

The Swiss Society of Microbiology: Small Bugs, Big Questions and Cool Answers

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Abstract: The Swiss Society for Microbiology (SSM) represents around 700 scientists working in the fields of medical (human and veterinary), microbial biotechnology as well as fundamental, environmental, and food microbiology. Five sections: Clinical Microbiology, Environmental Microbiology, Mycology, Prokaryotic Biology, and Virology reflects the main interests of the membership.

Keywords: Clinical microbiology · Environmental microbiology · Mycology · Prokaryotic biology · Swiss Society for Microbiology (SSM) · Virology



Introduction

The Swiss Society for Microbiology (SSM) is an association gathering Swiss microbiologists, *i.e.* more than 700 persons, working with microbes. The SSM is active in the fields of medical (human and veterinary), microbial biotechnology as well as fundamental, environmental, and food microbiology. It includes the study of all microbes, including bacteria, viruses, parasites and fungi, whatever their pathogenic role or their symbiotic nature. Also broad in scope and open to all scientists studying microbes, the current member composition, biased towards bacteriologists, virologists and mycologists, led to the constitution of five sections:

- Clinical Microbiology
- Environmental Microbiology
- Mycology
- Prokaryotic Biology
- Virology

The SSM promotes the advancement of all these disciplines by organizing an-

nual meetings and workshops, and by participating in current political and public microbiology-related debates for the benefit of our society. Thus, the SSM also aims at being active in lay communication, which is of prime importance to promote future careers in microbiology among the youngest, but also to advance communication at the political & societal level, since microbes are so important in many of our everyday activities, such as food (just think of lactobacilli and yoghurt for example). The importance of microbes as human pathogens extends far beyond their role in the pathogenesis of infectious diseases as demonstrated by their role in non-infectious human disease such as obesity and asthma. Moreover, the role of pathogenic microbes extends to pathogens of animals (including domestic animals, cattle, wild-life mammals, and fish), arthropods, plants and algae.

Bacteria and viruses being on earth for about 2 billion years earlier than eukaryotes, our society also includes several scientists fascinated by evolution and exploring the origin of life. Thus, the SSM bridges several specialities and partially overlaps with ecology, entomology, veterinary science, medicine, and biotechnology. Consequently, another task of the SSM is to advance the communication and exchange of scientific information among its members and other Swiss scientists. Special attention is given to the encouragement and career development of young and promising members by granting an annual SSM promotion award as well as by supporting PhD students and young post-docs with travel fellowships. This year, M. Stragiotti, F. Oechslin and P. V'kovski received the SSM poster award whereas G. Panis, received the SSM Encouragement award (Fig. 1).

Clinical Microbiology

Clinical bacteriology has benefited from major improvements in the last decade, and is about to be substantially transformed in the years to come. While the concept of culturing that is at the root of conventional bacteriology has not changed much since the Pasteurian times, the identification of bacteria and fungi has considerably been improved and accelerated (it requires 24 h now vs. 48 h before, *i.e.* through the use of MALDI-TOF^[1] mass spectrometry). The automation of laboratories that is currently being implemented should bring more standardization in the diagnostic process and improve the overall quality of results.^[2] Still, the biggest clinical issue in infections is resistance to antibiotics.^[3,4] In this field, very few improvements have been achieved and it currently takes at least 48 h to test the antibiotic susceptibility of the pathogens. During this time window, the patient is given a probabilistic antibiotic regimen that has to be active should the pathogen be antibiotic-resistant, but also not too broad to avoid the selection of resistant bacteria. So far, this Janus dilemma is not addressed by the latest techniques available in our laboratories. Nonetheless, the situation could change with the application of next-generation sequencing (NGS) tools directly on clinical samples, which can be referred to as clinical metagenomics.^[5] Indeed, the depth of sequencing should allow the recovery of the genetic information related to the pathogens putatively present in sample such as their identification, their antibiotic resistance genes (ARGs) and mutations leading to resistance. Still, several issues need to be tackled before clinical metagenomics can be applied in routine laboratories, namely the cost, turn-around time, human DNA removal, inference of

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Fig. 1. The SSM is encouraging PhD students and postdocs by giving three poster prizes (left) and one career encouragement award (right) each year. The poster prizes are sponsored by BioMérieux.

the antibiotic susceptibility profile from metagenomic data and linkage between ARGs and their host. Then, NGS could enter the routine laboratories through whole genome sequencing (WGS). Indeed, WGS has been shown to be a promising tool for assessing the relationships between strains,^[6,7] the detection of ARGs (in case of suspicion of multidrug-resistant bacteria such as those producing carbapenemase)^[8] or even the antibiotic susceptibility inference for fastidious-growing bacteria such as *Mycobacterium tuberculosis*.^[9] The use of NGS in clinical practice was extensively addressed during the Swiss MedLab 2016 in Bern (organized by the Swiss Union of Laboratory Medicine) and will be further discussed in the first International Conference on Clinical Metagenomics (October 13–14, 2016 in Geneva). In all, we believe that the next decades for clinical bacteriology are expected to include more automation, more bio-informatics, and fewer cultures.

Environmental Microbiology

Similar to clinical bacteriology, environmental microbiology has made major progress in the last decade due to techniques that do not require cultivation of microorganisms. For so-called *ex situ* analyses, DNA and RNA are extracted from samples originating from such complex environments as soils, aquifers, lake water and sediments, and biological treatment systems purifying wastewater. The nucleic acids are subsequently analyzed with

metagenomics approaches where all is sequenced or with more targeted approaches where specific genes are investigated. In a study investigating the effect of long-term organic and conventional farming on soil microbial diversity using a high-throughput pyrosequencing approach of bacterial and fungal ribosomal markers it was shown that organic farming increased richness, decreased evenness, reduced dispersion and shifted the structure of the soil microbiota compared to conventional managed soils.^[10] An investigation of the abundance of antibiotic resistance genes in 21 Swiss lakes using quantitative real-time PCR indicated higher abundance of certain of these genes with increasing number and capacity of wastewater treatment plants in the catchment.^[11] Another approach to analyze microbial communities are the *in situ* analyses where the cells are kept intact by fixation techniques and the nucleic acids inside the cells are used for analysis. A combination of fluorescence *in situ* hybridization and flow cytometry made it possible, after multiple efforts of technique optimization, to extract ultramicrobacteria affiliated with LD12 *Alphaproteobacteria* from the rest of the microbial community in the water of the lake – an achievement that had not been possible until now with traditional techniques.^[12] Despite the huge increase in understanding microbial community composition and functioning in numerous environmental systems, it became evident in recent years that only the combination of these novel nucleic acid-based techniques with traditional and novel culturing approaches will allow

many research questions of environmental microbiology to be answered. Such an approach has shown that there was not only an extensive taxonomic overlap between the *Arabidopsis* leaf and root microbiota but also a large overlap of genome-encoded functional capabilities.^[13] Finally, nucleic acid-based techniques also enable the investigation of bacterial pure cultures introduced into an environmental compartment. *Sphingomonas wittichii* strain RW1 for example was inoculated into soil to achieve increased pollutant degradation. It displayed a very different transcriptome signature than in liquid culture and evidence for numerous ‘soil-specific’ expressed genes was obtained.^[14]

Mycology

Activities in the section of Mycology, that are carried out under the flagship of the Swiss Society of Microbiology, are very diverse. The activities can be divided into different subcategories that reflect current research interests in the fungal community in Switzerland. The major fields of interest include Medical Mycology, Molecular and Cellular Biology of Yeast, Molecular Biology of Filamentous Fungi and Fungal Plant Pathogens. ‘Omics’-technologies have changed the way that research is carried out in microbiology across all types of microbial agents. In the field of Mycology, the progresses made during the past years in the area of genomics, including high-throughput deep-sequencing and transcriptomics, permit nowadays to undertake

studies that were not possible or just cost-prohibitive in the past.

For example, one of the challenges is, when following microbes such as fungal pathogens during a host infection, that it is difficult to investigate or isolate cells for further genome-wide transcriptional analysis. When total RNA is extracted from infected tissues, the proportion of fungal RNA is usually less than 1%, which makes it quite challenging to undertake fungal transcriptomics in such conditions. Recently, Amorim-Vaz *et al.* from the CHUV in Lausanne addressed this problem and applied a RNA enrichment procedure for extracting *Candida albicans* RNA from infected mice tissues.^[15] This procedure is based on exome sequencing in mammals. The approach uses 120-mer oligonucleotide baits corresponding to the ORFome of *C. albicans* (approximately 6300 genes) and which are able to capture *C. albicans* RNA. When successful, the RNA capture is devoid of most host RNA. From infected tissues, Amorim-Vaz *et al.* were able to enrich up to 1,600-fold the *C. albicans* RNA. This allowed an unprecedented resolution of the *C. albicans* transcriptome *in vivo* over the time course of an infection in an animal model and identified genes important for *C. albicans* pathogenesis. Interestingly, the fungal RNA enrichment procedure may be applied to other microbial pathogens, as far as their genomes are available.

The impact of genomics in fungal-oriented research can be also observed in plant pathology. Using genome wide association studies (GWAS), a recent study performed at the ETH Zurich identified in the plant pathogen *Fusarium graminearum* candidate genes that affect specific quantitative traits important for disease development.^[16] Out of 220 investigated fungal strains, 74 quantitative trait nucleotides (QTNs) were significantly associated to sensitivity of azoles, which are widely used fungicides for crop protection. Three QTNs associated with azole sensitivity were located in genes not previously associated with this phenotype. Such analyses may reveal critical genes that the fungus uses to develop antifungal resistance, which could lead to novel crop protection strategies. In conclusion, the development of efficient and high-resolution genomic technologies has profoundly changed the way fungal biology can now be approached and will continue to do so.

Prokaryotic Biology

Understanding how prokaryote cells grow and die not only dictates how we can best intervene with them or reprogram them to combat bacterial pathogens, but

it also provides insight into the principal mechanisms that most primordial cells use to control growth.

Bacteria can regulate their growth from within using venoms that are activated at times of stress, but also from outside using venomous harpoons that are deployed from competing bacteria. These venoms intoxicate their prey, arresting their growth and ultimately causing their lysis. The structure of the harpoon gun (also known as the type six secretion system, T6SS) resembles the puncturing device that bacteriophages use when infecting prey. In a tour de force of structural biology, Petr Leiman at EPF Lausanne and colleagues from the Biozentrum Basel recently illuminated the structure of the T6SS and phage harpoon guns and described in *Nature*^[17] how matching structural transitions in the constituents of T6SS and phage device occur at the atomic level. The team of Melanie Blokesch at the Global Health Institute of EPFL recently unveiled a new master transcriptional regulator of the T6SS in the cholera pathogen *Vibrio cholerae*.^[18] They showed that the TfoY integrates nutritional (environmental) and cell density signals to active expression of the T6SS and that the TfoY regulon only partially overlaps with that of the related protein TfoX. Might these proteins implement different fates in different *Vibrio cholerae* cells?

A distinctive fate of *Pseudomonas* cells has also been observed by Jan van der Meer and colleagues at the University of Lausanne.^[19] In this case they used clever tricks to indirectly visualize the excision, transfer and re-integration of a mobile genetic element from the chromosome of a donor cell into the chromosome of a recipient cell. By tracing each cell's history by imaging the transfer of the genetic element, they define the donor cell by reduced cell division rates or growth arrest, persistence, or lysis after the transfer has started. In a similar approach Mathis *et al.* also traced the *Caulobacter* cell history by live cell imaging in microfluidic devices after salt stress to monitor the history-dependence of bacterial stress responses.^[20] They observed the emergence of memory-like behaviour at the level of the population, indicating that past events can indeed modulate the behavioural traits of individuals and groups of bacteria.

Two different bacterial growth control mechanisms operating from within are reported by the groups of Christoph Dehio and Urs Jenal at the Biozentrum Basel and the group of Patrick Viollier at the University of Geneva. The Dehio lab described the mechanism of action of a new class of toxins that is activated inside the bacterium to inhibit DNA replication by modifying a special class of replication enzymes known as topoisomerases. These

enzymes are inactivated by the toxins by a modification known as adenylation.^[21] The Viollier lab studied a different class of toxins that degrades mRNA and showed that stress cause by DNA damage activates this toxin system to inhibit growth of *Caulobacter*.^[22] A recent benchmark paper from the Jenal team published in *Nature*^[23] showed that the ubiquitous second (dinucleotide) messenger cyclic diguanylate acts as tuner of cell cycle progression, licensing the onset of DNA replication by reversing the phosphate flow through an essential cell cycle kinase in the model system *Caulobacter*. A burst of cyclic diguanylate precedes the onset of DNA replication, explaining how the reversal in phosphosignaling is regulated in time.

Virology

Emerging and zoonotic viruses have received increased public attention during the past years. The Middle East Respiratory Syndrome (MERS) Coronavirus outbreak in 2012, the crisis in Africa with the outbreak of Ebola Virus, and the recent appearance of Zika Virus, has kept many virus laboratories busy world-wide, including Switzerland. Particularly the Ebola Virus outbreak exemplified that such events not only impact the countries that are directly affected. 'Raising Preparedness' appeared to be important in many ways. For example diagnostic tests have to be established and implemented^[24] for the case that travellers bring the Ebola Virus home from other countries. In addition, patient treatment under conditions of highest containment is needed to provide medical care of highest standard and at the same time to guarantee that the virus will not spread further inside or outside hospitals. The Geneva University Hospitals had been challenged with a case of a 43-year-old medical doctor who contracted an Ebola virus infection in Sierra Leone in November 2014 and was airlifted to Geneva University Hospitals on day 5 after disease onset.^[25] Due to the high standard of medical care and immediate treatment the patient recovered rapidly, despite an initial high viral load. The experience gained in such emergency units is invaluable and provides an impetus for further improved diagnostic methods and for a better understanding of Ebola Virus pathogenesis and evolution.^[25] This experience is currently needed as more and more cases of Zika Virus infections appear. Differential diagnosis is often needed due to simultaneous outbreaks of viruses, such as Dengue Virus and Chikungunya Virus, that show similar disease symptoms.^[26] Emerging and zoonotic viruses will certainly continue to keep virologists busy. The more we learn, and the more we know

about these viruses, the better will be our preparedness to future outbreaks.

Conclusion

The SSM is a very large and active society, which tackles a variety of themes and has members highly active in research, as well as in R&D activities, as demonstrated by the examples reported above. However, to be really inserted in the real life, it is essential for the SSM to also improve further its communication to the general population, by modifying the general perception of microbes, from beneficial servants, to accidental pathogens or even malicious agents of bioterrorism. Indeed, life has more evolved by cooperation than by competition and most microbes are just beneficial to life, with a major role in its evolution.

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