

March 5-6th, 2016, Miami

Fact sheet #1

Gut microbiota composition: A new kind of biomarker?

Without biomarkers modern healthcare would hardly exist. These measurable biological indicators allow physicians to assess the health state of their patients, diagnose conditions and predict disease risks. Over the last decade the highly dynamic field of gut microbiota research has made two essential discoveries: Firstly, the gut microbiota can be regarded as an organ in itself exerting such crucial functions as the digestion of fibers and the supply of the host with short chain fatty acids, vitamins and minerals. Secondly, the microbial communities inhabiting the human gut provide a huge potential of new biomarkers: As the composition of each individual's gut microbiota is closely linked to the food consumed as well as to the nutritional and gastrointestinal health state it is well suited to serve as an indicator for a wide range of bodily conditions: It might predict whether a certain diet is likely to induce overweight, it can mirror intestinal inflammation and help predict risk of colon cancer. Recent findings suggest that the compositions of gut microbial communities can be even more than mere indicators. They can also be causal factors in the onset as well as in the management and treatment of conditions. This fact sheet gives three examples of cutting edge research in the field of gut microbial biomarkers, presented at the Gut Microbiota for Health World Summit 2016 that has just finished.

Gut profiling: New biomarkers for metabolic diseases

For diagnosing or predicting metabolic diseases such as obesity, insulin resistance or type two diabetes (T2D), doctors commonly make use of biomarkers such as body mass index or glucose levels. These "classical" parameters are now joined by the gut microbiota composition as a new kind of biomarker. This is based on rapidly mounting evidence that the gut microbiota composition is significantly altered in patients with metabolic conditions. However, as **Prof. Max Nieuwdorp** (University of Amsterdam / The Netherlands) pointed out, not all kinds of changes of the microbial composition in patients with metabolic disease can be regarded as biomarkers of their condition.



Max Nieuwdorp,
The Netherlands

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This is due to the fact that not only antibiotics but also other drugs including anti-diabetic medications might impact the gut microbiota. “We recently demonstrated that subjects with T2D who used the anti-diabetic drug metformin had increased levels of *Enterobacteriaceae* and decreased levels of *Clostridium* and *Eubacterium* compared to those without this medication. Thus in cases like these the true microbial T2D profile may be masked by metformin or other drugs.”

However, after having excluded such biasing factors, it becomes plain that there truly are direct and tight connections between metabolic disease development and the intestinal microbial composition. Prof. Nieuwdorp presented the audience with studies performed by himself and other scientists that provide an increasingly detailed picture of what is going on: This includes for

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Max Nieuwdorp,
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example the finding that an enrichment of *Lactobacillus gasseri* and *Streptococcus mutans* in the gut serves as a good predictor for the development of insulin resistance which like obesity is a potential precursor to T2D. Equally important is the observation that the amount of bacteria that produce butyrate – a beneficial short chain fatty acid (SCFA) – such as *Roseburia* and *Faecalibacterium prausnitzii* is reduced in patients with this condition.

Examinations of the microbiota may thus help to identify individuals at an early stage who are at risk to develop metabolic diseases. What is more: Distinguishing different types of microbial composition and connecting these with classical clinical biomarkers may provide diagnostic patterns that allow to select the kind of prevention or treatment which is best suited for the individual patient. Personalization of treatment would be highly welcome as it would narrow down the broad range of possible health improving measures: While lifestyle interventions such as taking up sport activities might be appropriate for some patients others might need specific diets, prebiotics, probiotics, specific drugs or – in severe cases – bariatric surgery.

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Recent studies have demonstrated that the gut microbiota has not only disease indicating but also modulating potential. It could be shown that fecal microbiota samples from healthy donors that were transplanted into the guts of patients with metabolic syndrome improved insulin sensitivity. “This suggests that treatment of T2D in the future may, at least in part, be based on microbiota interventions. However, since fecal transplantations are associated with some risks, for example transferring of pathogens, safer and more appealing strategies need to be developed,” said Prof. Nieuwdorp. One promising path is the mining for bacterial strains with therapeutic potential that might serve as novel probiotics, adding to the spectrum of already known microbes with beneficial effects. Another future option might be vaccination. According to Prof. Nieuwdorp a strain of *Enterobacter sp* that fulfills the necessary criteria and is suited to this purpose was recently isolated from an obese individual. “These kinds of approaches may provide us with vaccines to treat metabolic diseases”, said Prof. Nieuwdorp.

Reducing colon cancer risk: How diet switch changes gut microbial metabolism

The gut microbiota is strongly associated with daily food consumption. Hence its composition can serve as a biomarker for nutritional habits as well as disease risks that are related to these habits. **Prof Stephen J. O’Keefe** (University of Pittsburgh/USA) and his team conducted a fascinating study focussing on connections between diet and colon cancer risk factors that shows how rapidly the gut microbiota can be altered by a change in diet. But what is more: Their research unveiled that gut bacteria are critically important not only for indicating disease risks but for mediating the link between diet and these risks, thus assigning the gut microbes a place in the causal chain of disease development. The findings of the study were presented by Prof O’Keefe’s colleague **Dr. Kishore Vipperla**.



Kishore Vipperla, USA

Colon cancer is known to be connected with a western lifestyle and in particular with a diet high in meat and fat but low in fiber. Accordingly, Colon cancer rates are much higher in the western world than in Africa or the Far East. To investigate the possible roles of diet and gut bacteria the scientists carried out a study with a group of 20 healthy middle-aged African Americans – the population with the highest risk of colon cancer in the USA – and another group of 20 participants from rural South Africa, who only very rarely get the disease. The two groups swapped diets

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under tightly controlled conditions and strict supervision for two weeks: Americans were given a 'traditional African' diet, high in fiber and low in meat and fat, while Africans were given a western diet, high in meat and fat, low in fiber. The volunteers underwent colonoscopy examinations as well as gut microbiota analyses before and after the diet switch. At the start, when the groups had been eating their normal diets, almost half of the American subjects had polyps which were subsequently removed as they can turn into tumours. None of the Africans had these abnormal growths.

Biopsy samples taken from the mucosa of different parts of the colon showed a significant suppression of inflammation as well as a decrease in mucosal cell proliferation in the American

"The gut microbiota can serve as a biomarker for nutritional habits as well as disease risks."

Stephen J. O'Keefe,
USA

subjects after they had switched to the "traditional African" low-fat and high-fiber diet. At the same time the food swap induced the reverse process in the guts of the African participants. Thus the risk to develop colon cancer was dramatically increased in the Africans after two weeks on the western diet, as inflammation and the proliferation rate of epithelial cells of the mucosa count as important biomarkers for this condition. These changes were associated with significant alterations in the gut microbial populations. However, these

alterations did not affect so much the gut composition of the intestinal microbiota as the metabolic interactions of the intestinal bacteria: The study found that a major reason for the changes in cancer risk was the way in which the bacteria in the gut altered their metabolism to adapt to the new diet. Bacteria known to be butyrate producers and those that can ferment complex carbohydrates seemed to have intensified their collaboration when being provided with a low-fat and high-fiber diet, while the alternative diet reduced these associations. The effects of these different modes of networking were significant: In the American group, the researchers found that the African diet led – among other things – to an increase in the production of the short chain fatty acid (SCFA) butyrate, a bacterial product of fiber metabolism. Like other SCFAs butyrate has important anti-cancer effects including the strengthening of the gut barrier, the support of the immune system and the reduction of pathogens by making conditions in the gut more acidic. On

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the other hand, secondary bile acids – a bacterial metabolic product which contributes to cancer onset – were reduced. Again the western diet induced the opposite effect in the African subjects.

Prior studies have shown that it takes one generation of westernization for immigrants to raise their originally low colon cancer risk to the rate of the immigration country. “Our findings suggest that it even takes only two weeks for a westernized diet to induce changes in biomarkers of colon cancer risk in the colonic mucosa and the gut microbiota and that gut bacteria metabolism is highly relevant for mediating these changes,” said Dr. Kishore Vippera. “However, looking at it from the opposite angle this is good news: It is probably never too late to lower one’s colon cancer risk by changing the daily nutritional routine. Our results suggest that increasing the fiber content of the western diet to about 50g per day and reducing fat by half is likely to reduce the colon cancer risk 10-fold. Additionally, gut bacteria now appear as a promising target in order to develop measures to prevent and treat colon cancer.”

Dangerous imbalance: Tracking down tumour inducing bacteria

Among the most important conditions that are linked to an imbalanced gut microbiota are Inflammatory bowel diseases (IBD) such as colitis and Crohn’s disease as well as colorectal cancer (CRC). These diseases are closely associated as the risk of patients with inflammatory bowel disease to develop CRC is about 60% higher than that of healthy people. Numerous studies have found that the overall diversity of the gut microbiota in these patients is decreased and that the proportions of certain bacterial species are changed. How bacteria, especially certain *E.coli* strains (belonging to *Enterobacteriaceae*) might be involved in the onset of colitis and CRC was at the centre of the talk of **Prof. Christian Jobin** from the University of Florida (Gainesville/USA).



Christian Jobin, USA

E. coli is a common resident also in healthy human guts, belonging to the so called commensal bacteria which feed on the same nutrients as their human hosts, albeit making use of different components. Thus one would not regard *E. coli*, from the outset, as the typical “bad guy” of the microbial community. However, as Prof. Jobin pointed out, there are certain strains, found in IBD and CRC patients that are particularly harmful as they are able to adhere to the epithelial cells

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lining the mucosa, and invade them. These so-called adherent-invasive *E. coli* (AIEC) can not only induce inflammation but are capable to utilize by-products of inflammation as energy sources, thus not only causing a detrimental microbial environment but at the same time feeding on it, a

“Certain strains, found in IBD and colon rectal cancer patients that are able to adhere to the epithelial cells lining the mucosa, and invade them.”

**Christian Jobin,
USA**

capacity not shared by competing bacteria. What is even more concerning: AIEC produce a genotoxin called colibactin, which damages DNA and is essential in generating tumours. The cancerous potential of this protein has been confirmed in preclinical models. As the colonization of the gut with AIEC is fostered by a western type diet (high in fat and sugar) nutritional habits are likely to play an important role in disease development. Experiments demonstrated that *E.coli* strains whose capability to produce colibactin was genetically removed could not promote CRC but were still able to trigger inflammation. This suggests that on a microbiological level

inflammation and tumour genesis have to be regarded as two separate processes. “The clinical benefit to be gained from investigating these and other host-microbiota-relationships in IBD and CRC is enormous as it will allow us to design innovative strategies to predict, detect and treat these conditions,” concluded Prof. Jobin.

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