



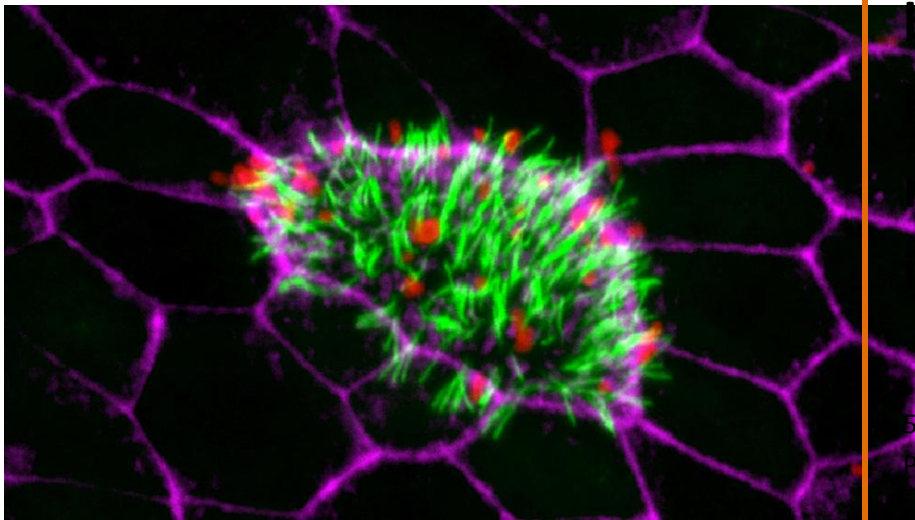
RESEARCH CONFERENCES



ESF-EMBO  
Conference

**Symbiomes:  
systems**

**Biology of  
host-  
microbiome  
interactions**



5 – 10 June 2015  
Pultusk, Poland

Chaired by: Claudio  
Donati  
Co-chaired by: Duccio  
Cavaliere & Marco Soriani

<http://symbiomes.esf.org/>

# Highlights & Scientific Report

## Conference Highlights

Please provide a brief summary of the conference and its highlights in non-specialist terms (especially for highly technical subjects) for communication and publicity purposes. (ca. 400-500 words)

It is now commonly accepted that the biology of most ecosystems, including the human body, cannot be understood independently from its colonizing microorganisms. However, until recently the researchers were limited to study those few species that could be isolated and cultivated on a Petri dish. Advancement in sequencing technologies, allowing the complete sequencing of human samples has shown that the microbiota encodes 100-folds more unique genes than the human genome itself, contributing in an essential way to many metabolic functions. In turn, many studies are showing that the composition and structure of the commensal flora is intimately correlated with both host genetics and environmental factors such as diet, age, and lifestyle.

The practical implications of this new approach are enormous, and largely unexplored. For example, the homeostasis between the gut microbiota, immune cells and mucosal components (such as mucins) allows the maintenance of a beneficial microflora leading to a healthy intestine. In this context, the intestinal mucosa plays an active role and it is not merely an inert barrier preventing a direct access to the epithelium. These mechanisms indicate that co-evolution have moulded this human-microorganism interaction into a symbiotic relationship in which gut bacteria make essential contributions to human nutrient metabolism and in return occupy a nutrient-rich environment. This interaction involves a variety of molecular and cellular mechanisms, through which commensal microbiota guides the maturation of the immune system in children, suppresses inflammation, and protects against potentially harmful pathogens. Therefore, the idea is emerging that shaping of the human microbiome is a viable intervention strategy for conditions that have proved untreatable with conventional methods (obesity, IBD, Clostridium difficile infections, etc.). On the other hand, monitoring the microbial flora could have a potential for early diagnosis of a number of conditions allowing timely intervention and thus decreasing the economic and social costs associated to disease treatment.

Dissecting all the different aspects of these complex systems is possible only through the interdisciplinary effort of expert from many different fields including molecular and cellular biology, microbiology, immunology, computational biology, bioinformatics, genetics, population genetics, and epidemiology. Building on the idea that the hosting environment, be it the human body or any other environment, including soil and plant rhizosphere, and its microbiota form a unique system, the meeting "*Symbiomes: systems biology of host microbiome interactions*" has brought together a panel of experts in these different fields that have presented the latest advancements in microbiome research. The scientific presentations and the lively discussions during the round tables that closed each session has given an overview of the current status of research and set the grounds for further scientific collaborations.



I hereby authorise ESF – and the conference partners to use the information contained in the above section on 'Conference Highlights' in their communication on the scheme.

# Scientific Report

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## Executive Summary

(2 pages max)

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The meeting was structured into five sessions: i) the healthy human commensal flora and its alterations; ii) homeostasis between microbiota and immune system; iii) host-microbiome interactions; iv) environmental microbiomes; v) therapeutic and preventive manipulation of microbiota, including 18 invited speakers, 20 short talks by young scientists selected from the contributed posters, and 12 posters.

**The healthy human commensal flora and its alterations.** The session included three invited talks and two short talks. The invited talks, given by Prof J. Ravel, Dr. Julia Oh and Prof. D. Bogaert, reported the structure of the microbiome in three different districts of the human body in healthy subjects, namely the vagina, the skin and the respiratory tract. Different aspects were discussed, including the existence of discrete healthy states of the vaginal microbiota, one of which more susceptible to infection by pathogens, the importance of the often overlooked viral and fungal communities residing on the human skin, and the dynamics of colonization of the respiratory tract during the first weeks of life in healthy humans.

**Homeostasis between microbiota and immune system.** The session included two invited speakers, Prof. E. Oswald, and Prof. N. Cerf-Bensussan. Prof. Oswald discussed the importance of characterizing the structure of the microbiota beyond the species level down to the strain level, using the common gut colonizer *Escherichia coli* as an example, showing that a fraction of humans are colonized by strains able to synthesize Colibactin, a virulence factor that can cause DNA damage in epithelial cells. Prof. Cerf-Bensussan discussed the role of non-cultivable bacteria in the maturation of human immune systems, showing in particular how complex communities of Segmente Filamentous Bacteria are essential for this process.

**Host-microbiome interactions.** The session included three invited speakers, Prof. J. Marchesi, Prof. C. Belzer and Prof. S. Pettersson, and three short talks. Prof. Marchesi discussed the difficulties in extending the Koch principle to the health conditions that could be caused by an altered microbiome. Amongst the principal reasons why it is difficult to establish a causal link between microbiome and disease, Prof. Marchesi mentioned the impossibility to distinguish cause from association in the absence of a clear mechanism of action, confounding factors such as host genetics, diet, lifestyle etc, citing colorectal cancer as an example. In this case, even from biopsies it is impossible to establish whether altered local microbiota is the cause of cancer, or the consequence of an altered environment. Prof. Belzer discussed the structure and function of the mucobiome, i.e. the microbial community of the mucus layer covering the surface of the human gut, highlighting the role of Akkermansia. Prof. Pettersson discussed the energy balance in the human body, showing that the immune system and the brain are two major consumers of energy. The microbiome is an essential part of the metabolism of each individual, and are present in every tissue with barriers that limit the passage from one tissue to the other. The microbiome plays a role in the development of skeletal muscles, ultimately influencing behavior and brain development.

**Foresight.** The session included three invited speakers, Prof. C. Huttenhower, Prof. N. Segata and

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Prof. D. Cavalieri and two short talks. The speakers discussed technological advancements and future directions for microbiome research. Prof. Huttenhower presented new software tools for the analysis of metagenomics data, and discussed new data from the Human Microbiome Project showing how the structure of the stool microbiota correlate with that of the colon, while is less representative of the microbiota of the small intestine. Prof. Segata showed how sophisticated data analysis tools can extend the resolution of metagenomics down to the strain level. Prof. Cavalieri discussed the role of co-evolution with the host and adaptation to the environment in the shaping of the human gut microbiota.

**Environmental microbiomes.** The session included two invited speakers, Prof. S. Hacquard and Prof. P. Bork, and 6 short talks. Prof. Hacquard discussed the plant root microbiota, showing how it is essential for nutrient absorption and defense against pathogens. Despite both organs are devoted to nutrient absorption, the diversity of the plant root microbiota is much larger than those of the gut microbiota in animals. Amongst plants, there is a correlation between the evolutionary distance between hosts and the dissimilarity of the root microbiota. Using the *Arabidopsis thaliana* as a model system, he showed that the vast majority of root microbiota is cultivable and that bacteria have a role in defense against pathogenic fungi. Prof. Bork presented a general overview of the analysis of metagenomics data, discussing the concept of enterotypes and showing how confounding factors, amongst which he singled antibiotic usage as most consistently present in all studies, are a major problem in data analysis. Prof. Bork then discussed recent results on the global diversity of the microbiome of the oceans, showing that temperature is the main driver of diversification.

**Therapeutic and preventive manipulation of the microbiota.** The session included five invited speakers, Prof. M. Soriani, Prof. T. Lawley, Prof. J. van Hylckama-Vlieg, Prof. B. Berger, and Prof. K. Thuoy, and five short talks. Prof. Soriani discussed the role of vaccination in shaping the human microbiota, presenting the example of *E. coli*, for which one of the possible vaccine targets is mucinase, a protein that allows *E. coli* to degrade intestinal mucus and reach the epithelium. Prof. Lawley stressed the role of microbiology and epidemiology in microbiome research. He presented the case of *Clostridium difficile*, a component of the gut microbial flora that might cause severe diarrhea in individuals in which the protective gut microbial flora has been destroyed by antibiotic use. Whole genome sequencing of single isolates has shown that antibiotic resistant strains of *C. difficile* have repeatedly appeared and quickly spread across continents. Most components of the microbial flora can be grown under laboratory conditions, and it is possible to design artificial bacterial communities that are protective against *C. difficile* infection. Prof. van Hylckama-Vlieg discussed the role of food borne microbes, and of probiotics, in shaping the human gut microbiota, showing that while they are capable of changing the structure of the microbiota of the small intestine they cannot change the microbiota of the colon. Additionally, he showed that the response to probiotics is strain specific. Prof. Berger discussed the differences between the microbiota of babies born with cesarean section and those born with natural delivery. He showed that the different microbiota can influence health status later in life, having a role in conditions like obesity. Prof. Thuoy presented a model of colon fermentation, showing that modern diet contains only a fraction of the fiber intake compared to the diet in the Neolithic.

There were three round tables discussions: i) Evolvability and robustness of host-microbiota interactions; ii) Standardization and validation of methods in microbiome research; and iii) Next steps – Translating microbiome research into intervention strategies.

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## Forward Look

*(1 page min.)*

- *Assessment of the results*
  - *Contribution to the future direction of the field – identification of issues in the 5-10 years timeframe*
  - *Identification of emerging topics*
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Since it emerged as a research area, the field of microbiome research is in constant change due to the changing technological landscape and to advancement in data analysis techniques. After an initial stage where microbiome research was mainly aimed at giving a description of the microbiome structure and composition in different environments, often trying to define differences that are associated to health conditions, age, diet or lifestyle in humans, there is now a growing awareness that turning basic research into applications will still require the effort of researchers from many different fields, from computational scientists to immunologists to microbiologists. The symposium has given a broad overview of the status of microbiome research, focusing on the importance of treating the host and the colonizing microbiota as a unique system. Many issues have been identified that will constitute the main points of microbiome research in the coming years. A non-exhaustive list of these issues includes: distinguishing correlation from cause; identifying mechanisms of action of microbiota on health conditions; using multi-omics approaches to characterize both the microbiota and its hosting organism; assessing the role of the immune system in maintaining the equilibrium between microbiota and the host; identifying and validating intervention strategies to shape the microbiota and drive it towards a status compatible with health.

Going into the details of the identified issues, so far microbiome research has mainly identified correlations between specific conditions and microbiome structure. However, it is becoming clear that these correlations can be due to many different reasons, and that proving causal relationships between microbiome structure and any specific condition will need identifying a mechanism of action. In this sense, many improvements upon existing experimental and data analysis techniques are necessary and will constitute the focus of research in coming years. First of all, many participants pointed out how strain-level characterization of the microbiota is essential. It is well known that strains with different metabolic potential can coexist in the same species, having dramatically different impact on the surrounding environment. In addition, causal relationships will need to be validated by conventional microbiological essays. To achieve this, many independent efforts are ongoing to improve cultivation techniques and build libraries of bacterial isolates that can be used to build simplified synthetic communities to be tested in in-vitro and in-vivo essays. An important contribution will come from the characterization of samples using multi-omics techniques. Being able to characterize at the same time the structure of the microbiota, its metabolic potential, the gene expression of both the microbiota and the host and the inflammation status of the host will be pivotal to understand the mutual interactions between host and microbiota and design viable intervention strategies.

The meeting included three round table discussions concerning topics that will be key in microbiome research in the coming years. The titles of the round table were:

- i. Evolvability and robustness of host-microbiota interactions
- ii. Standardization and validation of methods in microbiome research
- iii. Next steps – Translating microbiome research into intervention strategies

During the first round table, the main discussion was the role of host immune systems in maintaining the equilibrium with the microbiota. While many researchers underlined the active role of immune systems as a regulator of the structure of the microbiota through a baseline level of inflammation, others pointed out that this would constitute an unjustified waste of resources for the hosting organism, and considered the role of the immune system more as a line of defense that is activated only in case of severe unbalances of the homeostasis between host and microbiota. Resolving this issue will be instrumental for shaping our view of the symbiosis between host and microbiota and will constitute the theoretical basis for medical applications of microbiome research.

The second round table concerned the technical issues related to standardization of methods in microbiome research, and the members of the panel reported the major initiatives in this direction. Standardization of experimental techniques, meta-data documentation of samples and of analysis techniques is emerging as the most pressing needs in microbiome research, and the participant to the meeting agreed that its importance is going to grow with the amount of data potentially available for meta-analysis. The consensus was that in the absence of robust standards, comparability of data between different studies is not guaranteed preventing the scientific community from fully exploiting the large amount of data that is accumulating in public databases.

The third round table concerned the feasibility of intervention strategies that aim at shaping the microbiota. The discussion was centered mainly on human gut microbiota, and the proposed intervention strategies were mainly centered on the use of probiotic products. The consensus was that this approach is the most promising, but intense research is still needed to prove its effectiveness and define its fields of applicability. Main issues are quantitatively assessing the ability of probiotics to change the microbiota composition in the different districts of the gut and the duration of their effect, identifying mechanisms of action and characterizing the variability of the probiotic effect at the species and strain level.

The round tables were highly participated, with intense discussions between the panelists and the audience.

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▪ Is there a need for a foresight-type initiative?

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The field of microbiome research is highly dynamic, due to the continuous evolution of the technologies available. After an initial exploratory stage, research is now focussing on identifying ways to practically exploit the wealth of information produced by large scale sequencing efforts that are now becoming feasible also for medium size laboratories. In this sense, a forward looking initiative centred on the identification of the priorities for translating microbiome research into common medical practice (from bench to the bedside) and developing industrial applications of microbiome research would be highly desirable.

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## Business Meeting Outcomes

- *Election of the Organising Committee of the next conference*
  - *Identified Topics*
  - *Next Steps*
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The consensus of the participants was that the meeting was highly successful and that a second edition would be desirable. The participants in particular appreciated the format of the meeting that guaranteed ample occasions for discussions and establishing collaborations. The consensus was that this first meeting should be the first step towards the building of a scientific community that share common research interests and viewpoints. It was decided that the invited speakers will work together to identify opportunities to fund another meeting with similar format to be held in Summer 2017.

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## Atmosphere and Infrastructure

- *The reaction of the participants to the location and the organisation, including networking, and any other relevant comments*
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The reaction of the participants to the location and organization was highly positive. In particular, the participants appreciated the ample space for informal discussion after the talks and during the coffee breaks. The three round tables were highly participated and were characterized by lively discussion amongst the panellist and with the audience. The young scientists were well integrated and took active part to the discussions.

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## Sensitive and Confidential Information

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