although the study is still in the preliminary stages, it could open the doors to using early detection markers and experts are looking at the possibility that these bacteria may also play a role in causing cancer. This would happen when the bacteria go from the mouth to the gut and from there to the pancreas, where they may cause inflammation that fosters the appearance of tumors.

BACTERIA AND BEHAVIOR: THE MICROBIOME AND AUTISM

Chaysavanh Manchan, head of the Metagenomics Lab at the Vall d'Hebron Research Institute, believes that the microbiome may play a causal role in the brains of children with autism. Some test show that microorganisms in the gut may affect behavior: in mice, scientists have seen that neurotransmitters like serotonin can be manufactured by bacteria and travel to the brain. Alterations in the microbiome have been associated with stress and anxiety. Elaine Hsiao, who pioneered the studies that found alterations in the microbiome of autistic children, is more cautious, but the research continues. Manchan has just completed a phase 1 clinical trial to show that a feces transplant can help alleviate the symptoms of autism. The results will be made public soon but the researcher explained at the B·Debate that said transplants had restored altered microbiomes in the autistic children for at least six months and that their behavior had improved. Max Nieuwdorp, director of Experimental Vascular Medicine laboratory in Amsterdam and one of the pioneers of feces transplants, however, warned of the possible placebo effect these often have and which can't be controlled in this phase of trials. Therefore, if the results were confirmed in autistic children additional studies would be necessary to ensure it is useful.

"The next AIDS vaccine will require a good microbiome"

Bonaventura Clotet

Director of the HIV Unit at irsiCaixa Foundation

The microbiome's role in HIV is a confirmed fact. **"The virus does so much damage to the intestine that it makes it permeable, which allows bacteria to spill out,"** explained Bonaventura Clotet, director of the HIV Unit at the irsiCaixa Foundation. The presence of bacteria in the blood causes the immune system to be permanently activated, leading to accelerated ageing. Roger Paredes, head of the Microbial Genomics group at irsiCaixa, showed how HIV infection decreases the bacterial wealth in the intestinal microbiome, although the composition of the microbiome in terms of bacterial strains seems to be influenced more by environmental factors. Studies currently underway will shed light on whether there are specific changes in the composition of bacterial strains associated with HIV infection. Breakthroughs in the study of the microbiome are key for AIDS researchers because, as Clotet explained, **"the next vaccine that we try will require a good microbiome."**

HOW CAN WE CHANGE OUR BACTERIA? PREBIOTICS, PROBIOTICS AND FECAL TRANSPLANTS

Although genetics does seem to have an effect on our microbiome, there are several ways to change and *improve* the bacteria we co-exist with. One of these is through our diet: eating different sources of fiber, mainly from fruit, vegetables and whole grains, is associated with a richer, healthier microbiome. Another is by taking prebiotics and probiotics. The former are substances, generally sugars, that promote the growth of beneficial bacteria. The second are living microorganisms associated with healthy effects. What is classified as a probiotic and the regulations it must follow is still the subject of much debate, but it is generally accepted that several strains of bacteria have been proven effective, for example, in treating some types of diarrhea. The problem, according to Guarner, is that there are "some 30 useful, well-studied probiotics but pharmacies sell up to 100 others whose efficacy hasn't been shown." The final way to alter the microbiome is through fecal transplants: transferring concentrated feces from one person to another through nasogastric intubation or a colonoscopy. Some studies have found this process helpful in treating persistent diarrhea and even in improving some symptoms of diabetes. But there are drawbacks: they aren't very specific, most of what is being transplanted is unknown, and the donor and recipient must be compatible, although the markers that could better identify the best matches have yet to be established.