GUT MICROBIOTA AND INFLAMMATORY BOWEL DISEASE

A selection of content from the Gut Microbiota for Health Experts Exchange 2014-2015

August 2015

In partnership with

ECCO European Crohn's and Colitis Organisation

GUT MICROBIOTA FOR HEALTH Experts Exchange

SUMMARY

Inflammatory Bowel Disease (IBD) research has made some exciting progress in the past decade, thanks to the myriad studies investigating the role of the gut microbiota. The Gut Microbiota for Health Experts Exchange has covered Crohn's disease and ulcerative colitis more than any other topics and, reflecting the importance of intestinal microbiota in IBD. Moreover, the European Crohn's and Colitis Organisation (ECCO-IBD) who share a common interest in the gut microbiota, has joined the European Society of Neurogastroenterology & Motility (ESNM) Gut Microbiota & Health Section in 2015.

Although patients stand to gain enormously from these advances in understanding, there is so far no consensus on how to take into account the gut microbiota when treating IBD. Research how probiotics dampen inflammation, modulate immunity, and enhance digestive health is promising, but much more human research must be carried out. This " Gut Microbiota and Inflammatory Bowel Disease " Best of document can be a starting point for doctors, patients, and associations to begin discussing how to move forward on personalized treatment strategies.

After reading through this document edited by Prof. Philippe Marteau and Harry Sokol, you'll have a picture of how probiotics, genes, the immune system, the intestinal microbiota, and environmental triggers might interact in the onset and course of IBD in both adult and pediatric populations. Below, you can read exclusive interviews with Harvard's Wendy Garrett, University of North Carolina's Balfour Sartor, University of Southern California's Brent Polk, and other leading IBD researchers, as well as the pioneering work on fecal microbiota transplantation to treat IBD. Finally, we bring you a selection of 10 Twitter accounts to follow if you have a particular interest in IBD related topics. Also don't forget to follow our *@GMFHx* Twitter account!

Check our website for more IBD research or sign up for our newsletter to stay up to date. Enjoy your reading!

The Gut Microbiota for Health Experts Exchange Publishing Team

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EDITO

Philippe Marteau

Research on the interface between Inflammatory Bowel Disease (IBD) and the microbiota is very productive and will for sure soon impact daily medical practice. Microbial profiles sometimes referred as "signatures" differ significantly and enough between patients with Ulcerative colitis (UC), Crohn's disease (CD) or healthy persons to be used by clinicians for diagnostic purposes. However, validation of a medical diagnostic tool is as long as that of a drug. Inflammation *per se* influences the microbiota so that the profiles should not be seen as only suggesting causality of the microbes in the inflammation process. They should rather be understood as markers of ecological conditions associated with the disease -- like C-reactive protein blood concentration is not a cause of IBD but a marker of inflammation. For proper validation, markers need to be checked in various countries and versus large control groups. This is expensive and highly competitive.

When looking at attempts to influence ecology in order to improve IBD, two concepts gain importance. The first is to try more sustained or repeated ecological pressure than in the first trials. Indeed, inefficacy or too short efficacy of some ecological treatments -- for example imidazole antibiotics to prevent postoperative relapse of CD or maybe fecal microbiota transplantation -- could result from a too short treatment period with resilience of the detrimental ecological condition after stopping the treatment. This idea is also driving the medical treatment of IBD using immunomodulators, which are nowadays prescribed for longer periods. Trying to shift the ecosystem towards a new one with more butyrate producers remains rational as several of them proved to exhibit anti-colitic effects in animal models be it also observed just with butyrate addition or not.

Harry Sokol

Many groups worldwide demonstrated that IBD patients exhibit a dysbiosis characterized by a restriction of biodiversity and an imbalanced bacterial composition. Among the many aspects of the IBD-associated dysbiosis, the decrease of *Faecalibacterium prausnitzii* in IBD patients is one of the most accepted. Moreover, this bacterium has been shown to exhibit anti-inflammatory effects in cellular systems and mice models suggesting that its defect could play an active role in gut inflammation. Recently, several studies brought some insight in the mechanisms involved. Using gnotoxenic models and a metabolomics approach, Miquel *et al.* showed that the

anti-inflammatory effects of *F. prausnitzii* are linked to the production of small anti-inflammatory molecules, such as salicylic acid in the gut lumen. The anti-inflammatory effects of *F. prausnitzii* have been shown on both intestinal epithelial cells and immune cells. Quevrain *et al.* showed that the effect on epithelial cells was, at least in part, mediated by peptides derived from a bacterial protein inhibiting NFkB activation with both *in vitro* and *in vivo* beneficial effects. On the immune cells side, Sarrabayrouse *et al.* showed that *F. prausnitzii* was able to specifically stimulate a new type of human IL10 producing Treg cells. Importantly, the abundance of these cells was decreased in blood and colon of IBD patients, mirroring the behavior of *F. prausnitzii* in the same population.

Besides bacteria, the gut microbiota is composed of other microorganisms such as virus and fungi which might play a role in bacterial population control and/or directly in IBD pathogenesis. Norman *et al.* recently described for the first time the enteric virome and its specific distortion in IBD. The authors observed that bacteriophages belonging to the Caudovirales and Microviridae families are the most abundant in the enteric virome. In IBD patients, the bacteriophage richness and particularly the Caudovirales one was an increased compared to healthy controls with some differences between UC and CD patients. Interestingly, inverse correlation between IBD-associated changes in the virome and bacterial microbiome was observed suggesting a possible predator-prey relationship with potential role in IBD pathogenesis.

The microbiota being a central actor in IBD pathogenesis, it is logical to try to modulate from a therapeutic perspective. Most of the available studies on fecal microbiota transplantation (FMT) in IBD are open label and uncontrolled. Two randomized controlled trials have been published recently testing FMT in mild to moderately active UC. In the study by Moayyedi *et al.*, FMT was given via enema once weekly for 6 weeks and showed superiority compared to placebo with some differences in efficacy according donor. In the study by Rossen *et al.*, FMT was given via nasoduodenal tube (two procedures with 3 weeks interval) but did not show any difference in efficacy compared to placebo. However, the microbiota of FMT responders had distinct features suggesting that some patients and/or donor might be more

EDITO

prone to benefit from FMT than others. These studies highlight our poor knowledge regarding microbiota modulation in IBD and suggest that donor, receiver and methodological factors might impact FMT efficacy. More studies are thus needed to evaluate if FMT could have a place in IBD, what patients could benefit from it and what factors should be taken into account.

SUMMARY FOR PRACTITIONERS

- **Gut microbial composition, sometimes referred as "signatures" differs significantly between patients with UC, CD and healthy persons, including a decrease of *Faecalibacterium prausnitzii* in IBD patients. No diagnostic tool available yet, but gut microbiota will become a factor to take into account for diagnosis, prognosic and treatment.**
- ***F. prausnitzii* has been shown to have anti-inflammatory effects on both intestinal epithelial cells and immune cells, as well as to stimulate a new type of human IL10 producing Treg cells.**
- **Besides bacteria, the enteric virome is entering the scene of gut microbiome, and exhibit specific distortions in IBD.**
- **Fecal microbiota transplantation (FMT) in IBD: Few randomized control trials, reporting some beneficial effect on mild to moderately active UC. More studies are needed including rationale for selecting proper donors.**

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GUILLAUME SARRABAYROUSE, ON HOW *FAECALIBACTERIUM PRAUSNITZII* INDUCES CELLS THAT CONTROL COLONIC INFLAMMATION

Published in: DIGESTIVE HEALTH - IMMUNE FUNCTION I Written on June 25, 2015 by Kristina Campbell

Guillaume Sarrabayrouse achieved his PhD in immunology at the *Claudius Regaud Institute of Cancer* Research in Toulouse, France. He was a post-doctoral fellow in the INSERM team of *Francine Jotereau* in Nantes (France), and recently joined the Chaysavanh Manichanh Group in Barcelona.

Dr. Guillaume Sarrabayrouse of Barcelona

Sarrabayrouse won the Young Investigator Award for his poster at the *2015 Gut Summit* in Barcelona. In his recent research, published *in PLoS Biology*, he defined a new subset of tumor-reactive T cells, part of the immune system, showing that CD4CD8 αα T lymphocytes from the lamina propria of the healthy colonic mucosa represent a previously unknown subset of regulatory T cells induced by the gut microbiota (in particular, *Faecalibacterium prausnitzii*). He also found these cells are present in blood and decreased in inflammatory bowel disease (IBD) patients. This illustrates the relationship between gut microbiota and the immune system.

Below, Sarrabayrouse answers some questions about his work for GMFH editors.

I Before the current study, how did you know *F. prausnitzii* was significant in inflammatory bowel disease?

When I joined the group of Professor Francine Jotereau, the aim of our study was to identify tumor-reactive T cells in colon cancers to develop immunotherapeutic strategies. In doing this, we observed two distinct subsets of double positive lymphocytes that we characterized in the tumors and healthy mucosa, and later in blood. The potent regulatory properties of the CD4CD8αα subset led us to ask if it could be induced by human *Clostridium* bacteria, as shown in mice for the colonic Foxp3 Treg. That *F. prausnitzii* was a good candidate became rapidly obvious from the important literature underlying its role in IBD. Fortunately, we could test this hypothesis rapidly using *F. prausnitzii* and a few other bacteria provided by the French INRA group that has been pioneering in demonstrating the anti-inflammatory properties of *F. prausnitzii*.

Source: Sarrabayrouse G, *et al.* (2014) *CD4CD8αα Lymphocytes, A Novel Human Regulatory T Cell Subset Induced by Colonic Bacteria and Deficient in Patients with Inflammatory Bowel Disease. PLoS Biology* DOI: 10.1371/journal.pbio.1001833

Read the original post online at:
http://www.gutmicrobiotaforhealth.com/guillaume-sarrabayrouse-faecalibacterium-prausnitzii-induces-cells-control-colonic-inflammation-8303

NOT THE USUAL PROBIOTIC SUSPECT: RESEARCH SHOWS *LACTOCOCCUS LACTIS* HAS ANTI-INFLAMMATORY EFFECTS IN MICE

Published in: DIGESTIVE HEALTH - NUTRITION - PROBIOTICS I Written on June 8, 2015 by Kristina Campbell

Research collaboration on a new potential probiotic: an «underrated» species of bacteria, *Lactococcus lactis* CNCMI-1631 conferred beneficial effects in mouse models of gut inflammation.

Dr. Wendy Garrett, Associate Professor at Harvard's Chan School of Public Health, says the line of research came out of an observation, several years ago, that a fermented milk product improved colonic inflammation in mice. "We wanted to understand what bacterial parts... were contributing to making mice with bad intestinal inflammation better," she says. "The landing on *Lactococcus* was one of those science things that wasn't expected and has really been serendipitous."

Dr. Wendy S. Garrett
of Harvard University

Lactococcus lactis, says Garrett, is not a 'usual suspect' when it comes to bacteria that have beneficial effects on a host. "Often this strain is used in the food industry to add textural elements to yogurts and cheeses, or flavor profiles, so it was unexpected that it was making the mice better," she explains. "Once we landed on *Lactococcus*, we focused on extending that observation to other mouse models where there was intestinal inflammation and figuring out what about *Lactococcus* was driving this effect."

The researchers gave a *Lactococcus lactis*-fermented milk product to three different groups of mice. Garrett says, "There are a bunch of mouse models that are good for studying intestinal inflammation. One is a model that has two genes that are missing: T-bet... and RAG2. That mouse spontaneously, just by the fact that it's missing those two genes, gets a bad ulcerative colitis-like disease. The other mice we look at are missing an important protein that dampens inflammation... called IL-10, and then the third model is one in which you give this sugar, called dextran sulfate sodium... and what this sugar does is it actually disrupts the mucosa or the lining cells of the large intestine. If you disrupt that important barrier you get very bad intestinal inflammation in the mice in the large intestine." In all three of the inflammation models, says Garrett, the fermented milk product had an effect, suggesting that this bacteria is a probiotic for mice at least.

The group found a particularly interesting mechanism behind these effects. Co-author Dr. Patrick Veiga says the bacteria seemed to work by producing enzymes that helped them survive oxidative stress in conditions of intestinal inflammation. "These beneficial effects were delivered through the ability of *Lactococcus lactis* to produce antioxidant superoxide dismutase," he says.

Source: Ballal, SA, *et al.* (2015) *Host lysozyme-mediated lysis of Lactococcus lactis facilitates delivery of colitis-attenuating superoxide dismutase to inflamed colons. Proceedings of the National Academy of Sciences of the USA* doi: 10.1073/pnas.1501897112

Read the original post online at:
http://www.gutmicrobiotaforhealth.com/usual-probiotic-suspect-research-shows-lactococcus-lactis-anti-inflammatory-effects-mice-8214

SKIP VIRGIN LAB: THE 'VOICE OF VIRUSES'

Published in: DIGESTIVE HEALTH - GUT MICROBIOTA - RESEARCH TOOLS | Written on April 25, 2015
by Kristina Campbell

"I'd like to get you to think differently about viruses," announced Dr. Herbert 'Skip' Virgin at the 2015 Keystone Symposium, *Gut Microbiota Modulation of Host Physiology* - an event where most researchers in attendance focus on the bacterial residents of the gut.

Virgin, of Washington University School of Medicine in St. Louis, drew attention to the importance of the enteric virome both in the keynote address and in question periods throughout the conference. Later, he gave GMFH editors three reasons why viruses are important in microbiota research.

Dr. Herbert 'Skip' Virgin,
Washington University in St. Louis

First, Virgin says, "Viruses are an important part of the microbiome and our overall genomes as composite organisms." Second, "They have documented effects on immunity and are altered in disease states." And finally, says Virgin, "They may be related to other components of the overall microbiome such as the bacterial microbiome."

The Virgin Lab recently released *a paper on viruses and inflammatory bowel disease* (IBD), showing that enteric virome richness increased in both Crohn's disease (CD) and ulcerative colitis (UC). They showed that the virome changed differently in CD and UC, and that the changes were independent of observed decreases in bacterial diversity and richness in IBD.

Source: Norman JM, *et al.* (2015) *Disease-Specific Alterations in the Enteric Virome in Inflammatory Bowel Disease. Cell* doi:10.1016/j.cell.2015.01.002

Read the original post online at:
http://www.gutmicrobiotaforhealth.com/skip-virgin-lab-voice-viruses-8069

https://www.linkedin.com/groups/Gut-Microbiota-Health-4825357/about

DR. R. BALFOUR SARTOR, ON A NEW UNDERSTANDING OF CROHN'S DISEASE AND THE MOVE TOWARD PERSONALIZED MEDICINE

Published in: DIGESTIVE HEALTH - GUT MICROBIOTA I Written on April 7, 2015 by Kristina Campbell

Dr. R. Balfour Sartor **is a gastroenterologist and mucosal immunologist working at the Center for Gastrointestinal Biology and Disease, Department of Medicine, Microbiology and Immunology, at the University of North Carolina (USA). He is co-director of the Center for Gastrointestinal Biology and Disease.**

Dr. R. Balfour Sartor, University of North Carolina

Sartor recently wrote an article called *"The Intestinal Microbiota in Inflammatory Bowel Diseases"*, published in Nutrition, Gut Microbiota and Immunity: Therapeutic Targets for IBD, from the 79th Nestlé Nutrition Institute Workshop. The article highlights the abnormal fecal bacterial profiles observed in pouchitis, Crohn's disease and ulcerative colitis. Sartor argues bacterial function is more important than composition; key pathways are shared, so the presence of certain bacterial groups can functionally compensate for the absence of others. In addition, he notes, different bacterial groups can synergistically interact.

Sartor says the goal of therapy for inflammatory bowel diseases should be to restore a more homeostatic profile of bacteria, fungi, viruses. He goes on to explain a current theory of Crohn's disease pathogenesis involving genes, environment, microbiota, and immune factors, aiming at restoring gut microbiota balance or improving its resilience.

GMFH editors interviewed Sartor about his recent article.

I What's your current hypothesis about how Crohn's disease occurs?

It's been an evolution. My belief is that Crohn's disease is the result of an overly aggressive immune response to a subset of resident intestinal bacteria (and maybe fungi and viruses) in a genetically susceptible individual, with onset and flares precipitated by environmental triggers. It's quite clear that genes are important. In identical twins, if one twin has Crohn's, there's about a 50% chance the other twin has Crohn's, where in non-identical siblings it's about 5%. In the normal population the risk is about 0.5%.

There is an obvious difference in risk between identical and non-identical twins, where environment is ostensibly the same. Yet you know just from those data that genes aren't the total answer, they're only part of the answer. So far 163 genes have been associated with Crohn's disease and/or ulcerative colitis (a related inflammatory condition) so there's clear genetic polymorphisms associated.

If genes are important but not the total story – necessary but not sufficient – then what else is driving it? We have strong evidence in animal models of colitis, and this has been the focus of my own work – that resident (normal) intestinal bacteria are involved.

Read the original post online at:
http://www.gutmicrobiotaforhealth.com/dr-r-balfour-sartor-new-understanding-crohns-disease-move-toward-personalized-medicine-8005

INTERVIEW WITH DR. BRENT POLK, ON INFLAMMATORY BOWEL DISEASE IN CHILDHOOD

Published in: DIGESTIVE HEALTH - IMMUNE FUNCTION - PROBIOTICS I Written on February 16, 2015
by Kristina Campbell

Dr. D. Brent Polk is a physician and professor of biochemistry & molecular biology. He is chair of the Department of Pediatrics at *Children's Hospital Los Angeles*, as well as chair of pediatrics and vice dean for Child Health at the *Keck School of Medicine* of the University of Southern California. His *lab* is located at *The Saban Research Institute*, where he also serves as director.

Dr. D. Brent Polk, Children's Hospital Los Angeles & Keck School of Medicine of the University of Southern California

Dr. Polk spoke with Gut Microbiota for Health Experts Exchange about the latest findings on childhood inflammatory bowel disease, the gut microbiome and genetics of immunology.

I You study childhood inflammatory bowel disease (IBD). What is your current understanding of how it arises?

To date, what we can tell is that there are environmental, genetic, and other factors such as metabolic, that seem to predispose a subset of kids to develop inflammatory bowel disease. There's been some significant advances in understanding, for that very early-onset inflammatory bowel disease, the particular relationship between the genetics of immunology, and triggers that are probably related to the gut microbiome, that result in IBD for kids under two years of age.

I think the best example of that is work by the *NEOPICS group*: Christoph Klein in Germany, Aleixo Muise in Toronto, and Scott Snapper in Boston, who have identified and created this consortium looking at children with very early-onset IBD and have found some very interesting genetic factors associated with IBD.

I Do you have an idea what the gut-microbiome-related triggers of IBD might be?

We have thought for some time that things like nonsteroidal anti-inflammatory drugs, and aspirin, could be triggers to induce alteration. From an epidemiology standpoint, there is association between prior use of those and increased incidence, or triggering specific episodes of IBD. So that one seems to have very strong evidence.

For children, there's also the *work out of Denmark* looking at the use of antibiotics in the first few years of life, and a direct correlation between that and likelihood of having IBD, so that the more rounds of antibiotics you had received in early childhood, the more likely you were to have inflammatory bowel disease. This suggests a role of the gut microbiota and its balance and resilience capacity.

I Can you tell us about your research on how "a protein produced by probiotic bacteria protects colon epithelial cells and treats colitis"?

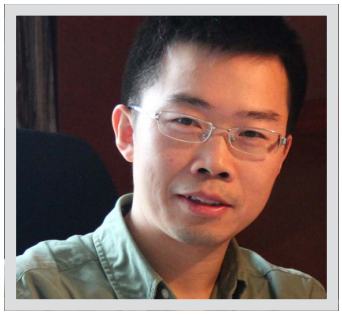
This is a protein that we isolated a number of years ago from the secreted materials of one of the well-known probiotics, *Lactobacillus rhamnosus* GG.

Read the original post online at:
http://www.gutmicrobiotaforhealth.com/interview-dr-d-brent-polk-inflammatory-bowel-disease-childhood-7443

DR. FAMING ZHANG, ON TREATING REFRACTORY CROHN'S DISEASE WITH FECAL MICROBIOTA TRANSPLANTATION

Published in: DIGESTIVE HEALTH | Written on January 12, 2015 **by Kristina Campbell**

Dr. Faming Zhang, MD, PhD, is a doctor and researcher at the Institute for Digestive Endoscopy & Medical Center for Digestive Diseases at *The Second Affiliated Hospital of Nanjing Medical University* in Nanjing, China. He is Vice Chief of the Medical Center for Digestive Diseases, and Director of Intestinal Diseases.



Dr. Faming Zhang, The Second Affiliated Hospital of Nanjing Medical University, Nanjing, China

His research group recently published a pilot study in which they treated patients with refractory Crohn's disease (CD) with a single fecal microbiota transplantation (FMT) through the mid-gut. In the paper, the authors noted that FMT for treatment of intestinal diseases was recorded in traditional Chinese medicine as far back as the fourth century. However, few modern clinical studies exist.

First, the researchers established a new standardized laboratory protocol for FMT. Then, they treated 49 patients, 30 of whom qualified for the study's analysis with at least a 6-month follow-up. Patients underwent a single FMT, and received a small sustaining dose of Mesalazine. They also received a 'food plan' to follow after FMT. After 1 month, clinical improvement was 86.7% (26/30) and clinical remission was 76.7% (23/30). Patients' body weight also increased.

Evidence indicated that the efficacy of FMT did not depend on the genetic relationship or close contact between the donor and patient, or on the dose of bacteria. The fresh fecal microbiota samples, however, were associated with a higher rate of clinical improvement and clinical remission than frozen microbiota. This suggests that some bacteria were missing to restore the gut microbiota balance or ease the resilience process. These findings need to be validated in larger studies.

Dr. Faming Zhang spoke with GMFH about this study.

| FMT has been used to successfully treat C. difficile infection. What gave you the idea to use it for patients with Crohn's disease?

C. difficile infection is an acute infection. However, inflammatory bowel diseases or IBDs, including Crohn's disease and ulcerative colitis, are chronic inflammatory diseases. If dysbiosis in IBD is a fact, then we don't know whether dysbiosis is a cause or a consequence of inflammation. We don't know which one comes before the other one, chicken or egg. But it doesn't matter for treatment; this study strongly supports the link between intestinal bacteria and IBD. Our hypothesis is that 'reconstruction', or resilience of gut microbiota should be helpful for treating those with Crohn's disease.

In the past 10-20 years, there are more and more cases of Crohn's disease in China. However, 20-30 years ago, Crohn's disease was very, very seldom seen in China.

Source: Cui, B, Feng, Q, Wang, H, Wang, M, Peng, Z, Li, P, Huang, G, Liu, Z, Wu, P, Fan, Z, Ji, G, Wang, X, Wu, K, Fan, D, & Zhang, F. (2015) *Fecal microbiota transplantation through mid-gut for refractory Crohn's disease: Safety, feasibility, and efficacy trial results. Journal of Gastroenterology & Hepatology* doi:10.1111/jgh.12727

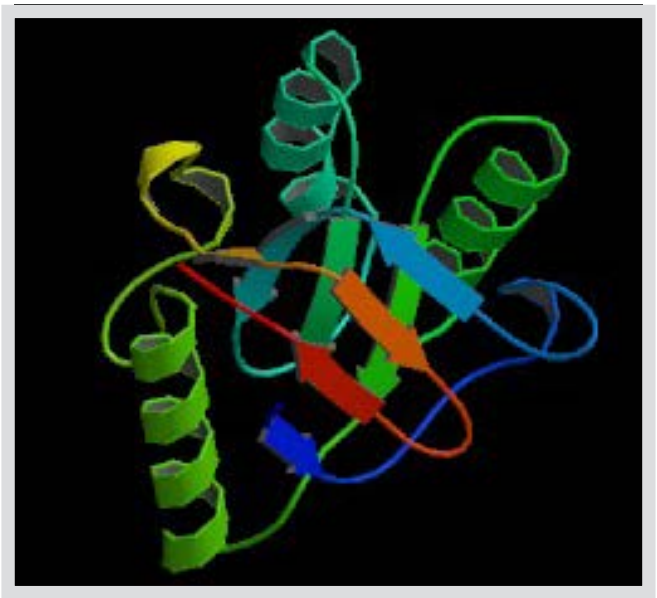
Further Reading: For a recent review that discusses the potential of FMT to treat IBDs, see this article from a Xi'an research group:
Liang, J, Sha, SM, & Wu, KC. (2014) *Role of the intestinal microbiota and fecal transplantation in inflammatory bowel diseases. Journal of Digestive Diseases* DOI: 10.1111/1751-2980.12211

Read the original post online at:
http://www.gutmicrobiotaforhealth.com/dr-zhang-crohns-fmt-7332

PROBIOTICS AND HEAT SHOCK PROTEINS IN ULCERATIVE COLITIS

Published in: IMMUNE FUNCTION - PROBIOTICS I Written on January 5, 2015 **by Marcello Romeo**

The Inflammatory Bowel Diseases (IBDs), which include Crohn's Disease (CD) and Ulcerative Colitis (UC) are chronic relapsing and remitting inflammatory disorders of the gastrointestinal tract.



Hsp60 protein structure. Source of Image: Walsh, M.A. *et al.* Acta Crystallogr., Sect.D v55 pp.1168-1173, 1999

The etiology of IBDs is not known yet but it is certainly multi-factorial and it includes genetic as well as environmental factors. Over the last years it has become clear, however, that IBD develops in genetically susceptible individuals as the result of a dysregulated and excessive immune response to luminal gut antigens. Therapeutic treatments for IBD are largely based on an understanding of immunopathology, and while newer therapies are being introduced, probiotics are still an active area of interest. Administration of bacteria for maintaining health or treating disease is currently very popular among modern researchers and clinicians.

Probiotics are living microorganisms, which upon ingestion in sufficient numbers exert health benefits on the human organism. Intense focus is also being placed on the role of specific probiotics in IBD and the possibility that gut flora or the immune response to them can somehow be favorably modified. Different studies have previously demonstrated the role of Heat Shock Proteins (HSPs) in the inflammatory process of IBDs. HSPs are a family of molecules highly conserved throughout evolution that are typically involved in folding, refolding, translocation and degradation of intracellular proteins under normal and stress conditions. HSPs have been implicated in the pathogenesis of a number of chronic inflammatory and autoimmune diseases like diabetes, rheumatoid arthritis and IBD.

In a recent work, we demonstrated that HSP 60 levels are increased in the affected intestinal mucosa from patients with CD or UC. Furthermore, we demonstrated that mucosal HSP 60 levels in UC patients decrease after therapy with either mesalazine (an anti-inflammatory drug) alone or mesalazine plus specific probiotic bacteria, with the decrease in the latter combined treatment being more pronounced than in patients treated with mesalazine alone. This result is largely in agreement with other studies assessing the value of probiotics in treatment of IBDs like UC, and it opens new avenues for the management of these diseases.

- Cappello F, Bellafiore M, Palma A, David S, Marcianò V, Bartolotta T, *et al. 60KDa chaperonin (HSP60) is over-expressed during colorectal carcinogenesis. Eur J Histochem* 2003;47:105-10
- Tomasello G, Rodolico V, Zerilli M, Martorana A, Bucchieri F, Pitruzzella A, *et al. Changes in immunohistochemical levels and subcellular localization after therapy and correlation and colocalization with CD68 suggest a pathogenetic role of Hsp60 in ulcerative colitis. Appl Immunohistochem Mol Morphol* 2011

Read the original post online at:
http://www.gutmicrobiotaforhealth.com/probiotics-heat-shock-proteins-colitis-7283

DR. JONATHAN BRAUN, ON 'METABOTYPES' AND INFLAMMATORY BOWEL DISEASE

Published in: DIGESTIVE HEALTH / GUT MICROBIOTA I Written on November 19, 2014 by Kristina Campbell

Dr. Jonathan Braun (MD, PhD) is a physician and researcher interested in how the immune system affects susceptibility to inflammatory bowel disease and cancer. He is exploring the concept of cluster of metabolites produced by cluster of microbes, the so-call enterotypes, and he calls it "metabotypes", and their potential role in managing the gut inflammation. He studies, among other things, the relationship between gut microbiota and immune system, call microbial-immune commensalism in the intestine, and new strategies in functional immune assessment. He is a professor at *UCLA's David Geffen School of Medicine.*

Dr. Jonathan Braun, MD, PhD
UCLA's David Geffen School of Medicine.

At the 2014 *Harvard Probiotics Symposium*, GMFH interviewed Dr. Braun about *his presentation and his ongoing research*.

I Tell us about the concept of 'metabotypes' that you shared in your presentation.

All those bacteria together in your gut are making a bunch of products. Thousands of different products. So with the spectral nature of all the organisms that live there, one might imagine that we're just a gradation of one person to the next in terms of their products.

The analysis that led to metabotypes indicated that, actually, people's microbial communities make one mode of products or a different mode of products. As a metaphor, you might imagine Chinese food as opposed to European food. It's good food, it's diverse, but it's different. And all the different ingredients together make for that type.

I How might the two human metabotypes relate to inflammatory bowel disease?

We know that almost everybody who has Crohn's disease has metabotype two. Whereas among 'healthies' it's about 50/50 between metabotypes one and two. In affluent, Los Angeles-based communities: that's our demographic.

The question we have now is 'chicken and egg'. It seems that metabotype two is a problem. But is it a problem because the disease has caused you to change your diet, your microbial community, and so it's secondary? Or is it that you have a certain metabotype and that puts you at risk for disease?

There's a few reasons why we think it's more likely to be the second situation than the first. In which case, metabotype one is a healthy one and if you have metabotype two it's making products or not making products which are a problem for you.

I How do you think genes might relate to metabotypes?

In two ways. One is that we know that many of your genes change the habitat of your intestine.

Read the original post online at:
http://www.gutmicrobiotaforhealth.com/jonathan-braun-metabotypes-measurement-7051

www.twitter.com/GFMHx

INTERVIEW WITH DR. JAMES VERSALOVIC, CHILDREN'S MICROBIOME RESEARCHER

Published in: IMMUNE FUNCTION I Written September 8, 2014 by Kristina Campbell

Dr. James Versalovic, M.D., Ph.D, is the director of the Texas Children's Hospital *Microbiome Center* and head of the Pediatric Infectious Diseases Section. He is also a professor at Baylor College of Medicine. As the Gut Microbiota for Health expert on research tools, Dr. Versalovic spoke with us about his pathology and immunology research related to the gut microbiome.

Dr. James Versalovic, M.D., Ph.D, Director of the Texas Children's Hospital Microbiome Center.

I What is unique about studying the microbiome in children?

Children tend to be less affected by these things... there are many confounding factors that influence disease, and children are relatively 'clean' to study. They're a little bit easier in that they haven't lived as long.

Every area has its complicating features, and temporal dynamics is certainly one in pediatrics. The changes over time are definitely more substantial than what we see in adulthood.

I How does your work with children contribute to knowledge about adult disease?

We have been very interested in mucosal immunity and intestinal inflammation since I started the laboratory because... we were studying colitis in the mouse as a model of inflammatory bowel disease (IBD). We were immediately interested in how gut microbes could suppress inflammation in general... But we also realized that children have intestinal inflammation and babies get necrotizing enterocolitis, and children and adolescents, but even pre-adolescents, get ulcerative colitis or Crohn's disease or IBD, so it is relevant to pediatrics.

Because of this whole framework that was developed in the last 10 or 15 years around the developmental origins of human disease... we're appreciating much more the impact of those disorders early in life and what it means in terms of lifetime risk of diseases that appear in adulthood. We know that IBD increases the lifetime risk of colorectal cancer, for example, and so by studying children with inflammatory bowel disease, we are hoping to make an impact on their risk of getting colorectal cancer later in life.

So things that may seem to be much more adult actually have their origins in childhood, like cancer... We're also studying recurrent abdominal pain, irritable bowel syndrome (IBS), which is very common in children and common in adults. In fact, many children who have IBS... will continue to have IBS as adults. So again, the connection between pediatrics and adult medicine is very important to us.

I Can you give us some highlights of your recent research projects?

In the area of intestinal inflammation and the gut microbiome... I'll highlight the story of histamine and amino acid metabolism.

Read the original post online at:
http://www.gutmicrobiotaforhealth.com/interview-dr-james-versalovic-6515

F. PRAUSNITZII AND CROHN'S DISEASE: NEW ANTI-INFLAMMATORY MOLECULES IDENTIFIED

Published in: DIGESTIVE HEALTH - TRENDS & DISCOVERIES | Written on July 6 2015 **by Pierre-Yves Arnoux**

Faecalibacterium prausnitzii is known for exhibiting anti-inflammatory effects in vitro and in vivo by secreted metabolites that block nuclear factor (NF)-κB activation. The low proportion of *F. prausnitzii* in the microbiome of Crohn's disease patients characterizes the microbial dysbiosis associated with that condition.

In a recent paper published in Gut, a team from the Gastroenterology & Nutrition Department from Saint-Antoine Hospital in Paris showed that *F. prausnitzii* produces anti-inflammatory bioactive peptides derived from a single 15 kDa protein named microbial anti-inflammatory molecule (MAM).

MAM expression in epithelial cell lines was able to block the NF-κB pathway with a dose-dependent effect. Furthermore *Lactococcus lactis* harbouring a MAM-cDNA encoding plasmid were able to alleviate DiNitroBenzene Sulfonic Acid-induced colitis in mice confirming the relationship between gut mcrobiome and digestive health.

Identification of anti-inflammatory molecules secreted by *F. prausnitzii* constitutes the first step toward designing new anti-inflammatory drugs to treat Crohn's disease. As *F. prausnitzii* is also known for the prediction of Crohn's disease relapse, MAM could one day constitute an interesting biomarker for Crohn's disease prognosis as well as an indicator of healthy microbiome or predictor of a better digestive well-being.

Source: Quévrain E *et al.* (2015) *Identification of an anti-inflammatory protein from Faecalibacterium prausnitzii, a commensal bacterium deficient in Crohn's disease. Gut*. doi:10.1136/gutjnl-2014-307649

Read the original post online at:
http://www.gutmicrobiotaforhealth.com/s/f-prausnitzii-crohns-disease-new-anti-inflammatory-molecules-identified

WHAT CAN THE MICROBIOTA OF PEDIATRIC IBD PATIENTS REVEAL ABOUT INFLAMMATION?

Published in: DIGESTIVE HEALTH - GUT MICROBIOTA | Written on June 12, 2015 **by Paul Enck**

Inflammatory Bowel Disease (IBD) involves aspects of both the host and the microbiota. Previous research in adults shows that IBD is associated with microbiota differences, but little is known about this association in pediatric patients.

This study from Helsinki, Finland, addressed the intestinal microbiota and inflammation in pediatric IBD. A total of 68 patients (9-18 years old) with IBD and 26 controls provided stool and blood samples. Researchers characterized the microbiota and measured blood and fecal inflammatory markers.

Results showed that the children's microbiota varied on continuum: increasing intestinal inflammation was associated with reduced microbial richness, abundance of butyrate-producing bacteria, and abundance of Gram-positive bacteria.

32 of the patients received anti-tumor necrosis factor-alpha (TNF-α) agents. In those who responded to the medication, microbial diversity increased and the microbiota looked more similar to that of controls by week 6; this pattern was not observed in non-responders. The abundance of certain groups of bacteria predicted response to the treatment.

This study was correlative so no inferences can be made about casuation. Authors say that further validation is needed, but that intestinal microbiota are a promising biomarker for inflammation level and therapeutic response in pediatric IBD patients.

Source: Kolho K-L, *et al.* (2015) *Fecal microbiota in pediatric inflammatory bowel disease and its relation to inflammation. American Journal of Gastroenterology* doi:10.1038/ajg.2015.149

Read the original post online at:
http://www.gutmicrobiotaforhealth.com/s/can-microbiota-pediatric-ibd-patients-reveal-inflammation

A NEW WAY TO DIAGNOSE 'DYSBIOSIS' IN IBS OR IBD

Published in: DIGESTIVE HEALTH - GUT MICROBIOTA I Written on June 2, 2015 **by Paul Enck**

Dysbiosis — an abnormal gut microbiota — is associated with several diseases, including irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD). Yet because of the great variation in gut microbiota composition between individuals, dysbiosis can be difficult to define.

In a recent article published in Alimentary Pharmacology and Therapeutics, researchers introduce a new diagnostic test that they say can help identify patients with dysbiosis. The "GA-map Dysbiosis Test" uses 16S rRNA gene sequencing to profile intestinal microbiota and identify dysbiosis.

To develop this test, they took fecal samples from healthy, IBS, and IBD patients and used PCA (principal component analysis) to build a profile of 'normobiosis'. They used the data to develop a Dysbiosis Index (DI) algorithm; the DI is a numeric representation of the degree of dysbiosis (*i.e.* deviation from normobiosis). They determined that a DI greater than 2 qualifies as potentially clinically relevant dysbiosis.

Next, researchers externally validated the test with an independent set of healthy, IBS and IBD subjects. Dysbiosis was detected in 73% of IBS patients, 70% of treatment-naive IBD patients and 80% in remission, but only in 16% of 'healthy' individuals.

Researchers say the test does not diagnose a particular disease, but it may allow monitoring of treatment regimens – perhaps by serving as a surrogate marker of treatment effects. Another potential clinical application is in the screening of FMT (fecal microbiota transplantation) donors.

Very little is known so far about how to address states of dysbiosis to improve health.

Source: Casén C, *et al.* (2015) *Deviations in human gut microbiota: a novel diagnostic test for determining dysbiosis in patients with IBS or IBD. Alimentary Pharmacology and Therapeutics* DOI: 10.1111/apt.13236

Read the original post online at:
http://www.gutmicrobiotaforhealth.com/s/new-way-diagnose-dysbiosis-ibs-ibd

www.youtube.com/channel/UCQLZz5EFC7tk2YgjTvIl6gA

FURTHER INVESTIGATION OF FECAL MICROBIOTA TRANSPLANTATION TO TREAT ULCERATIVE COLITIS

Published in: GUT MICROBIOTA | Written on May 12, 2015 **by Paul Enck**

Amsterdam researchers recently published an investigation of fecal microbiota transplantation (FMT) for the treatment of ulcerative colitis (UC). The TURN trial — Transplantation of feces in Ulcerative colitis; Returning Nature's homeostasis — was a double-blind randomized trial with 48 subjects who had mild to moderately active UC.

Participants received either a healthy donor's feces or their own feces (*i.e.* autologous FMT) via naso-duodenal tube.

No significant difference was observed between groups. In the per protocol analysis, 41.2% of patients in the donor group and 25% of controls achieved the primary endpoint, which was clinical remission of UC. Serious adverse events occurred in 4 patients but these were not considered related to the FMT.

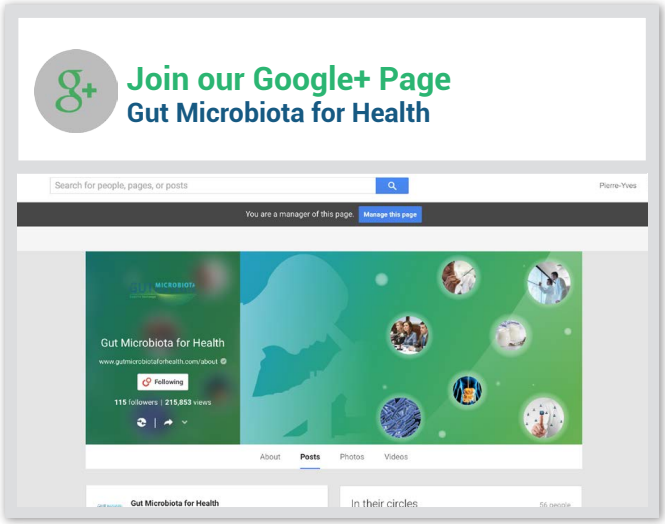
Patients who responded to FMT donor treatment showed a shift toward a donor-like microbiota composition. The microbiota of responders had distinct features from that of nonresponders after FMT.

This study contrasts with a recent study from Canada *(covered here on GMFH)* in which 24% of the FMT group and 5% of the placebo group achieved remission.

In the Canadian study, the placebo group received a water treatment, while in the Dutch study the placebo group received autologous FMT. Mode of administration was also different — enema and naso-duodenal tube, respectively. Also, while the Canadian study showed a possible donor effect, this was not assessed in the Dutch study because of low numbers in each subgroup.

Source: Rossen NG, *et al.* (2015) *Findings from a Randomized Controlled Trial of Fecal Transplantation for Patients with Ulcerative Colitis. Gastroenterology* DOI: *http://dx.doi.org/10.1053/j.gastro.2015.03.045*

Read the original post online at:
http://www.gutmicrobiotaforhealth.com/s/investigation-fecal-microbiota-transplantation-treat-ulcerative-colitis



plus.google.com/103497649210561693858/posts

NEW EVIDENCE FOR *F. PRAUSNITZII* BASED THERAPEUTIC STRATEGIES IN IBD

Published in: DIGESTIVE HEALTH - GUT MICROBIOTA- PROBIOTICS | Written on May 27, 2015
by Pierre-Yves Arnoux

Faecalibacterium prausnitzii is a commensal intestinal bacterium known for its anti-inflammatory activity, although its mechanisms of action on gut health are still unknown.

In a recent paper published in mBio, a team of INRA researchers proposed clues on how this anti-inflammatory effect is mediated in a gnobiotic mouse model of acute colitis.

An *E. coli* and *F. prausnitzii*-di-associated mouse model was subjected to 2,4,6-trinitrobenzenesulfonic acid (TNBS)-induced acute colitis. In this model, *F. prausnitzii* showed protective effects, associated with a specific metabolite profile along the gastro-intestinal tract and in the serum. Among the metabolites, a functional link was established in vitro for salicylic acid.

This study revealed the positive effects of *F. prausnitzii* on inflammation both locally and systematically. It paves the way for further research targeting *F. prausnitzii* metabolic pathways as a therapeutic approach in IBD.

Source: Miquel S. *et al.*, (2015) *Identification of Metabolic Signatures Linked to Anti-Inflammatory Effects of Faecalibacterium prausnitzii. mBio* doi: 10.1128/mBio.00300-15

Read the original post online at:
http://www.gutmicrobiotaforhealth.com/s/new-evidence-f-prausnitzii-based-therapeutic-strategies-ibd

NEW STUDY INVESTIGATING FECAL MICROBIOTA TRANSPLANTATION TO TREAT ACTIVE ULCERATIVE COLITIS

Published in: DIGESTIVE HEALTH - GUT MICROBIOTA | Written on April 14, 2015 **by Paul Enck**

Moayyedi *et al.* from Canada recently published a paper entitled Fecal Microbiota Transplantation Induces Remission in Patients with Active Ulcerative Colitis in a Randomized, Controlled Trial. Authors investigated the safety and efficacy of fecal microbiota transplantation (FMT) to treat active ulcerative colitis (UC) without infectious diarrhea; they say it is the largest placebo-controlled, randomized trial for FMT to treat any disease.

Patients were examined by flexible sigmoidoscopy and then given weekly treatment for 6 weeks: either FMT from healthy anonymous donors, or a placebo (water enema). The primary outcome was remission of UC.

Halfway through recruitment, the data monitoring and safety committee recommended discontinuing the trial for futility because they ascertained the primary endpoint was not likely to be achieved. However, patients already enrolled were allowed to complete the trial and the final results turned out more favorably than first anticipated.

70 patients completed the trial; 24% of the FMT group and 5% of the placebo group were in remission by the end of the study and there was no difference in adverse events. Researchers found no measurable difference in quality of life scores after the treatment.

A possible donor effect was observed, as 7 of 9 patients in remission after FMT had received stool from the same donor. Patients taking concurrent immunosuppressant therapy may have derived a greater benefit from FMT, and those with a more recent diagnosis appeared to be more responsive.

Microbiota analysis showed more diversity in the treatment group compared to the placebo group after 6 weeks; patients in the active therapy group were more similar to their donor sample than a control fecal sample.

This trial is an important addition to the literature on FMT for conditions other than *C. difficile*. It highlights the need for 1) stratification of different UC patients in clinical trials, and 2) investigation of specific donor effects that influence FMT success.

Source: Moayyedi P, *et al.* (2015) *Fecal Microbiota Transplantation Induces Remission in Patients with Active Ulcerative Colitis in a Randomized, Controlled Trial. Gastroenterology,* doi: 10.1053/j.gastro.2015.04.001

Read the original post online at:
http://www.gutmicrobiotaforhealth.com/s/new-study-investigating-fecal-microbiota-transplantation-treat-active-ulcerative-colitis

IBD MICROBIAL BIOMARKERS BEYOND GEOGRAPHICAL BORDERS

Published in: DIGESTIVE HEALTH - GUT MICROBIOTA I Written on January 13, 2015 **by Julien Tap**

Rehman and colleagues published in Gut a study about inflammatory bowel disease patients (who had Crohn's disease and ulcerative colitis), comparing gut microbiota between European and Asian countries. They found distinct patterns for each continent in mucosal microbiota, using microbial RNA and DNA profiling. However, microbial biomarkers specific to IBD in all geographic locations remained, like a decrease of *Feacalibacterium*. This confirms that gut microbiota functions are related to gut health.

Authors say, "Pathological community patterns observed in IBD are influenced by local, population-specific factors, but also show shared elements between the different cohorts."

Source: Rehman A, *et al.* (2014) *Geographical patterns of the standing and active human gut microbiome in health and IBD. Gut.* 2015 Jan 7. pii: gutjnl-2014-308341. doi: 10.1136/gutjnl-2014-308341.

Read the original post online at:
http://www.gutmicrobiotaforhealth.com/s/ibd-microbial-biomarkers-beyond-geographical-borders

MICROBIOTA ASSOCIATED WITH DISEASE IMPROVEMENT IN PEDIATRIC CROHN'S DISEASE DURING ENTERAL NUTRITION

Published in: DIGESTIVE HEALTH - GUT MICROBIOTA I Written on March 22, 2014 **by Julien Tap**

Exclusive enteral nutrition is a successful treatment in Crohn's disease context. Based on a study with 68 samples, the study showed that enteral nutrition is associated with a decrease of *Faecalibacterium prausnitzii* among the gut microbiota, and a decrease of global microbial diversity. This dysbiosis suggest strong relationship between gut microbiota and gut health. Exclusive enteral nutrition changed fecal metabolic activity.

Source: Gerasimidis K, Bertz M, Hanske L, Junick J, Biskou O, Aguilera M, Garrick V, Russell RK, Blaut M, McGrogan P, Edwards CA. (2014) *Decline in presumptively protective gut bacterial species and metabolites are paradoxically associated with disease improvement in pediatric Crohn's disease during enteral nutrition. Inflamm Bowel Dis.* 2014 May;20(5):861-71. doi: 10.1097/MIB.0000000000000023.

Read the original post online at:
http://www.gutmicrobiotaforhealth.com/s/microbiota-crohn-enteral-nutrition

A DECREASE OF THE BUTYRATE-PRODUCING SPECIES *ROSEBURIA HOMINIS* AND *FAECALIBACTERIUM PRAUSNITZII* DEFINES DYSBIOSIS IN PATIENTS WITH ULCERATIVE COLITIS.

Published in: DIGESTIVE HEALTH - GUT MICROBIOTA I Written on January 10, 2014 **by Philippe Marteau**

Machiels *et al.* recently described that the composition of the faecal microbiota of patients suffering from ulcerative colitis differs from that of healthy individuals: they found a reduction in two well-known butyrate-producing bacteria of the Firmicutes phylum, *Roseburia hominis* and *Faecalibacterium prausnitzii*. This has been confirmed in other studies. The dysbiosis found in the two inflammatory bowel diseases (IBD) *i.e.* Crohn's disease and ulcerative colitis share common characteristics but also specificities. Such discoveries will soon help establishing new diagnostic tools and preliminary data are encouraging. These tools will receive a high interest from clinicians, as they will improve the diagnosis in difficult cases, especially at early stages of the disease when treatments are usually more effective. Studies in families and follow up studies are also expected to provide major breakthroughs. As these bacteria are butyrate producers, the "old idea" of trying to improve butyrate production during IBD by various means is still very rational. One should also try to decipher the role of diet, especially low in fiber, in the dysbiosis. Obviously this is an important topic to follow for gastroenterologists and ecologists.

Source: Machiels K, Joossens M, Sabino J, De Preter V, Arijs I, Eeckhaut V, Ballet V, Claes K, Van Immerseel F, Verbeke K, Ferrante M, Verhaegen J, Rutgeerts P, Vermeire S. (2013) *A decrease of the butyrate-producing species Roseburia hominis and Faecalibacterium prausnitzii defines dysbiosis in patients with ulcerative colitis. Gut*. 2013 Sep 10. doi: 10.1136/gutjnl-2013-304833.

Read the original post online at:
http://www.gutmicrobiotaforhealth.com/s/a-decrease-of-the-butyrateproducing-species-roseburia-hominis-and-faecalibacterium-prausnitzii-defines-dysbiosis-in-patients-with-ulcerative-colitis

SACCHAROMYCES BOULARDII DOES NOT PREVENT RELAPSE OF CROHN'S DISEASE

Published in: PROBIOTICS I Written on February 18, 2014 **by Julien Tap**

This article reports a clinical study, which aims to test *Saccharomyces boulardii* as one probiotic to prevent relapse Crohn's disease patient during their remission phase. The hypothesis was that a probiotic may improve gut microbiota diversity and reduces dysbiosis of gut microbiota, or help to restore an improved balance or ease the resilience of the gut microbiota and improved gut health. Another hypothesis was that a probiotic may replace the function of a part of the gut microbiota. The study showed that there is no difference with the placebo arms whatever the treatment.

Source: Arnaud Bourreille, Guillaume Cadiot, Gérard Le Dreau, David Laharie, Laurent Beaugerie, Jean–Louis Dupas, Philippe Marteau, Patrick Rampal, Dominique Moyse, Ashraf Saleh, Marie–Emmanuelle Le Guern, Jean–Paul Galmiche, FLORABEST Study Group (2013) *Saccharomyces boulardii Does Not Prevent Relapse of Crohn's Disease. Clinical Gastroenterology and Hepatology* DOI: http://dx.doi.org/10.1016/j.cgh.2013.02.021

Read the original post online at:
http://www.gutmicrobiotaforhealth.com/s/microbiota-crohn-enteral-nutrition

INFLAMMATORY BOWEL DISEASE: THE 10 BEST TWITTER ACCOUNTS

Patients, doctors, associations, below we bring you 10 Twitter accounts to follow to keep up to date with what is hot in the field of #IBD.

1 ASSOCIATION

ImproveCareNow

- *https://twitter.com/ImproveCareNow*
- *http://www.improvecarenow.org*

2 ASSOCIATION

Crohn's & Colitis

- *https://twitter.com/crohnscolitisuk*
- *http://www.crohnsandcolitis.org.uk*

3 PATIENT

Queen Bee

- *https://twitter.com/sahara88uk*
- *http://www.getyourbellyout.co.uk*

4 PATIENT

Marisa Lauren Troy

- *https://twitter.com/journalingibd*
- *http://JournalingIBD.org*

5 DOCTOR

Edward Loftus

- *https://twitter.com/edwardloftus2*
- *http://www.mayo.edu/research/faculty/loftus-edward-v-jr-m-d/bio-00078086*

INFLAMMATORY BOWEL DISEASE: THE 10 BEST TWITTER ACCOUNTS

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6 DOCTOR

Charlie Lees

- *https://twitter.com/charlie_lees*
- *http://www.ibdscotland.org/researchers/charlielees*

7 PATIENT

Corinne Vanessa

- *https://twitter.com/cozziecorinne*
- *http://www.youtube.com/cozziecorinne*

8 PATIENT

Colitis and ME

- *https://twitter.com/colitisandme*
- *http://www.colitisandme.blogspot.co.uk/*

9 ASSOCIATION

CCFA

- *https://twitter.com/ccfa*
- *http://www.ccfa.org*

10 PATIENT

Lorna

- *https://twitter.com/lornamary_1981*
- *http://www.getyourbellyout.co.uk*

GUT MICROBIOTA AND INFLAMMATORY BOWEL DISEASE

August 2015

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