Biofortis publication on microbiota alteration related to chemotherapy

HOST MICROBE INTERACTIONS

16S rRNA Gene Pyrosequencing Reveals Shift in Patient Faecal Microbiota During High-Dose Chemotherapy as Conditioning Regimen for Bone Marrow Transplantation

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KEY FINDINGS

Following BMT conditioning chemotherapy in cancer patients, we observed (i) alterations in the diversity of faecal microbiota, (ii) a reduction in the abundance of organisms with anti-inflammatory properties, and (iii) dysbiosis characterized by a significant establishment of Escherichia. These chemotherapy-induced changes in the faecal microbiota may have strong implications for immunocompromised cancer patients. Future work will be directed at correlating clinical consequences with microbiota alterations in a larger cohort of patients, specifically gastrointestinal disturbances and bacteremia.

SUMMARY

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Biofortis Microbiota Research: Expertise to support your innovation goals

Biofortis is an international Contract Research Organization (CRO), designing and implementing customized scientific research platforms for innovation in health, nutrition, cosmetics. The company specifically partners with a wide range of customers including companies in food, ingredient, pharmaceutical, medical device, supplement, cosmetic, and healthcare-related industries, through our four dedicated divisions in Europe, China, North America and Brazil.

Biofortis is uniquely positioned for research services in a number of scientific areas including, lipid/carbohydrate metabolism, cardio-metabolic health, satiety, weight loss, and cognitive function, as well as the microbiome, which is the focus of this newsletter. We strive to meet the innovation needs of our clients through collaboration and customization of each project.

“Today, we are convinced that human well-being cannot be reached without considering a new dimension: the microbiota. By using adapted tools targeting the intestinal, skin and oral microbes, we are able to evaluate the efficiency, safety or tolerability to treatment or nutritional products.” Thomas CARTON, PhD, R&D Manager, Biofortis, citation, 2014 June, 10th.
Understanding the microbiome(s) is a new focus for ‘evaluating physiological equilibrium’ (homeostasis) with the potential for improving human health. In the field of gastrointestinal disorders, the characterization of the microbiota should contribute to a better understanding of the relationship between gut microbiome and human health. A role for the gut microbiota has been established in simple gastrointestinal discomfort, malnutrition, and chronic diseases such as cancer.

In this relatively new field of investigation in human health, Biofortis scientists employ validated methods to monitor and characterize the gut microbiota via fecal DNA extraction. Identification of the populations present in gut microflora allows comparison of specific ‘cohorts’ grouped by microbiota bio-indicators and contribute to evaluate the effect of specific interventions in health and disease (pre-treatment vs post-treatment analyses). Microbiota characterization offers new opportunities for personalized medicine and the development of novel treatment strategies.

Microbiota Research at Biofortis, expertise dedicated to:

- Provide scientific support directed at reinforcing the effect of your product on microbiota equilibrium.
- Screen the right formula in medical nutrition to move to the clinical trial phase.
- Investigate the efficacy and safety of ingredients on microbiota.
- Improve medical treatment through microbiome remodeling.
- Develop ‘biomarkers’ – ‘health indicators’...

The IMODI project: at the heart of future personalized medicine in oncology

Biofortis is the expert partner for microbiome analysis for IMODI (Innovative MODels Initiative for Cancer) - the breakthrough innovative project that is being launched in France. Biofortis is providing Gut Microbiota biomarkers and CRO services, has been launched in France. In March 2012, IMODI was inaugurated in the presence of the France’s President in the Oncodesign facilities.

IMODI led by Oncodesign, brings together five industrial pharmaceutical partners Ipsen, Sanofi, Servier, Pierre Fabre, and Transgene and five small/medium-sized enterprises including Biofortis to answer industry’s need for access to an organized and standardized system for developing experimental cancer models.
It is being coordinated around three key R&D efforts:
- Developing models for xenotransplanting tumors to immunodeficient mice.
- Modelling a human tumor microenvironment in mice for certain targeted diseases.
- Demonstrating model predictability, including developing IT tools (database, data mining, in vivo and in silico models, etc.), clinical patient monitoring, and carrying out comparative clinical studies (Phase 0 / Phase I) as opposed to preclinical studies.

At our Scientific Advisory Board Meeting in November 2013, Dr. Eugene Chang, MD, discussed recent work describing the impact of diet on host-microbial populations. He stressed the importance of host-genetic interactions, and the exciting new research suggesting gut microbes are instrumental in gene regulation. Dr. Chang’s research program is focused on the interaction amongst host, microbiome, and environmental factors. He is specifically interested in the role of the microbiota in emergence of diseases such as inflammatory bowel diseases, diabetes, obesity, and cancer. Dr. Chang, is the Martin Boyer Professor of Medicine and Associate Director for Academic Programs and Training in Gastroenterology at the University of Chicago.

Biofortis is the expert partner for CRO services & Gut Microbiome analysis

- Clinical monitoring of patients
- Characterization of patients’ intestinal microbiome
- Identification of biomarkers

IMODI program may also contribute to a better understanding of the gut microbiome, described in the last few years as a “new organ,” and its relationship with disease, immunity, and chemotherapy tolerance. This project will position Biofortis as a key contributor to the field of cancer and public health.

‘Go inside the human microbiome to better understand human health’.

During an IMODI meeting, Florence Meyer Losic, Director of in vivo Oncology at IPSEN, discussed IPSEN’s involvement in the IMODI project alongside with Biofortis scientists. Dr. Meyer Losic commented: ‘After the successful CREMEC project that allowed IPSEN to access models to advance studies on colon cancer, and with the same view to develop useful medicines for patients, IPSEN decided to participate in IMODI. This new project aims to develop in vivo models to study patients’ response to treatments for prostate, liver, and pancreatic cancers. The main idea is to define the therapeutic benefit of new treatments for patients compared to traditional therapies’. According to Dr. Meyer Losic, ‘the microbiota represents a rapidly developing field that will open the way to new areas of research in the diagnosis, monitoring of patients, side effects and predictive factors in cancers. Today, we are still at the “discovery” stage more than at the clinical application stage and microbiota analysis on patients before or after a treatment will represent interesting biomarkers to define how patients are likely to react to treatments from either tolerability or efficacy standpoints’.
Take care of your microbiome for healthy skin and scalp

Skin flora is another important player in human health and disease prevention. Being exposed to the outside environment and in close relation with the inside environment, skin microflora interact with other microbes, and with skin human cells including immune cell system. The skin is the largest human organ and even larger if you consider that total number of bacteria on an average human skin has been estimated at $10^{12}$, and that up to 1 billion bacteria inhabit a typical square centimeter of skin (1). The healthy human skin microbiome corresponds to approximately 1000 bacterial species that represent 2 million genes (2).

A common inter-individual microbiome has been defined (2). Four major phylum of bacteria have been identified as part of this microbiome: Bacteroidetes, Firmicutes, Proteobacteria and Actinobacteria. Based on 16S sequencing analysis from the inner elbow of 5 healthy human subjects, 113 phylotypes belonging to these four bacterial phyla have been identified, and in this analysis, proteobacteria was the dominate species. Bacterial communities and density greatly depend on the body site where they reside and condition of the skin (1, 2, 3), it is therefore important to consider these variability to investigate skin microbiota researches and any skin health disorders.

Skin flora (including scalp flora) contribute to the equilibrium of the skin, and desequilibrium can result in disease (e.g., dermatitis, eczema, psoriasis, acne and dandruff) (1-4). Skin flora disequilibrium can be therefore a clinical sign for skin diseases (the NIH HMP working group et al, 2009, Genome research). The skin can be exposed to abiotic stressors (pollution, smoke, UV…) and exogenous pathogens. The flora defend against these insults through competitive exclusion and biological reactions (co-aggregation, biosurfactant expression, bacteriocin production, defensins…) that can trigger activation of the immune system (release of immune mediators) (5, 6). Several studies have reported a link between the gut microflora and skin microbiota, related to the release of immune mediators in systemic circulation (2, 7).

A recent interesting functional study of skin microflora (high throughput sequencing) has provided access to the major functions carried out by dominant skin colonized taxa including *Corynebacterium*, *Staphylococcus* and *Propionibacterium* (8). Furthermore, parallels found between the complexity and identity of mouse skin microbiota and human skin flora reinforces the interest of preclinical studies related to skin flora.

Microbiota as a potential targets for promoting skin health

Probiotics & skin flora. We have chosen to expand into this interesting field, which has opened up innovative research avenues in cosmetic & neutraceutic ingredients. Beyond their potential benefit in the intestinal microbiota realm, it is thought that both oral probiotic’s ingestion and topical application of ‘bacterial extract could i) improve barrier function ii) help to balance beneficial vs. harmful microflora iii) upregulate immune response to opportunistic pathogens iv) downregulate inflammatory reactions in response to allergens v) modulate host gene expression to promote function and delivery of functional proteins to prevent skin diseases (see below the interview with A. Gueniche). In particular, skin microbes have been shown to promote photoprotection (9 and references therein), modulate cutaneous inflammation related to atopic dermatitis (10-13), improve skin barrier and reactive skin (14), and activate antioxidant and antimicrobial defenses (15).
Specifically, *Vitreoscilla filiformis* extract (a hydrothermal species) and *Bifidobacterium longum* extract topically applied were shown to be beneficial on atopic dermatitis (AD) and reactive skin, possibly by stimulating antimicrobial peptide (e.g., organic acids or bacteriocins) and immunomodulatory pathways (e.g., IL10, TGF) (10-15). The probiotic strain *Lactobacillus salivarius* LS01 (DSM 22775), taken orally, has been shown to modulate cytokine secretion from type 1 and 2 helper cells and could be considered as an important adjunctive therapy in the treatment of adult AD (16). *Lactobacillus paracasei* ST11 has been reported to improve skin resistance to physical and chemical aggression by reducing inflammation. *L. johnsonii* was also shown to modulate cutaneous immune function altered by UV exposure (9). Moreover, a recent study has demonstrated some probiotic effect of *Lactobacillus paracasei* ST11 in reducing scalp disorders (e.g., dandruff) (SFA Journey on Microbiota, ‘Le microbiote la medicine de demain’).
This newsletter highlights promising opportunities for applied research on skin flora in cosmetics and dermatology. Major considerations for cosmetic products are demonstrating non-toxic nature of ingredients, as well as establishing efficacy for the skin. Exploring the effect of these ingredients on the skin flora equilibrium need also be considered to support healthy skin. Moreover, this bioindicator gives innovative opportunities in personal care and health care consumer products.

‘Skin microbiota equilibrium’ a new indicator of the health of your skin

Applied research in skin microbiota

- Prediction of skin disorder (characterization -‘microbiota health indicators’)
- Prevention or treatment of skin disorders (modulation of skin flora)
- To develop personalized product (according to skin flora characteristics/ethnicities, life habit, environnement)

Biofortis expertises on skin microbiota : ‘ad hoc’services for customers needs

**Explorative studies on skin microbiota for ‘characterization’**
- Comparative studies among ethnicities, aging, sexes, body sites, healthy vs pathological skin or scalp.

**Studies of the beneficial effects of a product to improve ‘skin or scalp condition’ – ‘Modulation of the microbiome’**
- Skin pathologies improvement (Inflammation, reactive skin, UV effects, AD, psoriasis, dandruff, acne, etc.)
- ‘Malodour treatments’

=> To study the benefit effect of probiotics (oral ingested or with topical application) on both skin and gut microbiota

**Biofortis expertises:**

- **Clinical Studies**
  - In house study design, subject recruitment, statistical analysis…
- **Biological analysis**
  - e.g. oxidative stress, immune and inflammatory markers…
- **Skin and Gut Microbiota characterisation**
  - Sampling, logistics & processing.
  - Microbiota characterization (taxonomical metasequencing, quantitative studies)
  - Bioinformatics and statistical studies.
- **Report and scientific communications**

**Testing the tolerance of your ingredient or product to launch**
- Comparative studies : skin microbiota equilibrium (composition, diversity and richness, homeostasis).
Reference list:


Participation at workshop and congress:

- Probiota 2014, Feb, 4-5th 2014 in Amsterdam.
- In Cosmetics, April 1-3rd 2014 in Hamburg.

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