Translational Research

Host-Pathogen Interactions

3rd Edition

FACULTÉ DE MÉDECINE
FACULTÉ DES SCIENCES

UNIVERSITÉ DE GENÈVE

Microbiology and Immunology at the University of Geneva

Microbes are not visible to the naked eye. Nevertheless, they represent approximately 98% of the total biomass: it is indeed estimated that our world is colonized by more than 10^{30} bacteria, and even more viruses. In addition to bacteria and viruses, fungi, Archaea and Protozoa complete the microbial universe. Microbes are playing a central role in shaping and maintaining our environment, but also have a major impact on our health.

At the public health level, infectious diseases also mirror the changes and inequalities in our societies, where the poorest and children are the most affected. At a time when Plasmodium parasite infections cause 214 million cases of malaria and 438 000 deaths worldwide, when viral epidemics such as Ebola can destroy a whole country health systems in a few months, or, more recently, when Zika virus left thousands of children disabled for life, and when a rather frightening perspective of a possible return to a pre-antibiotic era because of omniresistant bacteria stands at our door, a multidisciplinary research on microbes and their interactions with their hosts becomes a prime necessity.

This research comes in many different flavours, varying from fundamental to clinical research, and from natural sciences to medicine, including pharmaceutical sciences and new public health approaches. The University of Geneva has the great privilege to harbour many groups working on microbe-host and host-microbe interactions in different faculties, sections, or departments. This diversity, reflected in this booklet, contributes to a truly stimulating environment fostering translational research. All these research groups also have the possibility to profit from state-of-the-art knowledge offered by various in-house platforms that represent an invaluable support.

An important reorganisation took place in 2016, when clinical research groups relocated to the newly extended "Centre Médical Universitaire" (CMU), where they joined basic research groups. This mixing will be an important drive in developing further translational research. At the same time, pharmaceutical sciences researchers moved to the CMU, which will broaden even further translationnel research activities. Finally researchers from the University Clinic of Dental Medicine will also join in the very near future.

Being in a University, researchers also participate in teaching at undergraduate and graduate levels, a mission that contributes to prepare our students to the challenges of their future careers, as scientists or as physicians.

Prof. Patrick Linder
Director Department of Microbiology and Molecular Medicine

Prof. Laurent Kaiser
Department of Internal Medicine Specialties
Head, Division of Infectious Diseases, HUG

Translational research, a priority for the Faculty of Medicine

The Faculty of Medicine of the University of Geneva was founded in 1876 and is the second Faculty of our Alma Mater in terms of personnel and budget. It benefits from its situation at the heart of "International Geneva" and its proximity to the World Health Organization headquarters, as well as from a close partnership with the University Hospitals of Geneva (Hôpitaux Universitaires de Genève, HUG). The Faculty of Medicine is composed of three different sections: Fundamental (SMF), Clinical (SMC) and Dental Medicine (CUMD). Research in microbiology is carried out in all of them as well as in many different departments. Host-pathogen interactions are thus studied using a variety of techniques and from very different angles providing an excellent environment for fundamental, applied and translational research. The mutually beneficial contacts are supplemented by an array of different platforms that provide expertise and equipment in state-of-the-art techniques (genomic analyses, imaging, proteomics, etc.).

The Faculty of Medicine in figures

The Faculty of Medicine employs 1794 people who contribute to first-class treatment of patients at the University Hospitals of Geneva, excellent research and pioneering teaching.

- 263 professors
- 974 staff in research and teaching
- 557 administrative and technical staff
- 1525 pre-graduate students (2015)
- 1240 post-graduated students (2015)

The Faculty of Science

Several groups at the Faculty of Science have host microbe interactions as their research projects. They are present in the section of chemistry, biology, and pharmaceutical sciences. Although approaching the microbes and their hosts from different angles, they all have the same passion: understanding the molecular mechanism of host-microbe interactions and how to interfere with them in the case of pathogens.

The Faculty of Science in figures

- 139 professors
- 785 staff in research and teaching
- 425 administrative and technical staff
- 1682 pre-graduate students (2016)
- 928 post-graduate students (2016)

Host-Microbe at the University of Geneva

Fundamental Medicine

- Department of Microbiology and Molecular Medicine
- Department of Pathology and Immunology
- Department of Cell Physiology and Metabolism
- Department of Genetic Medicine and Development

Clinical Medicine

- Department of Internal Medicine Specialties
  Division of Infectious Diseases (HUG)
  Infection Control Programme (HUG)
- Department of General Internal Medicine, Rehabilitation and Geriatrics
- Department of Paediatrics
- Department of Anaesthetesiology, Pharmacology and Intensive Care
- Department of Community Health and Medicine
  Division of Tropical and Humanitarian Medicine (HUG)

University Clinic of Dental Medicine

- Division of Oral Physiopathology and Periodontics
- Division of Cariology and Endodontics

Science Faculty

- Department of Biochemistry
- Department of Plant Biology
- Section of Pharmaceutical Sciences

Teaching at the Faculty of Medicine

The groups listed hereafter participate in the training of medical students in microbiology, immunology and infectious diseases, important areas in all medical disciplines.
Various aspects of microbiology and immunology are tackled throughout the teaching modules. During their first year, students follow a basic introduction to microbiology in the form of ex-cathedra lectures. In their second year, they start problem-oriented teaching, using virology as an example. In their third year, an entire module is dedicated to immunity and infection. Students then learn the bases of infectious diseases through lectures and problem-oriented teaching, and begin their hospital training in their fourth year. Throughout the Bachelor programme, students are also trained in clinical skills. Several optional courses and practical work are offered during second and third years.
In September 2017, the Faculty of Medicine will launch a new Bachelor programme in biomedical sciences, in collaboration with the Faculty of Science. In addition to basic science and biological science, this new programme will focus on the biology of the human body, diseases, and the development of treatments. Scientific communication and practical courses will represent a significant part of the curriculum. It will also introduce students to ethical, societal, economical and industrial aspects of drug development and prepare them for academic or applied research, or the various facets of drug development in pharmaceutical or biotechnology companies.

Our research groups also host students from the Faculty of Sciences for their Master work and PhD thesis. A doctoral programme with international recruitment and several devoted teaching activities is in place to guarantee a solid training

Host-Pathogen Interactions at the University of Geneva Faculty of Medicine

Bacteriology

Virology

Parasitology

Mycology

Host Response

Bioinformatics

Vaccinology

Dental Bacteriology

Hygiene and Infection control

Global Health Institute

Host – Microbe interactions at the Faculty of Science

Bacteriology

Pharmaceutical Sciences

Dominique Belin

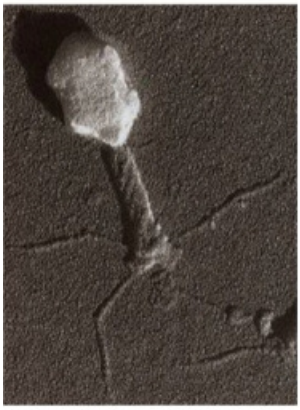
Department of Pathology and Immunology

Dominique Belin obtained his PhD in 1979 at the University of Geneva. He attended Rockefeller University in New York for three years as a postdoctoral Fellow, and later became visiting Associate Professor at Harvard Medical School, Boston (1990-1994). He was appointed Associate Professor (2002) and then full Professor (2009) of the Department of Pathology and Immunology.

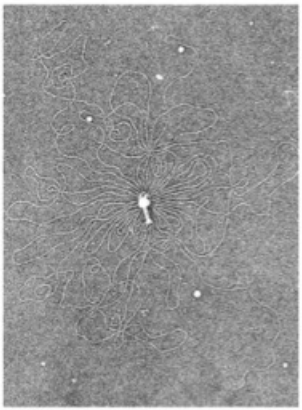
Genetic analysis of the translocation machinery in *E. coli* and of unknown genes of T4 bacteriophage

Our studies of the interaction of signal sequences with the translocation machinery in *E. coli,* has led to the identification of a new class of mutations that selectively decrease export mediated by mutant or foreign signal sequences. We have also developed a gain-of-function bio-informatics and biochemical system to define the parameters of signal sequences.

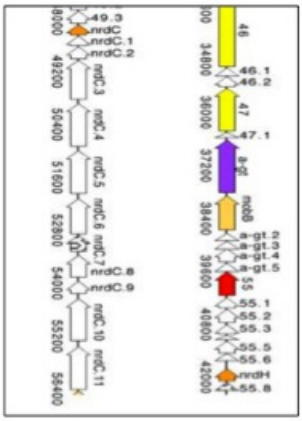
We are currently investigating the potential functions of phage T4 unknown genes. We have identified inserts that are toxic when expressed from inducible plasmids, and are concentrating our efforts on gene 55.1 and 55.2. High expression of 55.1 prevents growth while low expression confers a high sensitivity to UV irradiation caused by a deficient repair. We have isolated phage and bacterial suppressors of these phenotypes. High expression of gene 55.2 affects the topology of plasmids, while low, non-toxic expression prevents depletion of TopA. In addition, sub-lethal concentration of a gyrase inhibitor abolishes the toxic effect of 55.2. We have introduced null mutations in these genes. While single growth infections are essentially normal, competition assays over multiple parallel cycles of infection showed that 55.1 provides a slight evolutionary advantage, whereas the effect of 55.2 is much stronger. This approach will be extended to the other toxic unknown genes of T4.



A T4 particle



The chromosome



Unknown genes: white

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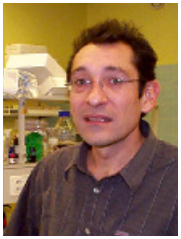
Keywords: Bacteriophage, phage T4, ORFans, E. coli genetics

Contact: Dominique.Belin@unige.ch



Patrice François

Department of Internal Medicine Specialties
Division of Infectious Diseases

Patrice François obtained his PhD degree at the University of Paris XIII in 1996. In 2000, he was involved in the creation of the Genomic Research Laboratory at the University Hospitals of Geneva. His primary research interests are mechanisms of *S. aureus* adhesion to foreign body and roles of small RNAs on bacterial pathogenicity. He obtained his Privat Docent in 2011.

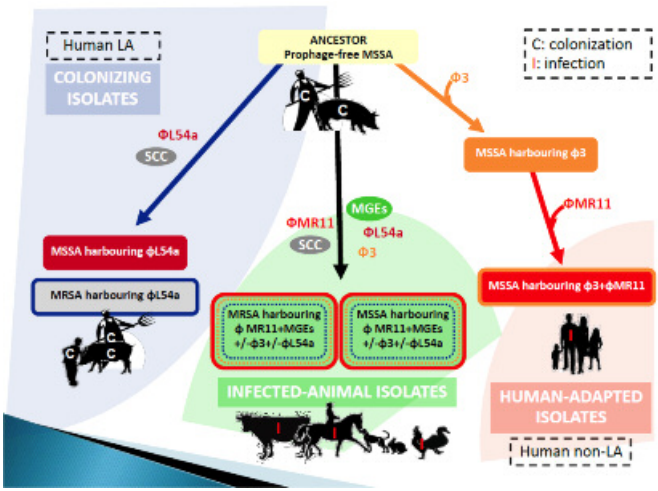
Deciphering the evolution toward virulence of various S. aureus lineages

Staphylococcus aureus is a versatile human and veterinary pathogenic bacterium recognized as a worldwide health problem, and responsible for a wide spectrum of infections, ranging from local skin to severe disseminated diseases. Using the capacity of massively parallel methods allowing studying the bacterium at the genome scale, we identified bacteriophage content as an important mediator of different features of this pathogen; adaptation against environmental stresses, host specificity and spreading as well as virulence and protection of genome integrity.

Some lineages (e.g. clonal complex 398) of *Staphylococcus aureus* have been initially described exclusively in animals. Recently, major epidemiological changes have been observed worldwide as specific lineage only responsible for animal infections are found in humans even without contact with animals. Following comparative genomic studies in various strain populations, we identified a number of mobile genetic elements allowing discriminating human from animal strains.

Recently, we isolated bacteriophages responsible for new phenotypic characteristics related to bacterial virulence and pathogenicity. Transduction of specific bacteriophages in “naïve” non-pathogenic staphylococcal strain leads to significant increase in expression of several virulence factors and important regulators. Consequently, increase in adhesion capacity to human extracellular matrix proteins is correlated with increase severity in a rat model of infectious endocarditis. Our main efforts rely to elucidate the mechanisms triggered by phage genes yielding to increase abundance of virulence factors; our main fields of interest are the regulatory role of intergenic regions and the protection of specific RNAs, especially those known to mediate regulation of virulence and adaptation factors.

We are currently characterizing phage genes as well as small RNA molecules that we have discovered in *S. aureus* for their potential roles as regulatory molecules during the infectious process.



Schematic representation of the diversification within a staphylococcal lineage. Representatives of the ancestral prophage-free population were identified in the form of pig-borne colonizing isolates (upper part). The acquisition by such prophage-free isolates of the φ3 prophage and the φL54a prophage resulted in the ancestral MSSA isolates: human isolates carrying the φ3-prophage and pig-borne colonizing isolates carrying the φL54a prophage. The acquisition of the φMR11-like prophage by the human isolates resulted in human-adapted (non-Livestock Associated) MSSA carrying φ3- and φMR11-like-prophages; the acquisition by the pig-borne colonizing isolates of the SCCmec cassette resulted in the pig-borne colonizing MRSA isolates. The acquisition of MGEs, including the φMR11-like prophage, which contains genes contributing to bacterial virulence, resulted in the emergence of MSSA and MRSA isolates responsible for infections in both livestock and pet species (lower part).

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Keywords: Staphylococcus, bacteriophages, genomic plasticity, small RNA, transcription

Contact: patrice.francois@genomic.ch

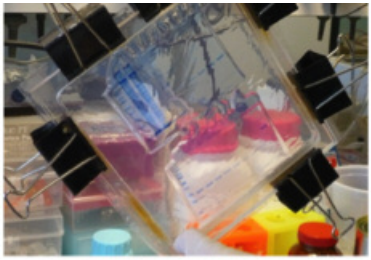
William L. Kelley

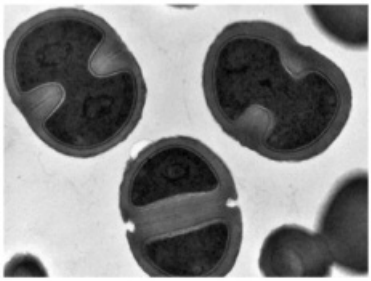
Department of Microbiology and Molecular Medicine

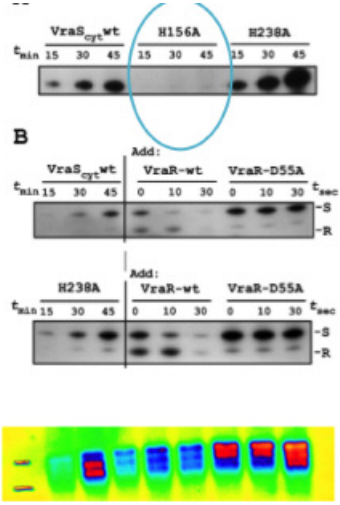
William L. Kelley graduated in 1981 from Williams College (USA), with a BA in Biology. In 1991 he obtained a PhD in microbiology-immunology with supplemental specialisation from the University Program in Genetics, Duke University Medical Center(USA). Following postdoctoral studies with molecular chaperones and protein folding in the laboratory of Costa Georgopoulos, he focused his research on Staphylococcal genetics. In 2007 he became Privat-Docent in the Department of Internal Medicine Specialities, in 2014, was appointed Senior Lecturer at the Department of Microbiology and Molecular Medicine.

Staphylococcus aureus environmental sensing systems

Our laboratory studies the range of mechanisms *Staphylococcus aureus* possesses that link extracellular signals to changes in gene expression. We are particularly interested in the family of histidine kinase two-component systems, which are widely found in the microbial world. Our work focuses on two of these systems: VraRS, which responds to cell wall active antibiotics such as penicillins and glycopeptides, and SrrAB, which responds to aerobic/anaerobic shift and orchestrates adaptations in energy production and redox balance. Curiously, SrrAB is also intimately involved in the transcriptional regulation of toxins, such as toxic shock superantigen, as well as *S. aureus*' defence against nitrogen monoxide (NO), a key effector of the innate immune response. We recently discovered that Spx, a non-DNA binding RNA polymerase interacting protein and global regulator of thiol and oxidative stress defence, is essential in *S. aureus*. Using deep sequencing and genetic methods we have uncovered novel genes that are Spx-regulated and suggest an important link between sensory pathways governing redox homeostasis and the general stress response. This finding has also led to ongoing studies with transcription initiation, exploring new properties of RNA polymerase, and explaining the mechanism underlying the remarkable physiological consequences associated with the acqusition of rifampicin resistance. Collectively, our work delves into drug resistance mechanisms including MRSA, virulence factor regulation, Sec-pathway secretion, extracellular protein folding factors, transmembrane signaling, penicillin binding protein biochemistry, and the discovery of novel processes that constitute promising targets for therapeutic intervention.







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Keywords: Staphylococcus, antibiotic resistance, oxidative stress, cell wall assembly, toxin regulation

Contact: William.Kelley@unige.ch

Patrick Linder

Department of Microbiology and Molecular Medicine

Patrick Linder obtained his undergraduate training in Basel and his PhD on replication in *Escherichia coli* at the University of Geneva in 1984. He spent three years in Gif-sur-Yvette in France as a postdoctoral Fellow, before coming to Switzerland as Junior Group Leader at the Biozentrum, University of Basel. He was appointed Lecturer at the University of Geneva in 1994, Associate Professor in 2000 and full Professor in 2007 in the Department of Microbiology and Molecular Medicine.

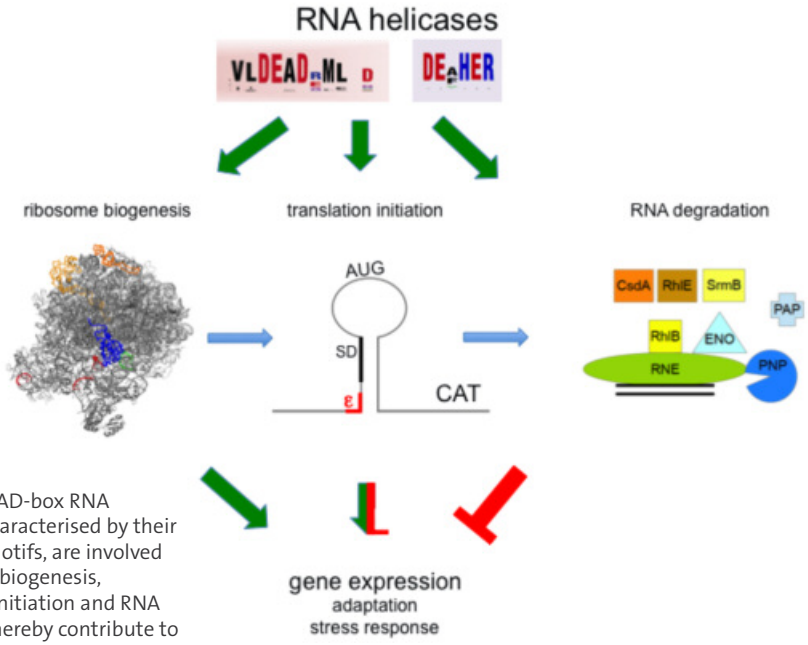
RNA metabolism and control of gene expression in *Staphylococcus aureus*

Staphylococcus aureus is an opportunistic pathogen that causes a variety of infections from skin infections to life threatening infections such as osteomyelitis, endocarditis, or sepsis. Colonising quietly the upper nares of roughly a third of the population, this bacterium needs to compete for its niche and adapt to rapidly changing conditions during infection.
Our group has a long-standing interest in the biological role of DEAD-box RNA helicase family proteins. These RNA helicases unwind short RNA duplexes, displace proteins from RNA, or function as regulated clamps on RNA. They are therefore ideal players to control gene expression. Bacterial DEAD-box proteins are involved in ribosome biogenesis, translation initiation, and RNA decay. We are interested in two RNA helicases, CshA and CshB, and their role in virulence expression and adaptation to different growth conditions in *S. aureus*.

We have shown that CshA is required for mRNA turnover of certain RNAs, including the *agr* mRNA encoding a quorum sensing system. It is part of the degradosome and thereby functionally interacts with RNase Y, RNase J1 and J2, and the PNPase. Present work aims at identifying the molecular signature of the RNAs that require CshA for efficient turnover and the role of this RNA helicase in helping the RNases to degrade the target molecules.
RNase J1 and J2 are main players in bulk RNA degradation and their inactivation leads to a very narrow spectrum of permissive growth conditions. RNase Y is an endonuclease that affects degradation of approximately 100 mRNAs and is likely to be tethered to the membrane to avoid promiscuous degradation.

At the same time we analyse CshB and its role for the survival of the bacterium in answer to innate immunity and the role of this helicase in gene expression.

We are using NGS methods, classical genetics, and biochemical analyses to further identify the functional and physical interactions of these enzymes and their function in the bacterium.



Bacterial DEAD-box RNA helicases, characterised by their conserved motifs, are involved in ribosome biogenesis, translation initiation and RNA decay and thereby contribute to the versatility of these microorganisms.

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Keywords: Staphylococcus aureus, RNA degradation, RNA helicases, ribosome, translation initiation

Contact: Patrick.Linder@unige.ch

Adriana Renzoni

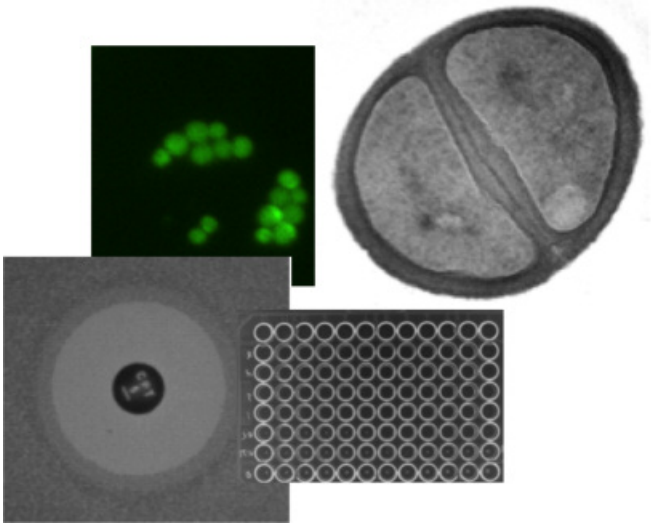
Department of Internal Medicine Specialties
Division of Infectious Diseases

Adriana Renzoni obtained her PhD degree in microbiology from University Paris 7 in 2000, working in the Unité des Intéractions Bactéries-Cellules at the Pasteur Institut. Since 2001, she has been working on antimicrobial resistance in the Infectious Diseases Service (University Hospital of Geneva). In 2010 , she was appointed Biologist, and she is currently preparing the FAMH certificate.

Identification of molecular markers to detect emergence of low-level glycopeptide resistance in *Staphylococcus aureus*

Methicillin-resistant *Staphylococcus aureus* (MRSA) are major pathogens of hospital infections and are associated with high risks of mortality and complications. Despite the recent introduction of antimicrobial agents, glycopeptide antibiotics (vancomycin or teicoplanin) remain the first-line therapy for severely MRSA-infected patients. Their intensive use leads to the selection of low-level glycopeptide-resistant isolates, designated as glycopeptide-intermediate *S. aureus* (GISA). The therapeutic efficacy of glycopeptides is widely debated, and there is a growing concern that their use will select resistance, not only to glycopeptides but also to newly introduced antibiotics such as daptomycin via unknown cross-resistance mechanism(s). The emergence of GISA clinical isolates during antimicrobial therapy represents a special risk, because their phenotypic detection is frequently difficult and no reliable molecular assay for detecting such resistance is available.

For this reason, my laboratory conducts basic and translational research to unravel molecular mechanism leading to bacterial drug resistance and to develop resistance detection methods. Basic research methods have identified key bacterial resistance genes, implicated in glycopeptide, ß-lactams and daptomycin resistance, such as *trfA* and others. We are exploring their function that should help to design an integrated molecular model describing the development of antibiotic resistance. Concomitantly, basic research results are used to build preliminary molecular-detection methods for antimicrobial resistant phenotypes.



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Keywords: Staphylococcus aureus, glycopeptide resistance, stress response, cell wall biosynthesis

Contact: Adriana.Renzoni@hcuge.ch

Jacques Schrenzel

Department of Internal Medicine Specialties
Division of Infectious Diseases
Genomic Research Laboratory

Jacques Schrenzel obtained his medical degree in 1989 at the University of Geneva. After his clinical training at the University Hospitals of Geneva (HUG) he carried out research on neutrophils in infectious diseases. He was postdoctoral Fellow at the Mayo Clinic in Rochester, Minnesota from 1997 to 2000. On his return to Geneva he was awarded an Assistant Professorship Grant by the Swiss National Science Foundation and became a pioneer in the genomic analysis of pathogens (**www.genomic.ch**). Since 2004 he has been responsible for the Central Bacteriology Laboratory of the HUG and was appointed Associate Professor in 2010.

Persistence and virulence in Staphylococcus aureus infections

Metagenomics of infectious diseases

We study the pathogenesis of S. aureus infections with a special focus on its ability to persist as well as to survive host defenses. This more specifically concerns the mechanisms of biofilm formation and the capacity of the bacteria to survive within eukaryotic cells by regulating the gene expression of numerous bacterial metabolic and virulence-related targets. These approaches use bacterial genetics, home-brew high-density microarrays and, more recently, next generation sequencing (NGS). This explains the creation of our own bioinformatics group and the more recent research development using metagenomics to address clinically relevant questions, within local and international consortia.

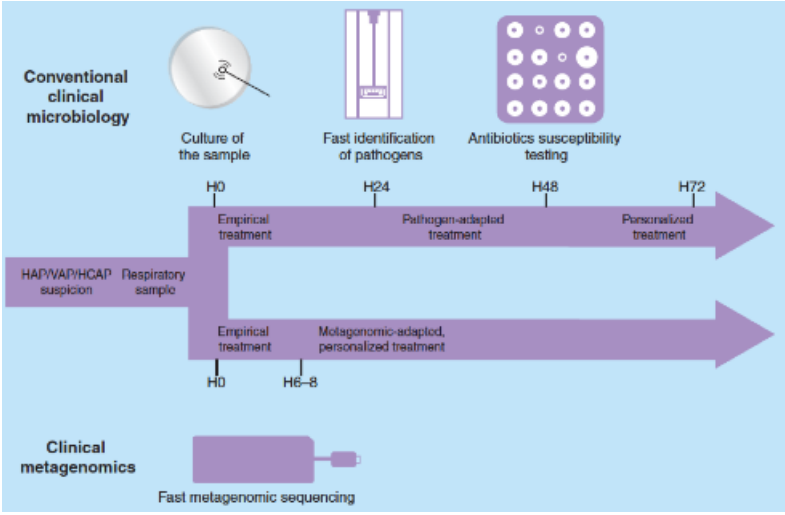
Deciphering the virulence of S. aureus infections

Using the capacity of massively parallel methods such as microarrays or NGS, we aim to explore all genomic elements potentially involved in epidemiological or virulence traits of MRSA. We study at the genome scale those genetic events that potentially trigger bacterial adaptation. Our main efforts involve genomic regions that remain poorly explored to date, namely the segments considered as intergenic regions, in order to unravel genomic elements responsible for “the success of S. aureus” in clinical or epidemiological settings.

Clinical metagenomics

Our group developed a computer application allowing de novo whole-genome sequence assembly with the Illumina system. This is one of the most powerful applications of its kind that has been developed so far. We then reported the first metagenomic study based on the utilization of the Illumina high-throughput sequencing technology and our manuscript presenting the method was cited over 200 times.

We are especially interested to use these methods to study the impact of antibiotics on intestinal and oral microbiota using culture-free approaches. We are now engaged in a series of local and international collaborations, within specific research consortia.



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Keywords: Pathogenesis, Clinical microbiology, Microbiota, Next generation sequencing

Contact: Jacques.Schrenzel@genomic.ch

Jacques Schrenzel

Department of Internal Medicine Specialties
Division of Infectious Diseases
Clinical Bacteriology Lab

Clinically relevant and efficient microbiological diagnosis
The bacteriology lab is a production-oriented laboratory that aims to provide rapid and clinically relevant bacterial diagnosis for patients at the University Hospitals of Geneva (HUG). We host the National Reference Center for Meningococci. Efforts are concentrated on reducing turn-around times by implementing state-of-the art methods such as MALDI-TOF, PCR-ESI-MS or other molecular methods before they are commercially available. We also have a track record in assay development in the research lab followed by successful technology transfer to the routine lab, mostly for infection control purposes (detection and genotyping of MRSA, *Clostridium difficile*, ESBL, etc.). We always pay particular attention to building upon local competences (infection control service, etc.) and expanding them by creating international consortia whenever needed.

We are now actively **working on comparative whole genome sequencing** for epidemiological purpose (e.g. within our **national reference center on meningococci, www.meningo.ch**) to best characterize the development of *Neisseria meningitis* W135 in Switzerland.

Finally, we are actively developing metagenomic approaches (wet-lab and bioinformatic solutions) to **enable clinical metagenomics in routine bacteriology**. This should for example provide earlier delivery of medically important information (identification and antimicrobial resistance detection), on top of epidemiological surveillance.

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Contact: Jacques.Schrenzel@genomic.ch


Christian van Delden / Thilo Köhler

Department of Medical Specialties &
Department of Microbiology and Molecular Medicine

Christian van Delden obtained his M.D. in 1988 at the University of Geneva, his speciality board in Internal Medicine in 1995 and in Infectious Diseases in 1999. He performed a three-years research fellowship at the University for Rochester, and now leads a research laboratory in the Department of Microbiology and Molecular Medicine. His main research interest is the pathogenesis of Pseudomonas infections. He was nominated Associate Professor in 2011.

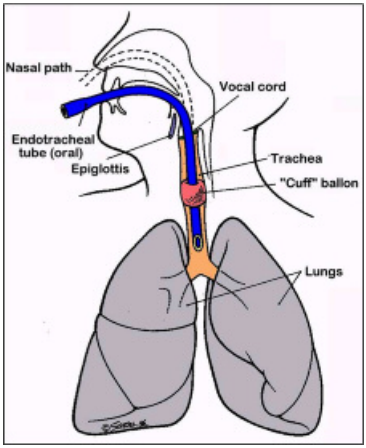
Thilo Köhler obtained his PhD in 1990 at the University of Geneva. After a two-year post-doctoral fellowship at the University of Berkeley, he returned to Geneva, and co-leads since 2003 a research laboratory in the Department of Microbiology and Molecular Medicine. He focuses his research on bacterial resistance mechanisms and new therapeutic approaches. He leads a workpackage of the Innovative Medicine Initiative "Translocation" of the European Community.

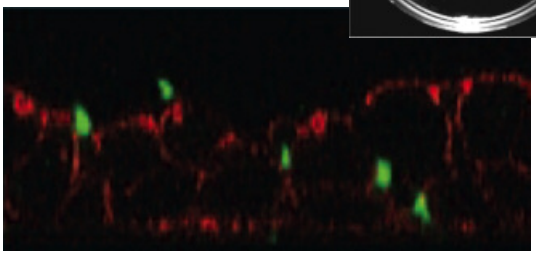
New approaches to combat *Pseudomonas aeruginosa* Infections

Our approach is translational, bringing clinical hypothesis and samples into the laboratory, and using metagenomics and molecular microbiology for both "*in patient*" and "in *vitro*" studies. With this approach we characterized the development of resistance upon therapy and identified Quorum-Sensing (QS) as a major risk factor for the progression from colonization to *P. aeruginosa* infections.

Ongoing projects include:

- Developing new antimicrobial biological dressings for burn patients in collaboration with a SwissTransMed network
- Studying the dynamics of allograft colonization and the adaptation of *P. aeruginosa* to a new microenvironement after lung transplantation
- Investigating in vitro bacterial interspecies competition and adaptation between *P. aeruginosa* and clinicaly relevant co-colonizing respiratory species (FNRS)
- Searching to improve antimicrobial uptake using bacterial iron transport systems (Innovative Medicine Initiative, ND4BB)





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Keywords: Pseudomonas aeruginosa, metagenomics, antibiotic resistance, quorum sensing, colonization

Contacts: Christian.vanDelden@hcuge.ch / Thilo. Kohler@unige.ch

Patrick Viollier

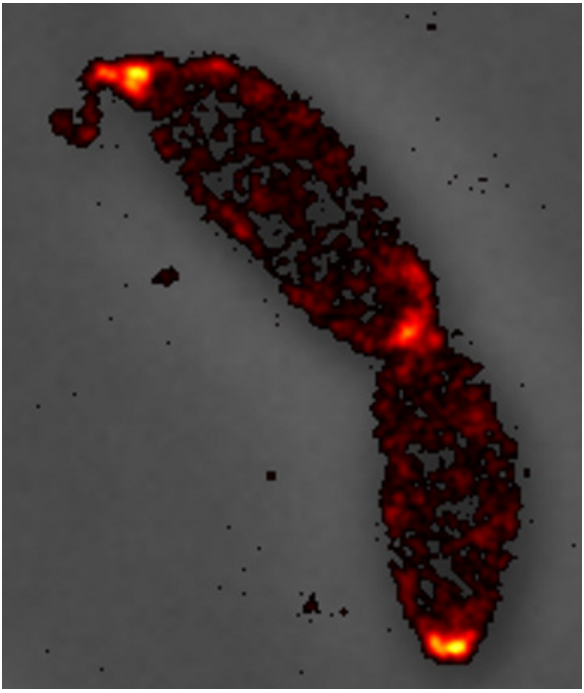
Departement of Microbiology and Molecular Medicine

Patrick Viollier graduated in 1999 with a PhD in microbiology from the Biozentrum University of Basel (CH). After a four-year postdoctoral stage at the Stanford University School of Medicine (USA), he joined the Case Western Reserve University School (USA) of Medicine as assistant professor in 2004. In 2009 he was appointed associate professor in the Department of Microbiology and Molecular Medicine at the Faculty of Medicine at the University of Geneva and was promoted to full professor in 2015.

Interplay between bacterial cell polarity and control of the (asymmetric) cell division cycle

Cell polarity is a universal trait exploited by eukaryotic and prokaryotic cells to control spatiotemporal organization and gene expression. Our goal is to illuminate the molecular mechanisms underlying cell polarity in the alpha-proteobacteria, a Gram-negative lineage that includes asymmetric free-living bacteria (e.g. Caulobacter), obligate intracellular pathogens (the rickettsiae) and the ancestors of modern day mitochondria. As the synchronizable model bacterium *Caulobacter crescentus* offers several convenient proxies to study polarity-based functions and their dysregulation as a function of the cell cycle, we rely on C. crescentus forward genetics to identify polarity mutants and then study the regulation and localization of these polarity factors, especially conserved ones that are also encoded in rickettsial genomes. Additionally, we have recently started to use chemical (antibiotic) profiling to probe for new (antibiotic sensitivity) phenotypes of our polarity mutants. Such analyses turned our attention onto a specific class of genetic modules, known as type II toxin-antitoxin systems (TASs). TASs are known to protect bacterial cells (including pathogens) form certain antibiotics. The toxin component of these TASs usually has RNase activity and therefore controls gene expression by cleaving specific transcripts in the bacterium, while the antitoxin directly inhibits the activity of the toxin. We are taking a holistic approach to define the determinants for TAS specificity and to link mRNA cleavage with certain antibiotic phenotypes.

Lastly, we recently identified a regulator that localizes to both cell poles and that reinforces the accumulation of cell cycle transcriptional factor CtrA in stationary phase *Caulobacter* cells. As the conserved alarmone guanosine tetra/penta-phosphate [(p)pGpp] has been shown to act in a similar way on CtrA in stationary phase cells, we are also investigating the mechanism(s) by which (p)pGpp signaling reprograms transcription in the alpha-proteobacteria.



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Keywords: cell cycle, cytokinesis, peptidoglycan, Alpha-proteobacteria, Chlamydia

Contact: Patrick.Viollier@unige.ch

Alexandra Calmy

Department of Internal Medicine Specialties
Service de maladies infectieuses – consultation VIH/Sida

Alexandra Calmy obtained her medical diploma in 1994 and was trained in internal medicine and in Infectious diseases (FMH, 2001 and 2010), she also holds a PhD in clinical research in HIV/AIDS, obtained in 2009 in Sydney, Australia. She was nominated Associate Professor in 2014 and is head of the HIV/AIDS Unit of the University Hospital of Geneva. Professor Calmy's research interest focuses on public health and humanitarian response to HIV/AIDS, specifically the provision of antiretroviral therapy and management of side effects in resource limited-settings. She worked with Médecins Sans Frontières in Cambodia in 1996 and has subsequently supported MSF's HIV/AIDS work for more than 10 years. She is a member of the WHO working groups on the writing and the implementation of guidelines related to the treatment of HIV in developing countries since 2001, head of CSS6 committee at the "Agence National de Recherche sur le SIDA" (ANRS), member of the scientific board of the Swiss HIV Study Cohort (SHCS), and the Federal Commission of Sexual Health in Switzerland.

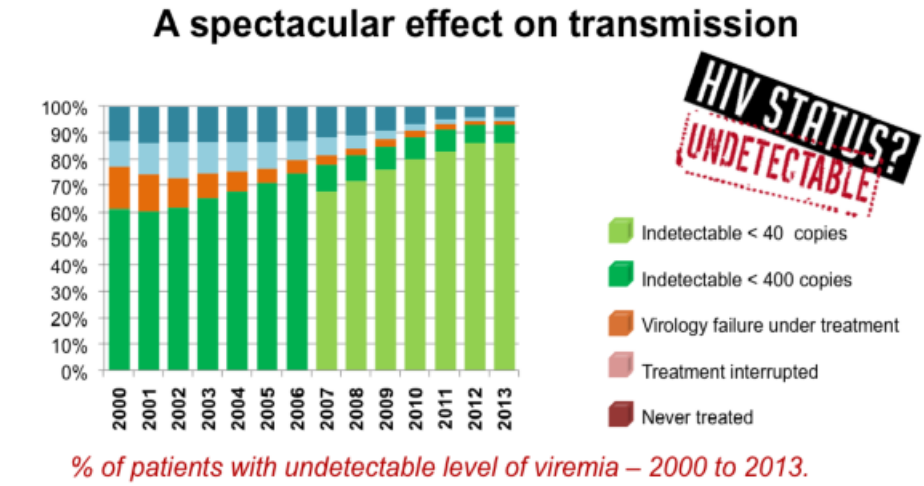
Research activities

Our research projects include Swiss and international interventional clinical trials, epidemiological studies based on data from the Swiss HIV cohort study, as well as cohort studies focusing on metabolic effects associated with antiretroviral therapy (ARV).

The clinical trials focus on progression of atherosclerosis in HIV patients under ARVs after 48 weeks of lipid lowering drug intervention and a Swiss multicenter trial designed to assess the need for a statin prescription in patients whose antiretroviral treatment was changed

Other epidemiological projects use the data of the Swiss cohort study to investigate patients with coronary heart disease, comparing their mortality with that of patients not infected with HIV. A cohort of patients with metabolic complications and lipodystrophy (LIPO and Metabolism Group) was established 5 years ago. This work has demonstrated that a model of integrated multidisciplinary care can be beneficial for patients with complex comorbidities.
We are currently assessing the simplification of ARV in stable, virologically suppressed patients. Patients will agree to switch from standard HIV-therapy to a dolutegravir-based maintenance therapy. The study aims to demonstrate that this maintenance therapy is non-inferior in terms of viral suppression compared to standard therapy, and that simplified monitoring is superior compared to standard monitoring in terms of costs and quality of life.

Our research group has a strong interest in clinical and epidemiological research projects conducted in countries with limited resources. Partnerships have been established with "*Médecins Sans Frontières*", WHO, the Bill & Melinda Gates Foundation, and hospitals or hospital networks (Esther).



Treatments allow for a reduction in virus multiplication in the blood.
Patients HIV status then become undetectable

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Keywords: HIV, inflammation, antiretroviral agents, co-morbidities, humanitary medicine

Contact : alexandra.calmy@hcug.ch

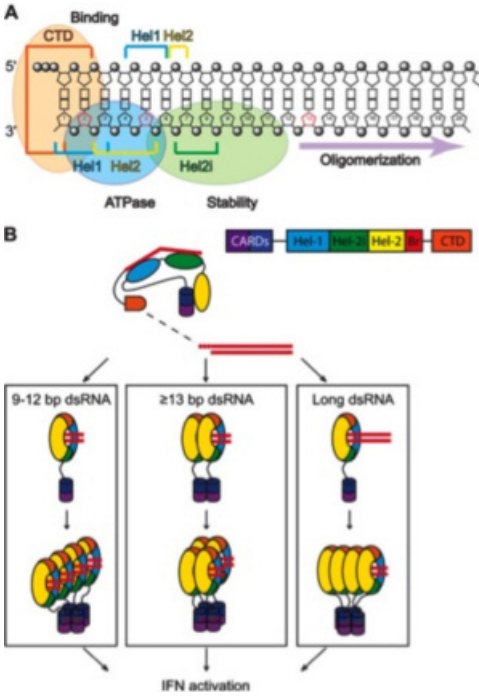
Dominique Garcin

Department of Microbiology and Molecular Medicine

Dominique Garcin obtained his PhD at the Ecole Normale Supérieure in Lyon in 1989. Then joined the Department of Microbiology and Genetics (the current department of Microbiology and Molecular Medicine) of the Faculty of Medicine, where he was appointed Senior Lecturer in 2010.

Molecular virology and innate immunity

Viral infections are responsible for extensive human and animal suffering and death, resulting in heavy human and economic cost. Moreover, very few antiviral molecules are available and more importantly escape mutants resistant to existing antiviral agents generally emerge rapidly for RNA viruses, due to their high mutation rate. One of the first lines of defense against viral infection is innate immunity. Detailed knowledge of how this first line of defense is established and how viruses escape these antiviral defenses is therefore critical to understand how to prevent viral infection. The crucial step that determines the entire immune response is the detection phase of the viral infection. It involves specific detection of nucleotidic molecular signatures inherent in viral infections. Because this step is crucial, it is the focus of a constant battle between the viruses and the infected host cells. Our laboratory is interested in the identification and characterization of the RNA PAMPs (pathogen-associated molecular pattern), of viral or cellular origin, that activates RIG-I in vivo during the course of a viral infection. Because immune responses are always a matter of discrimination between self and non-self, we are also interested in the role of LGP2 in the RIG-I capacity to discriminate between self and non-self RNAs. In connection with this, we also explore the viral strategies that are aimed to manipulate this crucial step either by generating viral RNA molecules mimicking self-molecules or by interacting with LGP2. In this regard we are interested in the viral evolutionary potential to select for natural mutations in genes involved in the innate immune response



RIG-I binding and activation.

(**A**) Schematic representation of the contacts of various RIG-I motifs to 5′ ppp-dsRNA (adapted from reference 19).

(**B**) Model of RIG-I activation depending on the length of the dsRNA. If a tetrameric RIG-I/RNA complex is the minimal structure required for RIG-I activation (42).

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Keywords: Innate immunity, Paramyxovirus, interferon, Pattern Recognition Receptors, RNA PAMP, RIG-I ;

Contact: Dominique.Garcin@unige.ch

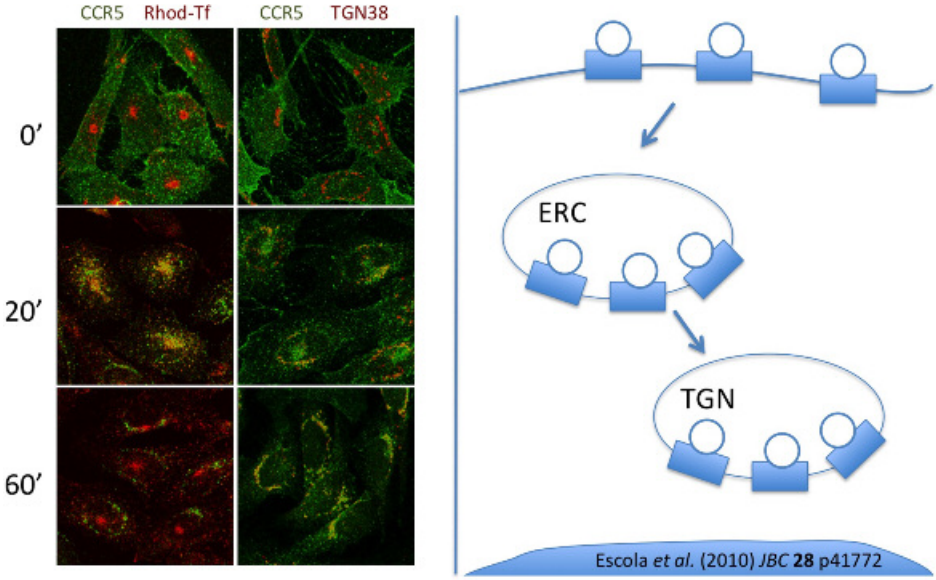
Oliver Hartley

Department of Pathology and Immunology

Oliver Hartley completed his PhD in protein engineering in 1997 at the University of Cambridge, UK. Following a brief fellowship at the Glaxo Institute for Molecular Biology in Geneva, he joined Robin Offord's lab as a post-doctoral fellow at the University of Geneva. He became a group leader in the Department of Structural Biology and bioinformatics in 2005, becoming an Assistant Professor in 2008, joining the Department of Pathology and Immunology in 2012, where he has been Associate Professor since 2017..

Macromolecular engineering to prevent infectious diseases

With a focus on the prevention of infectious diseases, our work is based on the engineering of proteins and peptides to identify new macromolecules with potential use as medicines. Our main work has involved the engineering of chemokine proteins to produce highly potent HIV entry inhibitors for use in the prevention of transmission of the virus during sexual intercourse. Our best molecule Has been taken into clinical development and a first Phase 1 study is expected to take place soon. The chemokine analogues we have developed act by blocking CCR5, the principal HIV coreceptor, which is also a member of the G protein-coupled receptor (GPCR) superfamily. Because they exhibit unusual inhibitory mechanisms that concern modulation of intracellular trafficking of CCR5, we are also able to use our analogues as tools for fundamental studies of the cellular and molecular processes that govern both the cell surface concentrations and signaling activity
of GPCRs.



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Keywords: HIV, Chemokines, G protein-coupled receptors, pharmacology, endocytosis

Contact: Oliver.Hartley@unige.ch

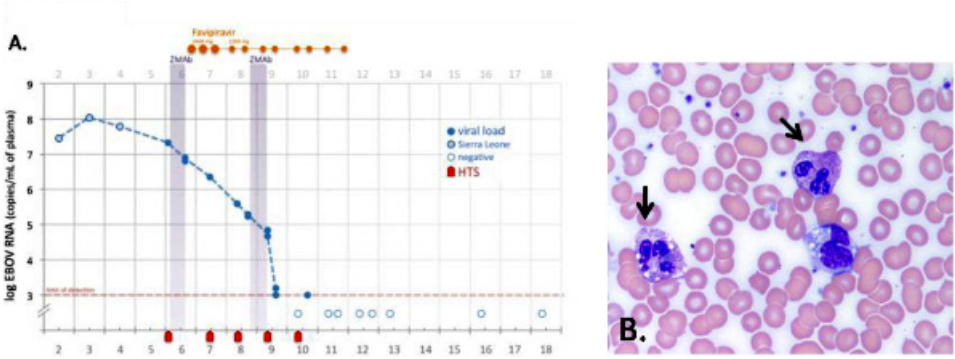
Laurent Kaiser

Department of Internal Medicine Specialties
Division of Infectious Diseases

Laurent Kaiser obtained his medical degree at the University of Geneva. He completed a full training in internal medicine and board certification in Infectious Diseases and Clinical Microbiology. He spent two years as a research associate at the University of Virginia, Charlottesville, USA. Appointed full professor of medicine, he is the Head of the Division of Infectious Diseases and Director of the Laboratory of Virology at the Geneva University Hospitals. The Division of Infectious Diseases covers the full spectrum of infectious diseases observed in a university teaching hospital. Highly specialized consultants have each a specific expertise in different fields, including HIV, transplant infections, osteoarticular infections, antibiotic stewardship, as well as clinical microbiology. These experts work closely together to provide the best clinical care, as well as to face the serious challenges in the field, including multidrug- resistant bacteria, complications related to highly immunocompromised patients and emerging viral infections.

At the academic level, the Division has created research groups in different fields and specialties of infectious diseases. All group leaders have their own independent research group (A. Calmy, J. Schrenzel, C. Van Delden). The division has established several close national and international collaborations and is recognized as one of the leading centers in Switzerland for the completion of a fellowship in infectious diseases or clinical microbiology. Together, these groups have secured major funding to conduct their research projects and produce more than 100 publications annually.

Laurent Kaiser leads also the Laboratory of Virology that performs more than 140,000 diagnostic procedures annually and provides highly specialized virological tests adapted to a large university center. The goal is to integrate new technologies and diagnostic assays to clinical care whenever this is relevant for patients or public health. The laboratory conducts basic research in the field of virology, as well as clinical investigations, and also functions as the Swiss reference centers for influenza and emerging viral diseases, including Ebola. Resistance testing for HIV and hepatitis C is part of our expertise also. Research topics focus on respiratory viruses, the impact of viral disease in highly compromised patients and new viral diseases. The laboratory has also developed a specific expertise on picornaviruses both at the level of clinical aspects and basic research. The laboratory hosts the Geneva Center for Viral Emerging Diseases, a center that aims to link clinical investigations, microbiological research and public health concerns in the field.



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Clinical features and viral kinetics in a rapidly cured Ebola virus disease: a case report. M. Schibler, P. Vetter, P. Cherpillod, T.J. Petty, S. Cordey, G. Vieille, S. Yerly, C.A Siegrist, K. Samii, J-A. Dayer, M. Docquier, EM. Zdobnov, AJH Simpson, PSC Rees, F. Baez Sarria, Y. Gasche, F. Chappuis, A. Iten, D. Pittet, J. Pugin and L. Kaiser. Lancet Infect. Dis. Sept. 2015; 15(9): 1034-1040. IF 21.372

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Keywords: Respiratory virus, rhinovirus, infectious disesases, virology, diagnostic

Contact: Laurent.Kaiser@hcuge.ch

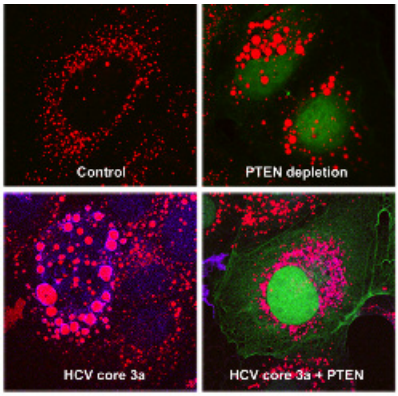
Francesco Negro

Department of Internal Medicine Specialties
Department of Pathology and Immunology

Francesco Negro obtained his Medical Degree in 1982 at the University of Turin, Italy. He was Postdoctoral Fellow at the Georgetown University School of Medicine, Rockville, MD, USA from 1986 to 1989, and then at the Laboratory of Infectious Diseases, National Institute of Allergy and Infectious Diseases, NIH, Bethesda, MD, USA in 1989. After having spent some time back in Turin, he joined the HUG in 1994. He was appointed Full Professor of the Faculty of Medicine in 2014. He is chairing the Swiss Hepatitis C Cohort Study, and is Educational Councilor of the European Association for the Study of the Liver.

Pathogenesis of chronic hepatitis C

Our laboratory studies the pathogenesis of chronic hepatitis C, including both hepatic and extrahepatic manifestations, with particular regard to: HCV-induced fatty liver; HCV-induced insulin resistance; interactions between HCV and the metabolic syndrome; and factors/mechanisms of liver disease progression (particularly host genetic and metabolic factors). This research is carried out through the following approaches: *in vitro,* using (i) different expression models of single HCV proteins (including lentivectors), (ii) subgenomic-length or full-length (infectious) HCV replicon systems, and (iii) co-cultures of HCV-expressing hepatoma cells with other cell types of major relevance in the pathogenesis of the metabolic syndrome as well as *in vivo*, using human tissues (liver, peripheral blood mononuclear cells, adipose and striated muscle tissue), taken in the setting of various observational and interventional clinical trials.



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Keywords: hepatitis C, fatty liver, insulin resistance, cirrhosis, hepatocellular carcinoma

Contact: Francesco.Negro@hcuge.ch

Mirco Schmolke

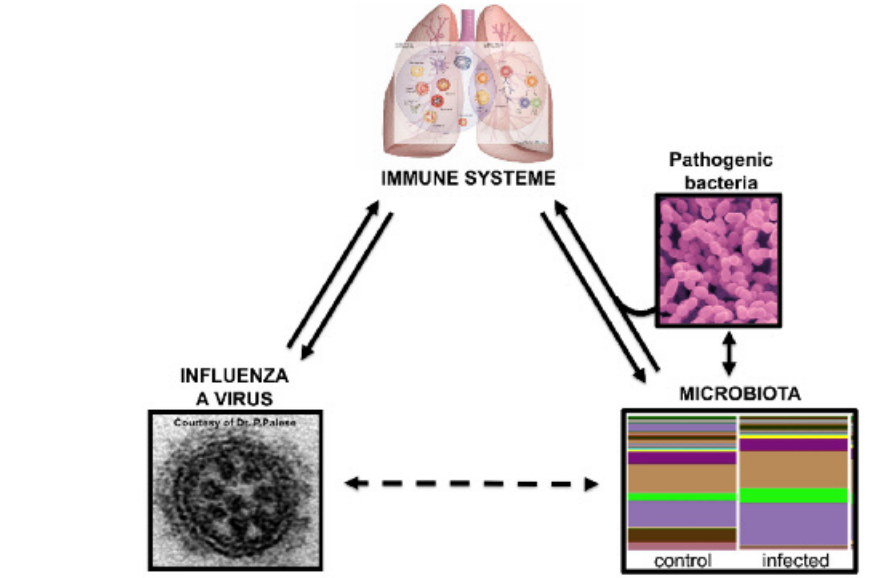
Department of Microbiology and Molecular Medicine

Mirco Schmolke obtained his undergraduate training in Biochemistry at the University of Münster in Germany and his PhD on “Mechanism of action of broadly neutralizing antibodies against the transmembrane protein gp41 of HIV” at the Robert Koch Institute in Berlin. He then spent five years as a postdoc at the Center for Molecular Biology and Inflammation (Zentrum für Molekulare Biologie und Entzündung) at Münster, before moving in 2009 for a second postdoctoral fellowship to Icahn School of Medicine at Mount Sinai, New York. In 2014 he was appointed Assistant Professor at the Department of Microbiology and Molecular Medicine.

Interaction of influenza A virus with its host

My group is interested in understanding the interplay of viruses with their host organism. Viruses highly depend on their hosts to replicate. Thus, they shape their environment to gain optimal conditions for replication. At the same time the host developed mechanisms to counteract the virus by means of its innate and adaptive immune system. This so called “molecular arms race” results in fascinatingly complex interaction networks. On a molecular level my team works on understanding the interplay of virus and host factors within their host cell and develops tools to identify new host proteins, which are either required for or counteract virus replication.

We are further addressing effects of acute viral infections on "healthy" commensal bacteria in mammalian model systems. These bacteria fulfill important functions in our body such as education of the immune system or processing of nutrients and colonize basically all of our body's surfaces, including respiratory and intestinal mucosa. This colonization by commensal bacteria prevents pathogenic bacteria from occupying niches. An imbalance of commensal microbiota (so-called dysbiosis) can co-incide with chronic inflammatory processes. In my group we are trying to unravel, how acute viral infections, e.g. with influenza A virus, disturb the fine-tuned balance of microbial communities in our body, and if these disturbances support invasion of pathogenic bacterial species (super infection, a common complication of influenza A virus infections).



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Keywords: Influenza A virus, bacterial super infection, innate immunity, microbiome, pathogenicity

Contact: mirco.schmolke@unige.ch

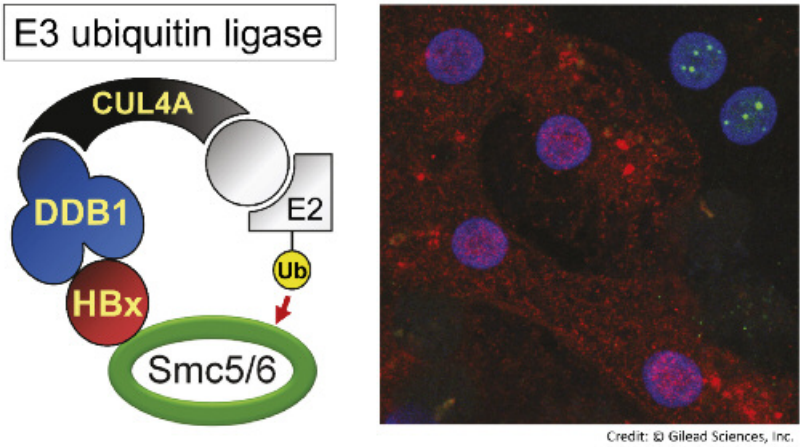
Michel Strubin
Department of Microbiology and Molecular Medicine

Michel Strubin obtained his PhD from the University of Geneva in 1987. After an initial post-doctoral training at the ISREC in Lausanne, he spent two years at Harvard Medical School in Boston, USA. In 1992, he joined the Department of Microbiology and Molecular Medicine with a START Fellowship from the SNSF. In 2001, he was appointed Associate Professor in the same Department.

The HBx protein of Hepatitis B Virus and Regulation of Gene Expression

The HBx protein of hepatitis B virus
Chronic infection by hepatitis B virus (HBV) is a leading cause of cirrhosis and liver cancer. A salient feature of HBV is that its DNA genome persists as an extrachromosomal DNA circle in infected cells. By studying the HBV-encoded HBx protein and its role in viral transcription, we discovered a previously unrecognized cellular antiviral factor. In the absence of HBx, this factor specifically binds the circular viral DNA to block its transcription and, thus, infection. However, during normal infection the viral HBx protein targets this factor for destruction thereby ensuring productive HBV gene expression. These findings pave the way for new antiviral strategies. We now aim to understand how this antiviral factor selectively silences extrachromosomal DNA transcription and whether it has a similar activity against other human pathogenic DNA viruses.

Regulation of gene expression
We are using yeast as a model system to address fundamental questions about the mechanisms by which gene transcription is regulated. We are particularly interested in understanding how the transcription machinery, a large complex that contains many proteins in addition to the RNA polymerase, assembles at the beginning of genes and how cells control this event. We also study the dynamics and epigenetic modifications of chromatin and their importance in transcriptional regulation.



The cellular antiviral factor Smc5/6 (green) is detected within the nucleus (blue) of uninfected human hepatocytes. In contrast, Smc5/6 is degraded by HBx in HBV-infected hepatocytes (red).

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Keywords: Transcription, Chromatin, Hepatitis B virus, HBx, Restriction factors

Contact: Michel.Strubin@unige.ch

Caroline Tapparel Vu

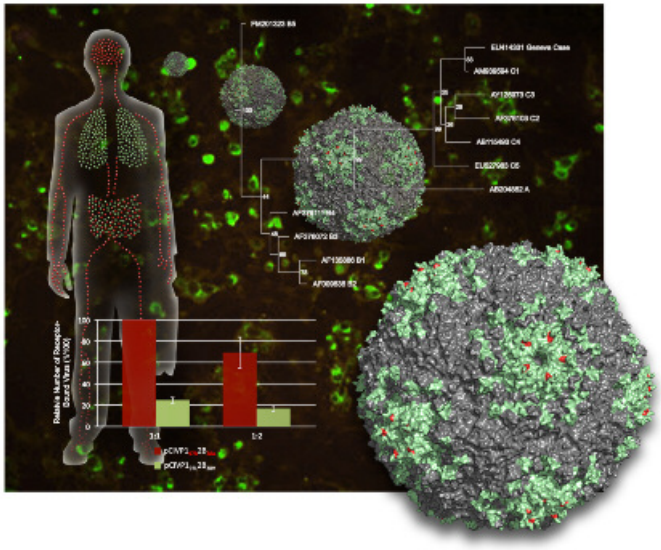
Department of Microbiology and Molecular Medicine
Department of Internal Medicine Specialties

Caroline Tapparel Vu obtained her PhD in Molecular Virology in 1998 at the Faculty of Medicine of University of Geneva. After postdoctoral training in human genetics and bacteriology, she has been conducting translational research on rhinoviruses and enteroviruses since 2005. 2014, she obtained the prestigious Sandoz Family Professor Fellowship, to pursue her work at our Faculty as assistant professor.

Identification of key viral and host factors modulating rhinovirus and enterovirus pathogenicity and search for antivirals

Viral infections can result in important morbidity and mortality worldwide. Respiratory infections are the main cause of death among children under 5 years, followed by diarrheal disease and malaria. Most respiratory infections are caused by virusesand the predominant etiological agent is rhinovirus (RV), followed by influenza virus and respiratory syncytial virus. Viruses are also the most frequent causes of infections of the central nervous system ahead of bacteria, fungi, and protozoa. Among neurotropic viruses, enteroviruses (EVs) account for the majority of viral meningitis and for 10–20% of identifiable cases of viral encephalitis. Despite this burden, supportive care is the only therapeutic option against most of these pathogens. A better understanding of their pathogenesis is therefore needed to develop effective antiviral drugs.

Our research seeks to better understand the pathogenic mechanisms of respiratory and neurotropic viral infections with special emphasis on RVs and EVs. We aim to elucidate the genomic determinants of phenotypic traits such as virulence, dissemination and neurotropism, and determine their interactions with the host and with other pathogens. To this end, we apply molecular, cellular and biochemical tools using clinical viral strains rather than laboratory-adapted viruses. In addition, these strains are grown in three-dimensional human airway epithelia and neural tissues rather than immortalized cell lines. We also use these model systems to develop efficient and broad-spectrum antiviral therapies against these highly common infectious agents.



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Keywords: rhinovirus, enterovirus, tissues, pathogenesis, antivirals

Contact: Caroline.Tapparel@unige.ch

Mathieu Brochet

Department of Microbiology and Molecular Medicine

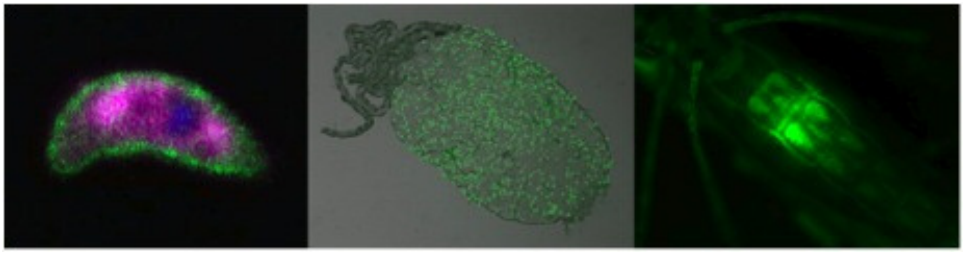
Mathieu Brochet obtained his PhD degree at the Institut Pasteur in 2007. He was then an EMBO and Marie Curie postdoctoral fellow at the Wellcome Trust Sanger Institute in Cambridge. He was appointed as a senior INSERM investigator in 2014. In 2015 he was awarded a Swiss National Fund Starting Grant to pursue his work at our Faculty.

Signalling in Malaria parasites

Malaria caused by *Plasmodium* parasites is a major health problem. The ability of *Plasmodium* parasites to respond to changing environments critically relies on intracellular signalling. Understanding signalling is of particular relevance to malaria because a portfolio of anti-plasmodials is predicted to target signalling pathways, inspired by the precedent of human kinases as major cancer targets. In malaria parasites, calcium signalling has received much attention as it is critical for symptomatic asexual blood stages, the preceding liver-stages and transmission through the mosquito.

Plasmodium is highly divergent from model organisms and how calcium regulates progression through the lifecycle remains elusive. Only few classical regulators of calcium homeostasis have been identified and effector pathways also differ significantly between Plasmodium and its human host. For example, Malaria parasites lack close homologues of classical calcium kinases but use plant-like calcium-dependent protein kinases (CDPKs) for which no molecular roles have been identified in *Plasmodium*. Studying calcium signalling in Plasmodium is thus challenging, but in addition to providing new insights into the origins of complex signalling in eukaryotes, it holds the chance to identify new drug targets to block Plasmodium development. In this context our research aims at:

1- Understanding how calcium signals are translated into cellular responses;
2- Characterising regulators of cellular calcium homeostasis;
3- Identifying calcium signalling molecules which can be targeted to block the development of the parasites.



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Keywords: Malaria parasites, mosquito transmission, signalling, egress and invasion

Contact: Mathieu.Brochet@unige.ch

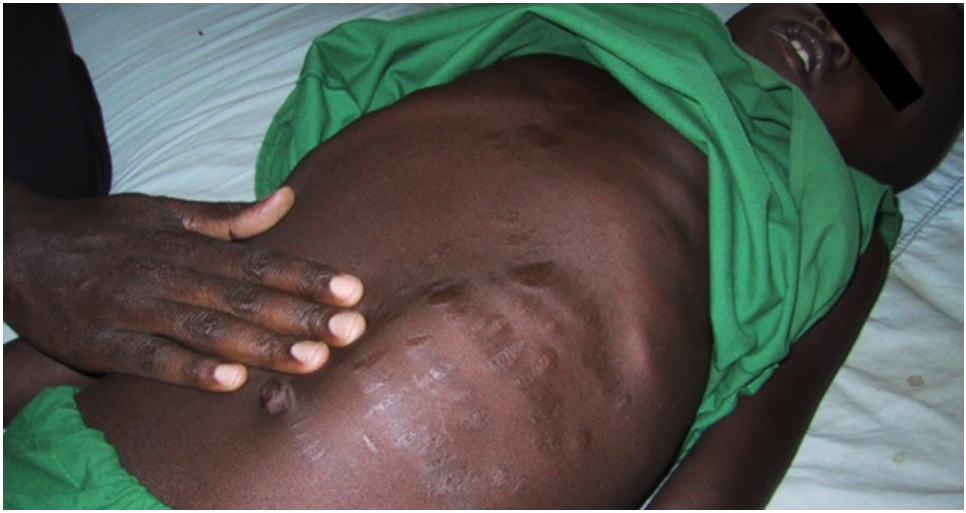
François Chappuis

Department of Community Health and Medicine
Division of Tropical and Humanitarian Medicine

François Chappuis obtained his Medical Degree in 1997 at the University of Geneva and a PhD in Medical Sciences in 2008 at the University of Antwerp, Belgium. He obtained his Privat-Docent in 2008 and was nominated Associate Professor in Humanitarian Medicine in 2012. He is currently heading the Division of Tropical and Humanitarian Medicine at the HUG and volunteers as medical adviser for trypanosomiasis programmes at Médecins Sans Frontières (MSF).

Improved diagnosis, treatment and control of leishmaniasis and trypanosomiasis

We are focusing our research efforts on improving case-management and control of some of the most neglected tropical diseases (NTDs) that affect poor communities in Asia, Africa, South America and Geneva (Latin American migrants). We validated rapid diagnostic tests (RDT) for use at point-of-care for visceral leishmaniasis and Chagas disease. On the treatment side, we have demonstrated the superiority of eflornithine, with or without nifurtimox, over melarsoprol for the treatment of advanced African trypanosomiasis, partially clarified the causes of antimonials treatment failure in patients with cutaneous (Peru) and visceral leishmaniasis (Nepal), and revealed the high toxicity of nifurtimox in adult patients with Chagas disease. On the control side, we have shown the lack of efficacy of large-scale distribution of impregnated bednets on the transmission of visceral leishmaniasis in Asia.



Young patient in eastern Uganda with splenomegaly due to kala-azar initially treated with scarification by a traditional healer.

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Keywords :neglected tropical diseases, leishmaniasis, trypanosomiasis, Chagas disease, sleeping sickness

Contact: Francois.Chappuis@hcuge.ch

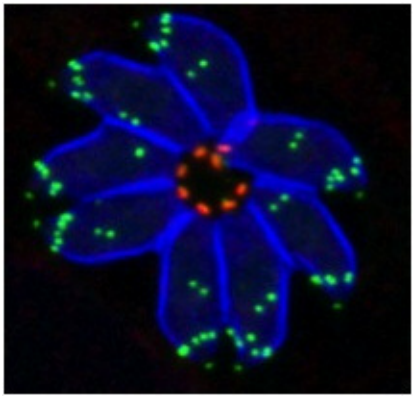
Dominique Soldati-Favre

Department of Microbiology and Molecular Medicine

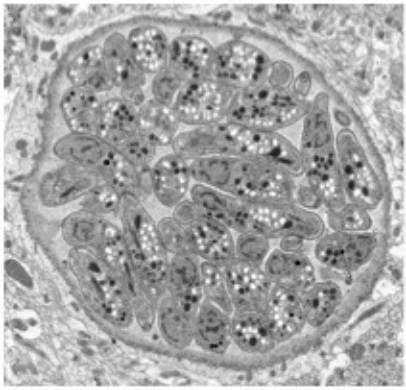
Dominique Soldati-Favre obtained her PhD degree at the University of Zürich in 1990. She was then a postdoctoral Fellow at Stanford University, Assistant Professor at the University of Heidelberg and Reader at Imperial College London. In Geneva, she was appointed Associate Professor in 2004 at the Department of Microbiology and Molecular Medicine, then full Professor in 2010. Dominique Soldati-Favre is Vice-Dean of the Faculty since 2011.

The biology of obligate intracellular parasites

The line of research of the group aims at studying the mechanisms that govern invasion and establishment of intracellular parasitism in Apicomplexa. Gliding motility is a unique attribute of the phylum, which is crucial for parasite migration across biological barriers, host cell invasion and egress from infected cells. Host cell entry is a tightly regulated and fast process that is governed by the concerted action of a large complex called the glideosome. Posttranslational modifications (such as protein methylation), lipid signaling and the action of proteases play a critical role in controlling the lytic cycle of the parasite. Our research also focuses on some fundamental biological questions related to parasite organelles biogenesis, central carbon metabolism, cyst wall formation and subversion of host cellular functions by effectors molecules that are critical to ensure successful infection.



Myosin I and Myosin J (red) are implicated in Cell-Cell Communication (IFA picture: Karine Frenal)



The Cyst Wall ensures Toxoplasma Persistence and Dissemination (EM picture: David Ferguson)

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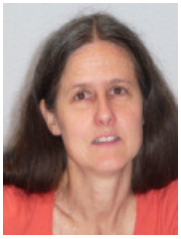
Keywords: Apicomplexa, Motility and Invasion, Cell Cell communication, Metabolism, Toxoplasma Cyst wall formation, Persistence

Contact: Dominique.Soldati-Favre@unige.ch



Martine A. Collart

Department of Microbiology and Molecular Medicine

Martine Collart obtained her PhD in 1990 at the University of Geneva. She continued her research at Harvard Medical School in Boston with Kevin Struhl, where she identified the NOT genes using a genetic selection in yeast. In 1993, she started her own independent group to pursue the characterisation of the NOT genes, in the Department of Medical Biochemistry of the Faculty of Medicine at the University of Geneva. She was appointed Associate Professor in the Department of Microbiology and Molecular Medicine in 2004, and Full Professor in 2011.

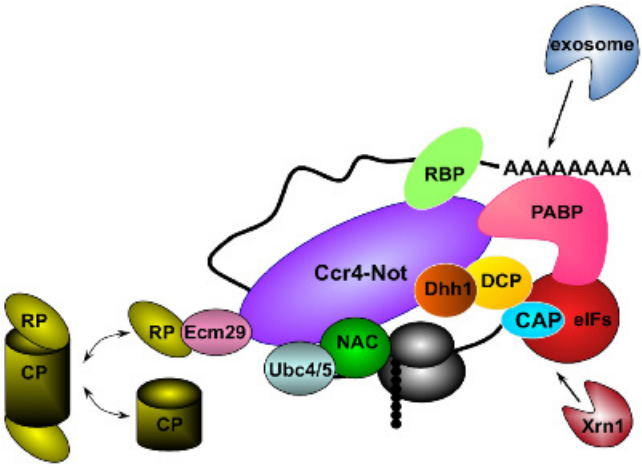
Genetic and Biochemical characterisation of the conserved Ccr4-Not complex in yeast

We work on characterising, in the yeast *S. cerevisiae*, the function of an essential multisubunit protein complex that is conserved across the eukaryotic kingdom, the Ccr4-Not complex. This complex is a major regulator of gene expression in all eukaryotes. It has two known enzymatic activities, ubiquitination provided by the RING finger Not4 E3 ligase, and deadenylation provided by the Caf1 and Ccr4 subunits. Recent evidence has indicated that the Ccr4-Not complex is at the core of the eukaryotic gene regulation circuitry and acts at all levels of mRNA metabolism: transcription, translation and mRNA degradation and it is also a major player in protein metabolism. It is an essential component of co-translational RNA and protein quality control.

The tremendous complexity of this system, in which a multisubunit complex contributes to regulate eukaryotic gene expression at all levels, makes the yeast a perfect model organism because of its powerful genetics that can be combined with biochemistry.

To be translated or to be degraded?

Global role of the Ccr4-Not complex in regulation of mRNA fate



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Keywords: Ccr4-Not, eukaryotic gene expression, transcription, translation, ubiquitination

Contact: Martine.Collart@unige.ch

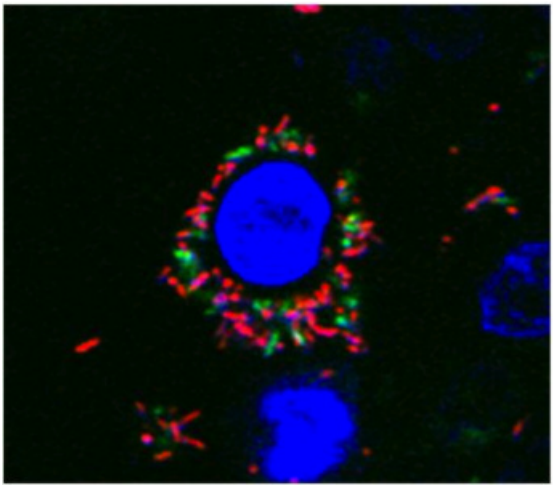
Marc Chanson

Department of Paediatrics
Department of Cell Physiology and Metabolism

Marc Chanson obtained his PhD in 1991 at the University of Geneva. From 1991 to 1993, he was Post Doctoral Fellow at the Albert Einstein College of Medicine, Department of Neurosciences, in New York. Before his return to Geneva in 1995, he was postdoctoral Fellow at the Department of Physiology at the University of Utrecht. He was nominated Lecturer in 2002 and Associate Professor in 2012.

Gap junctional intercellular communication in cystic fibrosis airway disease

Cells communicate between each other to coordinate their response to external stimuli. Gap junctions are transmembrane channels that directly connect the cytoplasm of cells in contact. Gap junctions interconnect airway epithelial cells that constitute the respiratory epithelium, a physical barrier at the interface between innate and adaptive immunity. This immunity, however, is jeopardized in cystic fibrosis (CF), a genetic disease caused by mutations of the cystic fibrosis transmembrane conductance regulator (CFTR) gene. We have found that CFTR regulates the activity of gap junction channels and that gap junctional intercellular communication contributes to the defense mechanisms of airway epithelial cells to infection. We aim to understand the relationship between infection, intercellular communication and the altered defense responses of the CF airway epithelium. Modulation of gap junctional communication may represent a therapeutic mean to reduce CF airway disease severity.



A human airway epithelial cell surrounded by Pseudomonas aeruginosa (in red) and expressing the apoptotic marker AnnexinV (in green).

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Keywords: gap junctions, connexins, CFTR, cystic fibrosis, host-response

Contact: Marc.Chanson@unige.ch

Carlo Chizzolini

Department of Internal Medicine Specialties
Department of Pathology and Immunology
Division of Immunity and Allergology (HUG)

Carlo Chizzolini obtained his MD degree in Parma, Italy, in 1979 and his doctoral degree in Geneva in 1986. He participated to a malaria vaccine program for several years in institutions located in Geneva, Atlanta (GA) and West Africa (Gabon). Since 1994 he is in Geneva where he leads a laboratory interested in inflammation and fibrosis using as disease model systemic sclerosis. He was nominated associated professor in 2010 and full professor in 2016.

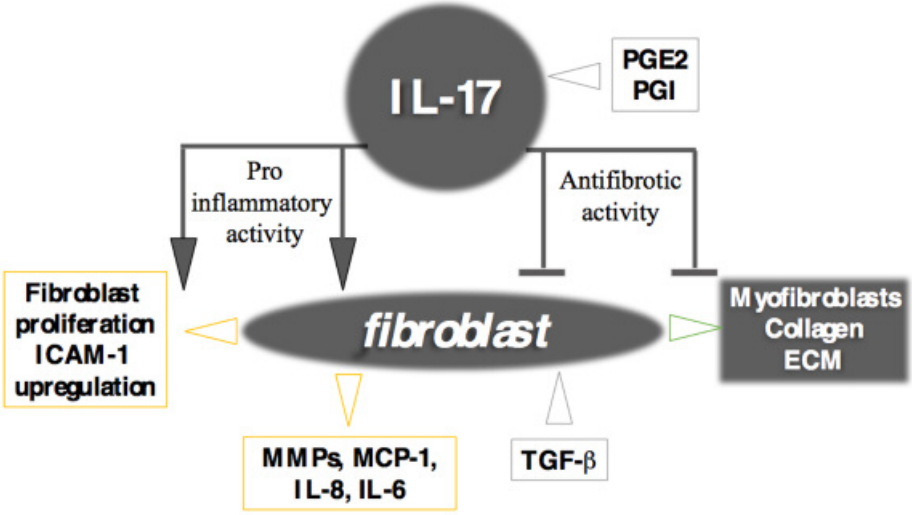
Deciphering the role of IL-17 in scleroderma

Skin and organ fibrosis in association with vasculopathy are hallmarks of systemic sclerosis (SSc), an autoimmune disorder of unknown origin, which pathophysiology is still incompletely understood. During the last several years, we have investigated the role of adaptive immune responses in relationship with the development of fibrosis. We (and others) have demonstrated that T cells producing high amounts of IL-4, IL-17 and IL-22 are characteristic of the disease. Why T cell responses in SSc are polarized remains speculative. Furthermore, while IL-4 has direct pro-fibrotic activities, the role of IL-17 (and IL-22) in SSc is unclear and seems to be inconsistent with the pro-fibrotic role of IL-17A demonstrated in murine models of fibrosis. A better understanding of these issues has direct consequences on medical management offered to SSc patients, for which at the moment, there are limited therapeutic options.

We are currently investigating the potential role of SSc sera in polarizing T cells responses, particularly toward the Th17 subset. The contribution of cells of the innate immune system, in particular plasmacytoid dendritic cells (pDC), is central to our interest in deciphering polarized T cell responses in terms of soluble factors released upon activation by immune-complexes (IC) and small autologous peptides ligands of toll-like receptors (TLR). In parallel, we investigate in novel experimental systems based on full human skin cultures and reconstituted skin the effect of IL-17A (and other IL-17 family members) on extracellular matrix deposition to solve the contrasting findings obtained in humans and mice.

To reach these aims, we use well-characterized biological samples form SSc patients with detailed clinical, immunological and genetic information and healthy controls obtained trough ongoing fruitful collaborations with international SSc expert centers.

In short, our original approach proposes to investigate in parallel in the one hand the molecular mechanisms leading to polarized T cell responses characteristic of SSc, and in the other hand the consequences of such polarized T cell responses on extracellular matrix deposition taking advantage of full human skin where complex cell-cell interactions and cell-matrix interactions take place, thus strengthening the physiological relevance of the findings.



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Contact: carlo.chizzolini@unige.ch

Pierre Cosson

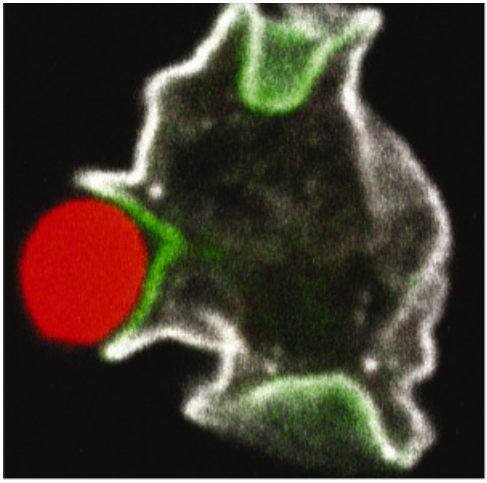
Department of Cell Physiology and Metabolism

After a stay at the European Molecular Biology Laboratory in Heidelberg, **Pierre Cosson** obtained his PhD in Immunology at the University of Marseille (1990). He spent three years as a Postdoctoral Fellow at the National Institutes of Health, Bethesda, USA, and then joined the Basel Institute of Immunology (Basel, CH) as an independent researcher. He was awarded a Swiss National Science Foundation START Fellowship in 1997 and joined the Faculty of Medicine in Geneva, where he was later appointed Associate Professor (2002) and Full Professor (2009) in the Departement of Cell Physiology and Metabolism. Since 2009, Pierre Cosson has held the Doerenkamp- Naef-Zbinden Chair for the development of alternatives to animal experiments.

Interactions between phagocytic cells and bacteria

In the human body, professional phagocytic cells (monocytes and macrophages) play a key role in the defense against invading microorganisms. These phagocytic cells must recognize, ingest and kill microorganisms. It is very clear that today, we still understand very poorly how bacteria are killed in phagocytic cells, what the main molecular mechanisms are, and how they are used to kill different types of bacteria. This knowledge is essential to better understand how pathogenic bacteria evade destruction by phagocytic cells and mount successful infections.

Our group is approaching these complex functions using a simple host model in which genetic studies can be conducted : the amoeba *Dictyostelium discoideum*. In this system we are identifying new gene products involved in intracellular killing of ingested bacteria. These genetic approaches are complemented by a vast array of Cell Biology studies, both in amoebae and in mammalian cells.



A Dictyostelium amoeba (white and green) ingesting a bacterium (red). The amoeba is trying to kill the bacteria, the bacteria is trying to kill the amoeba. Who is going to win?

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Keywords: Phagocytosis, Bacterial pathogens, Intracellular killing, Genetics, Cell Biology

Contact: Pierre.Cosson@unige.ch

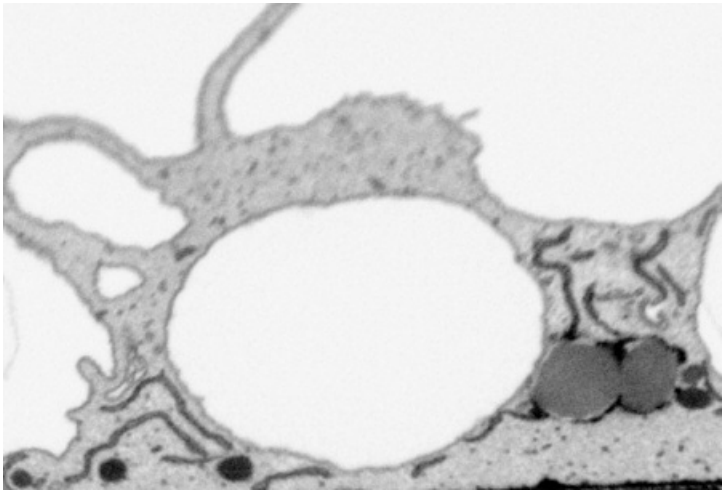
Nicolas Demaurex

Department of Cell Physiology and Metabolism

Nicolas Demaurex obtained his MD and Ph.D degrees at the University of Geneva in 1993. He was then post-doctoral fellow at the Sick Children Hospital in Toronto and obtained a career award from the Max Cloëtta Foundation in 1997 to start his research group in Geneva. He was appointed associate professor in 2004 at the Department of Cell Physiology and Metabolism, then full professor in 2010. Nicolas Demaurex is vice-dean of the faculty since 2012, in charge of the core facilities.

Cell signalling

Calcium elevations regulate several functions of immune cells including chemotaxis, phagocytosis, degranulation, and reactive oxygen production by neutrophils, macrophages, and dendritic cells, as well as the proliferation of T cells. The signal specificity is conveyed by the spatiotemporal pattern of the intracellular calcium signals generated at membrane contact sites, intracellular signalling platforms that allow the spatial confinement of biochemically active molecules inside cells. Our group studies the molecular basis of these cellular signals, using mouse genetics, ion imaging, and electrophysiology. Specifically, we study the role of Hv1 proton channels and of STIM-gated Orai and TRPC channels in the calcium, redox, and pH homeostasis of phagocytes. We aim to identify molecules that regulate the activity of these ion channels at membrane contact sites forming around phagosomes, the intracellular compartments where killing and degradation of invading pathogens occur.



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Keywords: Cell signalling, ion channels, innate immunity

Contact: Nicolas.Demaurex@unige.ch

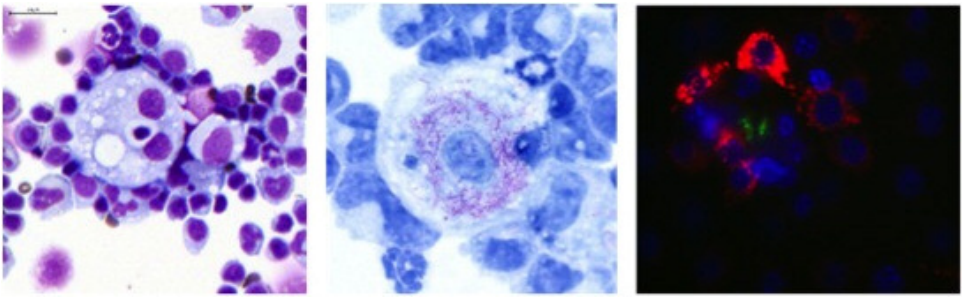
Irène Garcia-Gabay
Department of Pathology and Immunology

Irène Garcia-Gabay obtained her PhD in immunology at the University of Geneva in 1982. After a Fellowship at the Pasteur Institute, Paris, she did a postdoctoral work at the Swiss Institute for Experimental Cancer Research (ISREC), Department of Molecular Biology. She was a recipient of the Marie Heim-Vögtlin programme and was appointed Associate Professor at the Department of Pathology and Immunology.

Host defence mechanisms against mycobacterial infections

Mycobacterial infections mainly caused by *Mycobacterium tuberculosis* remains a major health problem leading to high mortality and morbidity worldwide. *Mycobacterium bovis* Bacillus Calmette-Guérin (BCG), the current vaccine used against tuberculosis (TB) which has been inoculated to two billion people, is also used for the immunotherapy of bladder carcinoma, and more recently, as an allergy treatment.

Our research aims to investigate host responses to *M. tuberculosis* and BCG infections and the mechanisms by which host resistance can be orchestrated and this intracellular bacteria eliminated. Our work analyses cells and mediators which are governing host reactions to fight mycobacteria. Phagocytic cellular populations producing inflammatory cytokines such as Tumor Necrosis Factor (TNF) have been a main topic in our laboratory. Identification of cellular sources of TNF and cells reacting to Mycobacteria-induced cytokines in vivo and in vitro and providing resistance or sensitivity to mycobacterial infection is investigated. TNF is a main target for the treatment of inflammatory diseases and its inhibition may reactivate latent tuberculosis. We are evaluating cellular expression of the different TNF molecular forms and TNF receptors which can enhance inflammatory reactions or in the contrary attenuate bacterial induced inflammation leading to resolution of the associated immunopathology. We also investigate in animal models how this knowledge can be considered for clinical practice in tuberculosis chemotherapy to improve bacillus elimination and reduce host inflammatory process.



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Keywords: Mycobacterial infections, tuberculosis, host immunity, cytokines, TNF

Contact: Irene.Garcia-Gabay@unige.ch

Alain Gervaix

Department of Paediatrics

Alain Gervaix obtained his medical degree at the University of Geneva in 1986, followed by specialty qualifications in Paediatrics in 1994, in Infectiology in 1999, and in Paediatric Emergency Medicine in 2014. He spent two years at the University of San Diego, California, USA as a Postdoctoral Research Fellow and came back to the HUG as Head of the Paediatric Infectious Disease unit (until 2010) and the Director of the Paediatric Emergency Division. He was appointed Associate Professor in 2006 and full Professor in 2012. Since 2011, he is Vice-Dean of the Faculty of Medicine for humanitarian and international affairs.

Inflammatory markers in bacterial infection

Our group works on the value of inflammatory markers such as procalcitonin and C-reactive protein in the prediction of serious bacterial infection in young children with fever without source.

Procalcitonin is a 116 amino acid protein produced by multiple organs in response to bacterial challenge. Investigations performed in fever without source, pyelonephritis, meningitis and pneumonia have shown that this protein is superior to other blood markers in predicting a bacterial infection. We recently validated and published a biological score, called LabScore, based on the results of procalcitonin, C-reactive protein and urine dipstick to help physicians in the diagnosis of severe infections in children less than 3 years of age.

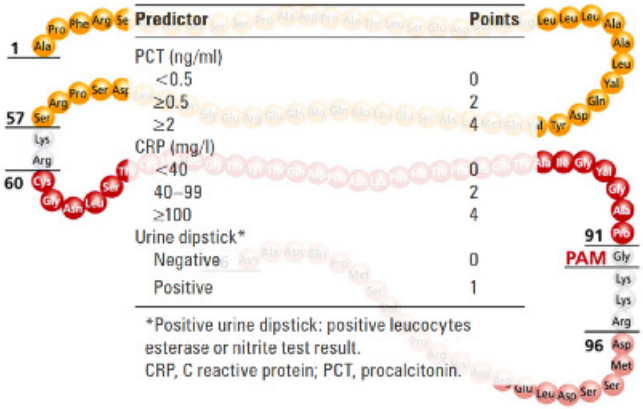
Streptococcus pneumoniae

Our group also works on the etiology of pneumonia using clinical characteristics and inflammatory markers to distinguish viral from bacterial pneumonia in children, and evaluates the impact of conjugate pneumococcal vaccines.

Table 1 Lab-score

Predictor	Points
PCT (ng/ml)	
<0.5	0
≥0.5	2
≥2	4
CRP (mg/l)	
<40	0
40–99	2
≥100	4
Urine dipstick*	
Negative	0
Positive	1

*Positive urine dipstick: positive leucocytes esterase or nitrite test result.
CRP, C reactive protein; PCT, procalcitonin.



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Keywords: Procalcitonin, Inflammatory markers, Pneumonia, Conjugate pneumococcal vacine, children

Contact : alain.gervaix@hcuge.ch

Stéphanie Hugues
Department of Pathology and Immunology

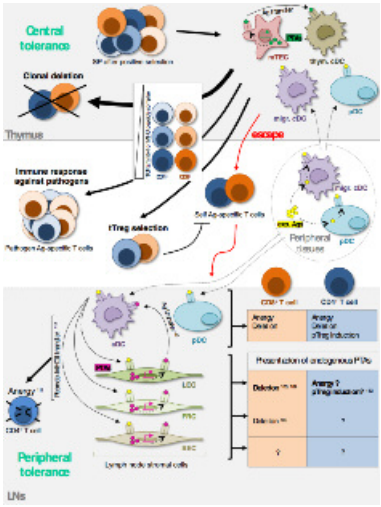
Stéphanie Hugues completed her PhD in Immunology in 2002 at the University of Nice, France. Following a post-doc fellowship at the Curie Institute in Paris, in Sebastian Amigorena's lab, she was awarded a CR1 INSERM position (Chargé de Recherche 1ere classe) in 2006. She moved to Geneva in 2008 to further establish an independent research program. At the University of Geneva Medical School, she first joined the laboratory of Prof. Walter Reith in the Department of Pathology and Immunology. She obtained in April 2010 a Swiss National Foundation Professorship Grant and was awarded Assistant Professor. She became an Associate Professor in 2016.

Maintenance of T cell tolerance by unconventional antigen-presenting cells

Immunological tolerance to self is essential in the prevention of autoimmune disease. Although central tolerance is remarkably efficient, potentially autoaggressive T cells can reach the periphery. Peripheral mechanisms of tolerance induction are therefore required to protect peripheral tissues from autoimmune attack. The two main types of dendritic cells (DC) are conventional DC (cDC) and plasmacytoid DC (pDC), both derived from the hematopoietic lineage. The prevailing model for peripheral tolerance involves the cross-presentation of tissue antigens by quiescent cDC. The exposure of cDC to selected inflammatory stimuli can change the outcome of the immune response from tolerance to immunity. In contrast to cDC, pDC were initially believed to be involved in innate immune responses via the secretion of type I interferons following viral or bacterial infections. However, recent findings demonstrate that like cDC, pDC are also implicated in adaptive immune responses. A first objective of our research is to analyze the impact of the selective loss of Ag presentation function by pDC on immune responses in vivo. Mouse models are used for multiple sclerosis and autoimmune diabetes.

These models, which involved cDC and/or pDC, nevertheless limit the presentation of particular Ags to the lymph nodes draining the tissues in which the Ag is expressed. An alternative mechanism, involving non-hematopoietic lymph node stromal cells, has recently emerged. In this mechanism, the lymph node stromal cells express various tissue self-Ag and could thus contribute to peripheral T-cell tolerance. A second part of our research investigates whether non-hematopoietic stromal cells can present tissue Ag in inflammatory situations in vivo, and whether this has an impact on T-cell responses during the development of diseases. Overall, we are investigating the respective contribution of hematopoietic and non-hematopoietic cellular compartments to the maintenance of peripheral T-cell tolerance and disease prevention.

Maintenance of T cell tolerance. Thymic central tolerance and peripheral T cell tolerance, Ag, Antigen; BEC, blood vessel endothelial cells; exo. Ags, exogenous antigens; FRC, follicular reticular cells; LEC, lymphatic endothelial cells; LNs, lymph nodes; LNSCs, lymph node stromal cells; MHC, major histocompatibility complex; MHCII, MHC class II; migr. cDC, migratory conventional dendritic cell (DC); mTEC, medullary thymic epithelial cells; pDC, plasmacytoid DC; PTAs, peripheral tissue-restricted antigens; pTreg, peripherally-derived T regulatory cell (Treg); SP, simple positive; TCR, T cell receptor; thym. cDC, thymus-resident conventional DC; tTreg, thymus-derived Treg.



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Keywords: T cell tolerance, antigen presentation, dendritic cells, lymph node stromal cells

Contact: Stephanie.hugues@unige.ch

Karl-Heinz Krause

Department of Pathology and Immunology

Karl-Heinz Krause obtained his medical degree in 1982 at the University of Munich, where he also trained in internal medicine. After Fellowships at the University Hospitals of Geneva (1984-87) and the University of Iowa Hospitals, USA (1987-89), he was recruited as a junior faculty member in Geneva. He was appointed Associate Professor in 1998 and Full Professor in 2001 Since 2005 he has been affiliated to the academic Departments of Pathology and Immunology, as well as the hospital Departments of Genetic and Laboratory Medicine and Internal Medicine Specialties.

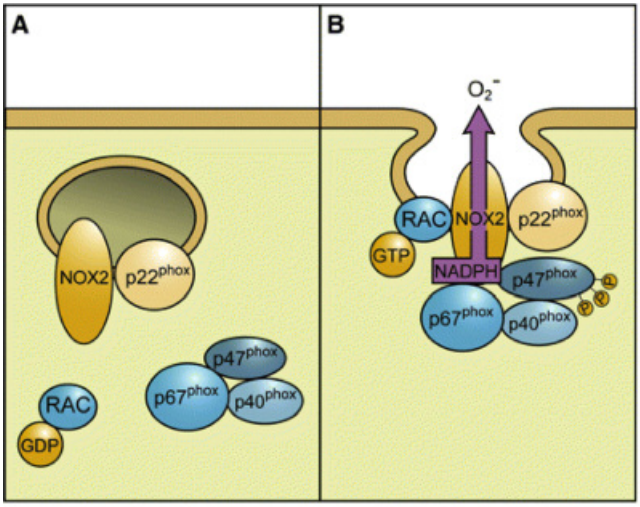
NADPH oxidases

Reactive oxygen species (ROS) are a doubled-edged sword. They have crucial physiological functions, from host defense to participation in biosynthetic processes and from intracellular signaling to regulation of gene expression. However, they can also be destructive and are linked to many disease processes. The NOX family of NADPH oxidases are one of the major sources of ROS and our laboratory is particularly interested in this enzyme family. ROS-generating NOX enzymes are a phylogenetically ancient system, which have emerged during development of eukaryotes. They have a range of complex functions in multicellular organisms, notably a role in host defense and inflammation. Much has been learned from patients with chronic granulomatous diseases CGD (genetic NOX2 deficiency), diseases characterized by the concomitant occurrence of immune deficiency and hyperinflammation. Projects in this domain focus – among others – on infection of CGD mice (mycobacteria in collaboration with I. Garcia, S. aureus in collaboration with J. Schrenzel and P. Linder) and on mechanisms of overshooting inflammation and immune response in CGD mice.

Stem cells as tools to study and treat infections

A second focus of the Krause are stem cells. The lab has developed various techniques to differentiate human pluripotent stem cells into neural cells and tissues (also referred to as ENTs=engineered neural tissues). Such human ENTs are particularly powerful tools to study viral infection of the central nervous system and the Krause lab is closely collaborating with virology groups (C. Tapperel, L. Kaiser) for this purpose.

The Krause lab has also a long-standing interest in the generation of transgenic stem cells using lentivector technologies. In collaboration with the research team of Roberto Speck in Zurich, this technology is now developed as a novel approach for HIV treatment: lentivectors carrying anti-CCR5 miRNA are transduced into hematopoietic stem cells, which upon transplantation render the human immune system resistant to HIV.



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Keywords: NADPH oxidase, reactive oxygen species, infection models, pluripotent stem cells, neurons

Contact: Karl-Heinz.Krause@unige.ch

Doron Merkler

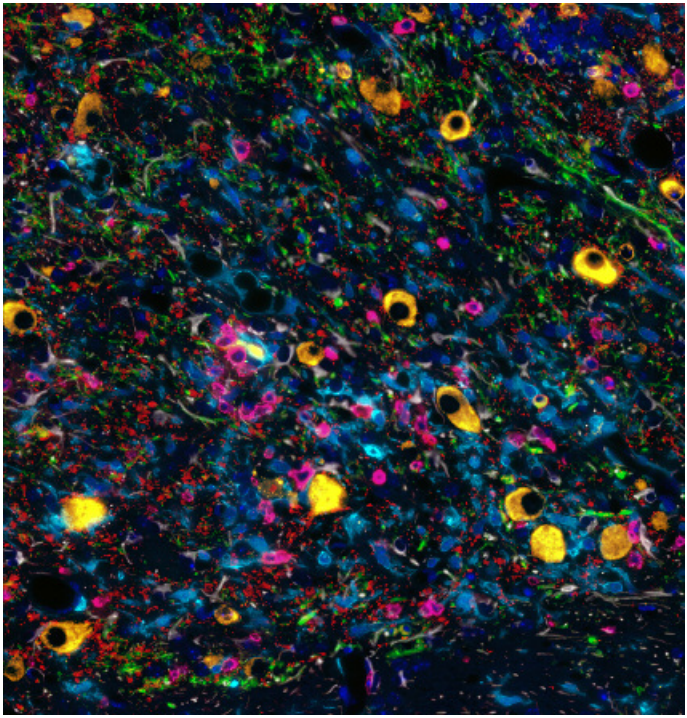
Department of Pathology and Immunology

Doron Merkler obtained his medical doctorate in 2002 in Zurich. He then attended the Postgraduate Course of Experimental Medicine and Biology and worked as postdoctoral fellow at the University Zurich. He became a licensed neuropathologist at the University Medical Center Göttingen (Germany) and worked as research fellow at the Institute of Experimental Immunology in Zürich. In 2010 he was awarded a SNSF professorship and is working as consultant in neuropathology in the division of clinical pathology. In 2016 he was tenured as associate professor at the University of Geneva.

Virus infection and autoimmune disease of the central nervous system (CNS)

Our laboratory has a general interest in inflammatory disorders of the CNS. This includes viral infection and autoimmune disease such as Multiple Sclerosis. Thereby our research focuses on following main aspects: a) viral pathogenesis of autoimmune diseases, b) mechanism of immune-mediated viral clearance and immunopathology in the CNS.

To explore the role of infectious triggers in autoimmune CNS disease, we investigate in experimental model systems the role of viral infection for CNS autoimmune disease precipitation. For this purpose we are using lymphocytic choriomeningitis virus (LCMV) mutant that we generate by reverse genetic approach. Thereby, we investigate how transient viral infection alters tissue homeostasis and how such alteration can modulate the formation of new autoimmune lesion in the CNS. Furthermore, we study the role of different effector mechanisms utilized by cytotoxic T cells leading to pathogen clearance and how these effector pathways can mediate protection and/or tissue damage in the CNS. Key experimental observations are confirmed on human brain samples to corroborate potential implication for human diseases. Our aim is thus to provide novel insights into immune-host balance of the CNS that can be of relevance for future preventive and therapeutic strategies in CNS inflammatory conditions.



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Keywords: Lymphocytic Choriomeningitis Virus, Central Nervous System, Viral infection, Autoimmune disease, Immunopathology

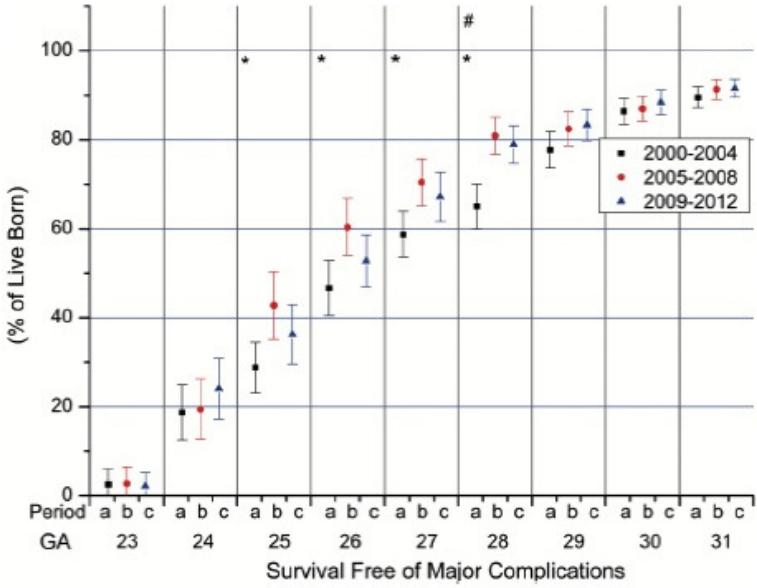
Contact: doron.merkler@unige.ch

Klara Posfay-Barbe
Department of Paediatrics

Klara Posfay Barbe obtained her MD in 1994 at the University of Geneva. After training in paediatrics at the HUG, from 2001 to 2004 she did a postdoctoral training in paediatric infectious diseases and clinical research at the University of Pittsburgh Medical Center, USA. In 2004, she returned to the Department of Paediatrics in Geneva. In 2011, she obtained her Privat-Docent and was appointed assistant professor in 2014. She is currently Head of the Paediatric Infectious Diseases Unit in the Department of Paediatrics and Director of the Clinical Research Platform in Pediatrics.

Immune responses to infection
We study antibody and cell-mediated immune responses against well-known antigens such as varicella, measles or *Streptococcus pneumoniae* in different settings, especially in immunocompromised hosts, such as solid organ transplant recipients or patients with inflammatory bowel disease. These studies aim to demonstrate that vaccination can be safe and immunogenic in the long term even in these high risk groups. Another study looks at the vaccination status and infections (especially parasites) in refugee children followed at our clinic in Geneva.

We also have several clinical research projects running, in collaboration with other groups. We currently investigate a group of children with viral meningo-encephalitis looking at enteroviral detection in different biospecimens, but also evaluating the role of next-generation high-throughput sequencing technologies to identify viral agents in selected cases with a presumed viral infection. This search of new (viral) pathogens also extends to another study in young children presenting to the emergency room with a fever without a source in which several body fluid specimens are investigated for possible pathogens and inflammatory markers. We also contribute to a large national study which looks at defects within innate immunity (single nucleotide polymorphisms) that increase susceptibility to sepsis in children and that predispose to severe or lethal sepsis by using genome-sequencing techniques. We conduct a national study looking at the outcome of children with congenital CMV. We are interested in how the work-ups and follow-ups are performed and which children are treated or not. We continue our involvement in the Swiss Mother-Child HIV Cohort Study, and the Swiss Transplant Cohort Study by contributing to new research projects.



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Keywords: children, immune response, vaccine, immunosuppression, infection, virus discovery,

Contact: Klara.PosfayBarbe@hcuge.ch

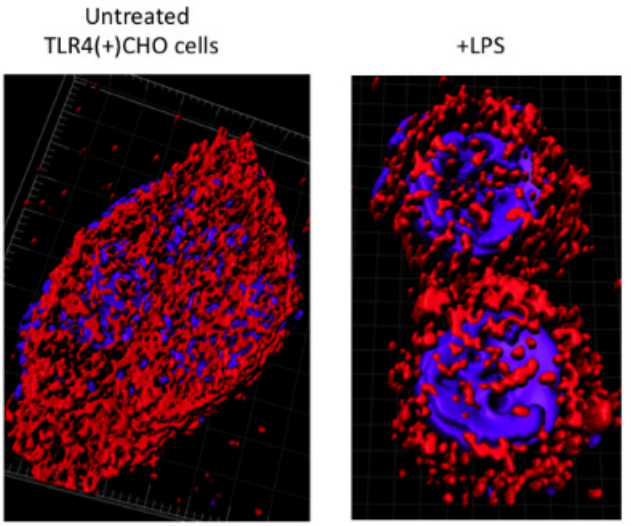
Jérôme Pugin

Department of Anaesthesiology, Pharmacology and Intensive Care
Department of Microbiology and Molecular Medicine

Jérôme Pugin obtained his MD in 1984 in Geneva, and later specialised in internal medicine and intensive care medicine. He shares his time between clinical work as a Deputy Head Physician of the Intensive Care Division at the University Hospitals of Geneva, and research in the Department of Microbiology and Molecular Medicine at the Faculty of Medicine of the University of Geneva. He spent three years between 1991 and 1994 in the Department of Immunology of the Scripps Research Institute in La Jolla, USA. Jérôme Pugin was appointed Associate Professor in 2007 and Full Professor in 2012 at the Faculty of Medicine of Geneva. Since 2011, he is Vice-Dean of the Faculty for Clinical Medicine.

Recognition of bacteria by innate immunity receptors

Our research interests have focused over the last 20 years on the molecular and cellular pathogenesis of sepsis. In particular, we have worked on soluble proteins involved in the innate recognition of bacteria such as soluble CD14 and MD-2, as well as in the Toll-like receptors activated by Gram-negative and Gram-positive bacteria. Another area of study is the molecular pathogenesis and cell signalling of ventilator-induced lung injury, and lung inflammation in the context of acute respiratory distress syndrome, with a recent focus on damage-associated molecular patterns (alarmins). We have also identified and tested biomarkers in the field of clinical sepsis.



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Keywords: Sepsis, Toll-like receptors, MD-2, ventilator-induced lung injury, alarmins

Contact: Jerome.Pugin@unige.ch

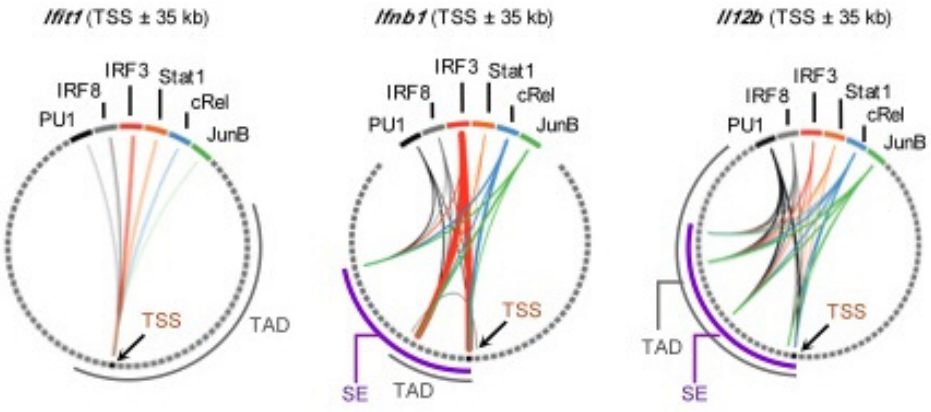
Walter Reith

Department of Pathology and Immunology

Walter Reith obtained his PhD at the Faculty of Sciences of the University of Geneva in 1985. He was appointed Associate Professor in 2004, then promoted to Full Professor in 2010, in the Department of Pathology and Immunology. He was elected chairman of the Department of Pathology and Immunology in 2011.

Regulation of antigen presentation and antigen presenting cells

Work in our laboratory has focused for many years on the molecular mechanisms that regulate the expression of Major Histocompatibility Complex class II (MHC-II) genes and the function of specialized antigen presenting cells (APCs) in humans and mice. MHC-II molecules are cell-surface proteins that are of central importance to the immune system because they present peptides to the antigen receptor of CD4+ helper T lymphocytes. MHC-II restricted antigen presentation by specialized APCs guides the development of CD4+ T cells in the thymus and instructs the function of these cells during the initiation, implementation and regulation of protective immune responses against pathogens. It is also pivotal for the maintenance of self-tolerance and the breakdown of tolerance in autoimmune diseases. Studying the molecular mechanisms that control MHC-II expression and the function of APCs thus represents an important contribution to molecular immunology and immunopathology. Our past work concentrated on the structure, function and expression of transcription factors regulating the expression of MHC-II genes in health and during the course of disease, and allowed us to generate valuable tools that are being used to study the role MHC-II expression by different APC subsets in vivo, particularly thymic epithelial cells and specific different dendritic cell (DC) subsets. More recently, we extended these investigations to encompass the regulatory circuits that control the activation and function of human and mouse DCs in response to individual and combined microbial and endogenous stimuli. We are notably studying transcriptional programs induced by the engagement of pattern recognition receptors (PRRs), particularly Toll-Like Receptors (TLRs), by single and combined pathogen associated molecular patterns in human and mouse DCs.



Enhancer mapping in PAMP (pIC and CpG) activated CD8+ dendritic cells

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Keywords: MHC class II, antigen presentation, antigen presenting cells, dendritic cells, gene regulation

Contact: walter.reith@unige.ch

Mirko Trajkovski
Laboratory of Metabolic Diseases

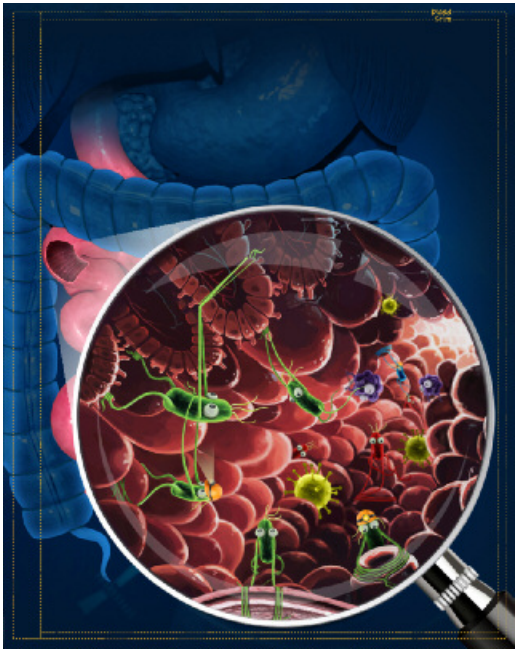
Mirko Trajkovski obtained his PhD at the Max Planck PhD School in Dresden in 2005, being awarded with the best doctoral thesis award at the Dresden University of Technology, and the Dresden Faculty of Medicine for his work on the link between regulated hormone secretion and gene expression in pancreatic beta cells. He did his postdoctoral work at the ETH Zurich with Markus Stoffel working on the miRNAs in obesity and insulin resistance, which led to him being appointed as a group leader and a Lecturer in Metabolism and Metabolic Diseases at the University College London (UCL) in 2012. End of 2013 he was appointed as Assistant Professor at the Geneva Faculty of Medicine awarded with the SNSF professorship. In 2014 he was awarded the prestigious ERC starting grant.

Adipose tissue plasticity and gut microbiota in obesity and insulin resistance.

Obesity is a major health problem associated with various metabolic disorders including insulin resistance. Brown adipose tissue promotes lean and healthy phenotype and improves insulin sensitivity. In response to cold or exercise, brown fat cells also emerge in the white adipose tissue (named beige cells), a process known as browning. We aim to understand the development of metabolic diseases, in particular the mechanisms of browning and intestinal plasticity in orchestrating the overall energy homeostasis.

First we focus on the role of the gut microbiota in the development of metabolic diseases. Gut microbiota co-develops with the host, and is influenced by several physiological changes. We showed that cold exposure leads to marked shift of the microbiota composition. Transplantation of this cold microbiota to germ-free mice increases insulin sensitivity, and enables tolerance to cold partly by promoting browning, thus increasing energy expenditure and fat loss. During prolonged cold however, the body weight loss is attenuated, caused by adaptive mechanisms maximising caloric uptake and increasing intestinal, villi and microvilli lengths; an adaptation transferable with the cold microbiota. The development of functional beige fat is also promoted by microbiota depletion and mediated by eosinophil infiltration, enhanced type 2 cytokine signaling and M2 macrophage polarization in the white fat depots. This suggests that the microbiota is a key factor orchestrating the overall energy homeostasis during increased demand.

The second part of our research aims at identifying metabolically active miRNAs and investigating their roles in animal models of obesity, as well as in primary cultures of precursor cells using systems biology and targeted approaches. We also generate tools to screen for drugs and peptides involved in brown and white adipose tissue differentiation and function, use lineage tracing studies to identify the origin of the brown adipocytes and develop rational strategies to enable miRNA delivery and silencing specifically in the brown fat.



Cold exposure markedly shifts the composition of the gut microbiota. This "cold microbiota" mediates remodeling of the fat and intestinal tissues, helping the host to withstand periods of high energy demand.

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Trajkovski M, Hausser J, Soutschek J, Bhat B, Akin A, Zavolan M, Heim MH and Stoffel M. (2011) MicroRNAs-103 and -107 regulate insulin sensitivity. Nature 474:649-53.

Keywords: obesity; gut microbiota; fat; adipocyte; miRNA

Contact : Mirko.Trajkovski@unige.ch

Jean Villard

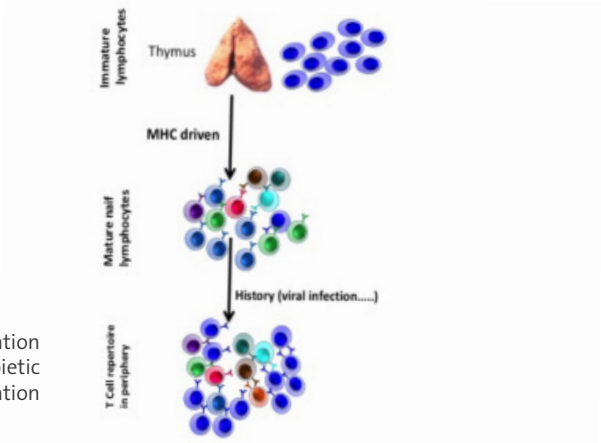
Department of Internal Medicine Specialties

Jean Villard is MD since 1988, after a complete clinical training in internal medicine he moved to research to obtain an MD-PhD. Then he went back to clinic to specialize in Immunology and Allergology He is currently professor of clinical and transplant immunology at the Geneva University Hospital, head of the transplant immunology unit and the National Reference Laboratory for Histocompatibility (UIT / LNRH).
In addition to its activity as medical director of the HLA laboratory and its clinical activity, he is involved as PI in several research projects in the field of transplant immunology and immunogenetics. Jean Villard has also undertaken at the national level the reform of the Swiss system of allocation of renal transplants as president of the medical committee of the foundation Swisstransplant.

Research projects:

New insight in the genetic of hematopoietic stem cell and solid organ transplantation transplantation

Haematopoietic stem cell transplantation (HSCT) is the standard of care to treat a large variety of haemato-oncology diseases, such as acute myeloid and lymphoblastic leukaemia, and severe primary immuno-deficiencies. For leukaemia, the five years survival rate is around 50%. Relapse of the disease, infections and graft versus host disease (GVHD) are the main complications of the therapy. Genetic compatibility between donors and recipients is one of the key factors of success, the HLA locus being the most important one. HLA compatibility is critical to limit the development of severe GVHD, but the HLA also contributes to the development of a new TCR repertoire from lymphoid precursors of the donors. The TCR repertoire will protect the patient against microbial infections, especially viruses. Thanks to the development of new technologies such as next generation sequencing (NGS), we are now able to explore in depth several key aspects of the immunogenetics of stem cell transplantation. We are currently analyzing the development of the new TCR repertoire after stem cell transplantation in various recipients according to their age and to the predominant viruses to which these patients are exposed. We also analyze in detail the alloreactivity of the TCR repertoire against HLA-C mismatches, considering the level of HLA-C expression and the TCR repertoire expressed by several patients. In the field of solid organ transplantation we focus our interest in the natural killer receptors KIR regarding immune response against viral infection (such as cytomegalovirus). Several publication including genetic association disease and in vitro analysis allowed us to demonstrate the importance of natural killer cells in the immune response against microbes in immunosuppressed patients.



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Contact: Jean.Villard@hcuge.ch

Evgeny M. Zdobnov

Department of Genetic Medicine and Development

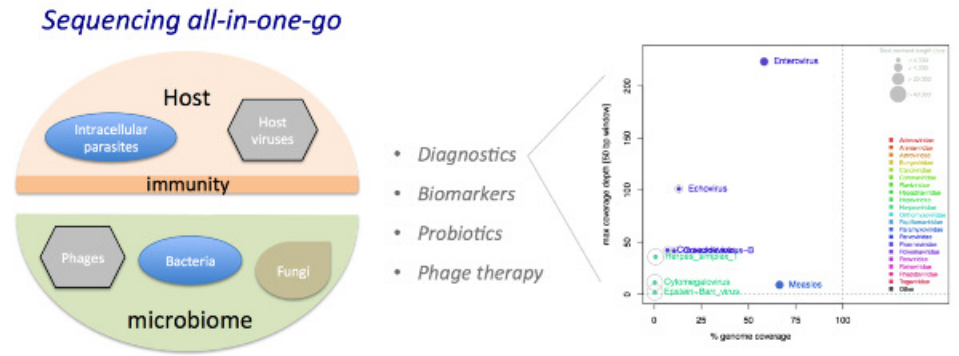
Evgeny M. Zdobnov is a full Professor at the Faculty of Medicine and a group leader at the Swiss Institute of Bioinformatics. He graduated and then obtained his PhD in 2001 from the Moscow Institute of Physics and Technology and the Engelgardt Institute of Molecular Biology RAS, Russia. Before coming to Geneva in 2005, he joined the European Bioinformatics Institute (EBI) in Cambridge, UK, and then the European Molecular Biology Laboratory (EMBL) in Heidelberg, Germany.

Comparative genomics

Bioinformatics is the art of computer-assisted analysis of the wealth of molecular biology data. With over 20 years of experience in bioinformatics, Evgeny is now expanding his focus on comparative genomics towards interpreting the accumulating metagenomic data readouts, i.e. sequencing of the total DNA/RNA extracted directly from environmental or clinical specimens. In fact, sequencing is the most high-throughput method for comprehensive molecular interrogation of biological systems that enables a remarkable array of subsequent studies. Relating the sequencing readouts to our current knowledge, and revising our knowledge from such data (in the light of evolution) is the subject of comparative genomics and of our research. Hence, Prof Zdobnov's laboratory mostly deals with devising computational data analyses to address key biological questions and developing software to achieve these aims (e.g. http://www.orthodb.org).

Our current focus is well exemplified by the following ongoing projects:

- SNSF 31003A_166483 "Shotgun metagenomics of circulating human viruses".
- SNSF IZLRZ3_163863 "Understanding the virome's role in the spread of antibiotic resistance through meta-analysis of human microbiomes".
- The Leenaards Foundation founded collaborative project with Prof Fellay (EPFL) "Understanding the impact of human genetic variation on chronic viral infections: a genome-to-genome approach".



Comparative genomics is key to interpret the data

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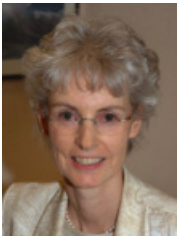
C Tapparel, T Junier, D Gerlach, S Van Belle, L Turin, S Cordey, K Muehlemann, N Regamey, J-D Aubert, PM Soccal, P Eigenmann, EM Zdobnov #, and L Kaiser # (2009) New Respiratory Enterovirus and Recombinant Rhinoviruses among Circulating Picornaviruses. Emerging infectious diseases 15(5).

Keywords: Comparative genomics, metagenomics, diagnostics, microbiota, gene repertoire

Contact: Evgeny.Zdobnov@unige.ch



Claire-Anne Siegrist

Departments of Pathology and Immunology
Department of Paediatrics
WHO Collaborative Center for Vaccine Immunology

Claire-Anne Siegrist graduated in 1983. She trained in paediatrics, infectious diseases and immunology prior to dedicating her professional life to all aspects of vaccinology. Associate Professor of Vaccinology (2000) and Full Professor of Paediatrics (2006), she is President of the Swiss National Advisory Committee on Immunization (2004), member of the UK National Committee (2008) and of the WHO Strategic Advisory Group of Experts on Immunization (2010). She leads the InfoVac expert network (www.infovac.ch), has developed vaccinology clinical decision support software for health care professionals (www.viavac.ch), and is the founder of the Swiss Electronic Vaccination Record (www.myvaccines.ch).

Vaccine immunology from early life to vaccine safety

Our research focuses on i) neonatal immunology in order to understand the postnatal development process of the immune system and how it is regulated to control early life immune responses to foreign antigens; ii) vaccine immunology, through which we study the mode of action of current and novel vaccines to identify strategies capable of strengthening immune competence, especially in the very young, and iii) clinical vaccinology to understand the determinants of vaccine responses in patients with varying levels of immune competence because of age, underlying disease or immunosuppression, and thus identify optimal strategies.

Among other recent projects, Claire-Anne Siegrist's group has been in the front line of the development of an Ebola vaccine. The team conducted a large, first-in-human phase I trial testing a recombinant VSV-based vaccine in Geneva; this investigation provided key immunogenicity and safety results informing the first successful phase III vaccination study in the field. Now leading a consortium of investigators across Europe and Africa, Professor Siegrist and her group are working on better characterizing innate and adaptive immune responses to new Ebola vaccines.

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Keywords: immunization, immunosuppression, neonatal immunity, follicular T helper cells, maternal immunization, ebola

Contact: Claire-Anne.Siegrist@unige.ch

Serge Bouillaguet

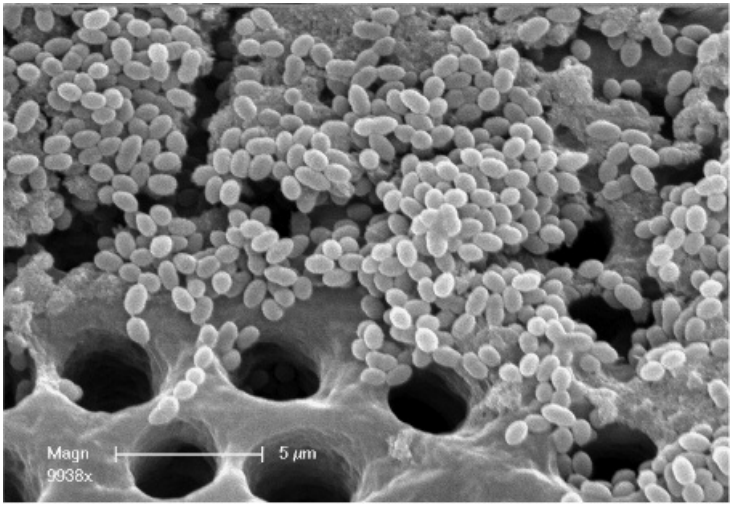
Division of Cariology and Endodontics

Serge Bouillaguet obtained his dental degree in 1983 and his Doctorate in Dental Surgery in Marseilles in 1984. He obtained a Doctorate in Medical Dentistry at the University of Geneva in 1989 and his Privat-Docent in 2003. He was appointed Lecturer in 2001 and Associate Professor in 2011.

Blue light-mediated inactivation of endodontic pathogens

Our research interests focus on the evaluation of current antimicrobial strategies used in endodontics together with the development of new approaches based on the photo-inactivation of endodontic pathogens. We have identified different photosensitisers, which can be activated with conventional light curing units used in dental offices. We work on biofilm models using plastic or glass surfaces, membranes or dentin disks. Biofilm formation and growth are monitored by LIVE/DEAD fluorescence microscopy to simultaneously detect intact cells and dead/injured ones. The expression of virulence genes after treatment is also evaluated by PCR.

In addition our group has routinely used cytotoxicity assays to evaluate the short or long term biological response of cultured cells (host cells) exposed to various disinfecting agents and endodontic biomaterials. We are assessing inflammatory reactions and oxidative stress induced by blue light-activated photosensitisers and the likelihood of lethal damage to resident cells resulting from such stress.



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Keywords: Dental, Endodontics, antimicrobials, Photodynamic therapy, Blue-light

Contact: Serge.Bouillaguet@unige.ch

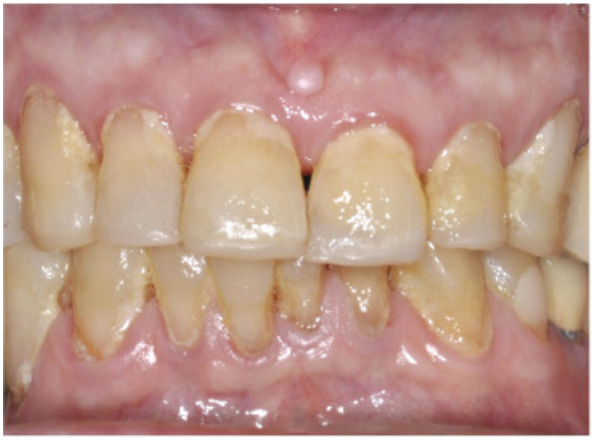
Andrea Mombelli

Division of Periodontology

Andrea Mombelli graduated from the University of Bern School of Dental Medicine and completed his post-graduate studies reaching the status of Privat-Docent in 1992. He has a swiss federal diploma in dentistry, a doctorate in dentistry (Dr. med. dent.) and is a Swiss board-certified specialist in periodontics. Before being appointed as professor and head of the division of periodontology at University of Geneva's School of Dental Medicine, he held the position of head of the Laboratory for Oral Microbiology at the University of Bern School of Dental Medicine (1992-1999). He was associate vice-dean of the medical faculty at the University of Geneva from 2005 to 2011.

Anti-microbial therapy of periodontal diseases and peri-implant infections – microbiological and systemic responses and clinical outcome

Bacteria forming biofilms on surfaces of teeth and dental implants are assumed to be the main cause of periodontitis and peri-implant infections. Mechanical debridement is beneficial but is unable to eliminate all incriminated bacteria completely. The added value of adjunctive antibiotics has been shown, but the specific relationship of benefit and risk in different clinical situations is nevertheless subject of a long-lasting debate. We study changes in the oral microbiota induced by various forms of anti-microbial therapy and relate them to clinical outcomes. Analyses focus on resistance development and on the diagnostic and prognostic utility of microbiological data.



The uninterrupted accumulation of bacterial deposits on teeth and dental implants during three weeks induces visible inflammation in the tissues around teeth and implants. Removal of these deposits resolves the inflammation. Experimental gingivitis is a convenient model for the study of host-parasite interactions in vivo. From Meyer et al. Clin. Oral Impl. Res. Online ahead of print, DOI: 10.1111/clr.12912, 2016.

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Keywords: Aggregatibacter actinomycetemcomitans, periodontitis, antimicrobial photodynamic therapy, antibiotics

Contact: Andrea.Mombelli@unige.ch

Benedetta Allegranzi

Department of Community Health and Medicine
Infection Control Programme, HUG
WHO "Clean Care is Safer Care" Programme

Benedetta Allegranzi obtained her medical degree in 1994 in Verona, Italy, and her postgraduate degrees in infectious diseases and tropical medicine in 1998. She came to Geneva in 2005 as a consultant at the World Health Organization. She is currently the coordinator of the new WHO Infection Prevention and Control (IPC) Global Unit in the Service Delivery and Safety department. Dr Allegranzi spent the first twelve years of her career working as a medical doctor and then specialist and Assistant Professor in infectious diseases at the University of Verona, Italy, focusing on clinical practice and research on HIV, TB, malaria, infections in critically ill patients, infection control and tropical medicine.

A worldwide perspective on infection control - prioritising settings with limitedresources

Prevention of healthcare-associated infection (HAI), the most frequent adverse event during Health care delivery affecting hundreds of millions of patients around the world, is the target of the WHO IPC Global Unit which was established in October 2016 and lies its foundations on the "Clean Care is Safer Care" programme.

Dr Allegranzi's research activities, conducted in the field of IPC in the context of global health, have focused on implementing core components of effective IPC programmes, hand hygiene improvement, epidemiology of HAI worldwide, the prevention of surgical site infections (SSI), and IPC implementation in settings with limited resources. In particular, Dr Allegranzi was the lead for IPC during the WHO response to the Ebola outbreak in West Africa; through her work, she has highlighted the burden of HAIs in low-resource settings and has studied interventions to reduce it. Among the IPC global unit activities led by Dr Allegranzi, several new global IPC guidelines that have major relevance for all countries and health care facilities worldwide, have been developed to reduce HAIs and contain antimicrobial resistance. Two global campaigns on injection safety and hand hygiene have been launched; the latter currently includes more than 19 000 in 177 countries and a network of 48 national campaigns.

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Contact: Benedetta.Allegranzi@hcuge.ch , allegranzib@who.int

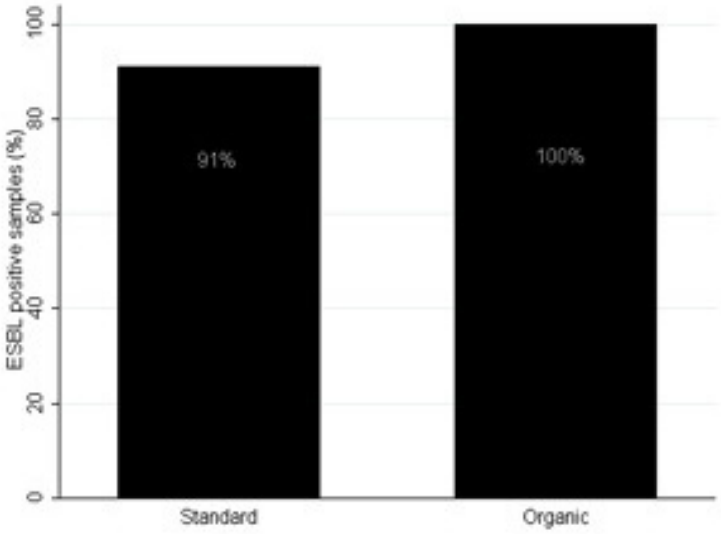
Stephan Harbarth

Department of Internal Medicine Specialties
Infection Control Programme, HUG

Stephan Harbarth earned his medical degree from Ludwig-Maximilians-University in Munich in 1993, Germany, and completed his residency in internal medicine and tropical medicine at Munich University Hospitals. After serving as a Clinical Fellow in the Infectious Diseases Division and Infection Control Programme in the Department of Internal Medicine at University Hospitals of Geneva, Dr Harbarth completed his Master degree in epidemiology at Harvard University. He is board-certified (FMH) in infectious diseases and was appointed Associate Professor in 2010. Dr Harbarth's work has garnered several awards, including the ICAAC Young Investigator Award from ASM (2003), the Young Investigator Award from ESCMID (2006), the Swiss Society for Infectious Diseases Award for epidemiological research (2008) and the SHEA Investigator Award (2011).

Control of antibiotic resistance – research activities

Our group is currently conducting several clinical and epidemiological studies to evaluate key questions related to the control of the acquisition, transmission and infection by multidrug-resistant microorganisms. We participate in several ongoing large-scale EU-funded studies (R-GNOSIS, Rapp-ID, AIDA, COMBACTE, DRIVE-AB) to address this important public health threat. We collaborate closely with the Genomics Research Laboratory at HUG, based on a productive translational research platform. The most notable examples of our research are the evaluation of different MRSA control interventions (JAMA 2008, BMJopen 2013), the advanced analysis of epidemiologic trends and the health-economic burden of multiresistant microorganisms (JAC 2011, ICHE 2013; EuroSurv 2016), the conduct of epidemiologic studies linking patient data with molecular investigations (Clin Infect Dis 2011, ICHE 2014; J Infect Dis 2016), the evaluation of antibiotic stewardship interventions (Lancet Infect Dis 2010, JAC 2011, Lancet 2016) and several placebo-controlled, randomised clinical trials to decolonise MRSA and ESBL carriers (JAC 2013, JAC 2016).



Contamination of raw chicken samples with multiresistant Gram-negative bacteria at the HUG hospital kitchen and different Geneva supermarkets, stratified by type of farming (Stewardson A et al, ICHE 2014)

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Keywords: Epidemiology, drug resistance, clinical trial, prevention, Staphylococcus aureus

Contact: Stephan.Harbarth@hcuge.ch

Didier Pittet

Department of Internal Medicine Specialties
Infection Control Programme, HUG

Didier Pittet obtained his medical degree in 1983 on "Inositol phosphates and cellular activation" from the University of Geneva Faculty of Medicine, and is specialised in infectious diseases, hospital epidemiology and public health. In 1992, he became Head of the Infection Control Programme at HUG. In 2008, the Programme was designated a WHO Collaborating Centre on Patient Safety. He was appointed Associate Professor at the Faculty of Medicine in 2000 and promoted to Full Professor in 2010. He has received several degrees and awards for his work as Lead Advisor of the WHO First Global Patient Safety Challenge "Clean Care is Safer Care" initiative and is an international expert for the WHO.

"Clean Care is Safer Care"
As a WHO Collaborating Centre on Patient Safety and in association with the WHO Patient Safety group, our recent work focused on the evaluation of the burden of healthcare-associated infection in low- and middle income countries with the aim of identifying and implementing the most feasible and effective solutions/measures for infection prevention worldwide. The strategy is endorsed by two-thirds of the United Nations' Member States and currently active more than 95% of countries worldwide. A foundation for the prevention of healthcare-associated infection in the developing world has been created (see www.CleanHandsSaveLives.org and www.icpic.org). The book "Clean Hands Save Lives" and the movie "Clean Hands" describe Prof Pittet team commitments and accomplishments.

Prevention and control of healthcare-associated infection
Our group is developing and testing innovative multidisciplinary and multifaceted approaches to prevent or contain healthcare-associated infection, including innovative tools to improve hand hygiene compliance. We have coordinated a large-scale EU-funded project (PROHIBIT) to improve implementation of best preventive practices across European hospitals.

Determinants and prevention of device-associated infections in adult and paediatric critical care.
We are investigating risk factors and multimodal prevention strategies to decrease device-associated infections, including novel tools.

Epidemiology of noma in Niger.
Our research focuses on the risk factors for noma and compares oral bacterial diversity of children with noma and controls from the same region. Prevention strategies will be tested following results of the current research.

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Keywords: hand hygiene, implementation science, health-care associated infection, global policy making, noma

Contact: Didier.Pittet@hcuge.ch

Antoine Flahault

Antoine Flahault MD, PhD in biomathematics, is full professor of public health at Faculty of Medicine, University of Geneva where he is the Director of the Institute of Global Health, at Campus Biotech (since Jan. 2014). He has been appointed founding director of the French School of Public Health (EHESP, Rennes, 2007-2012), co-director of Centre Virchow-Villermé for Public Health Paris-Berlin (Université Descartes, Sorbonne Paris Cité), co-director of the European Academic Global Health Alliance (EAGHA), president of the Agency for Public Health Education Accreditation (APHEA). He has conducted his research in mathematical modelling of communicable diseases ; has chaired the WHO collaborative center for electronic disease surveillance ; has coordinated research on Chikungunya in Indian Ocean and in French Caribean Islands (Inserm Prize, 2006; was scientific curator of a large exhibition Epidemik, la Cité des Sciences et de l'Industrie, Paris, Rio and Sao Paulo, 2009-2013). He was elected corresponding member at Académie Nationale de Médecine (Paris). He was in 2016 the current President of the World Health Summit, the M8 Alliance, and of the Geneva Health Forum.

The **Institute of Global Health**, founded in 2014, provides training programs in global public health at Master and PhD levels and conducts research activities in the field. Global health is defined according to six principles: first, global health addresses cross-border and multi-level health issues. Second, it is "trans-disciplinary", i.e. it mobilizes all relevant academic disciplines and also non-academic sectors of society. Third, it studies complex systems in the real world. This complexity requires trans-disciplinary system thinking to help finding solutions. Fourth, it seeks to provide affordable, effective and integrated innovation. Fifth, it looks for health for all in a sustainable world. It is no longer possible to develop health care facilities, devices, services without a deep commitment and respect for our planet. Sixth and last, global health is committed to the normative framework of human rights and equity. This is an essential aspect of global health; because health is considered a human right, access to affordable health care matters greatly. Geneva hosts most of the major actors of global health: the World Health Organization, UNAIDS, the Global Fund to fight AIDS, Tuberculosis and Malaria, ICRC, GAVI, FIND, MSF and many other NGOs and Foundations, with diplomatic permanent UN representations for more than 140 countries. The creation of the Institute of Global Health was inspired by a shared commitment to foster academic global health at the Faculty of Medicine of the University of Geneva. It is located in the facilities of Campus Biotech shared by the University of Geneva and Ecole Polytechnique Fédérale de Lausanne (EPFL). The Institute of Global Health is constituted with four divisions (Epidemiology of Cancer and Prevention; Environmental and Health Promotion; Global Mental Health; Health and Human Rights), and runs with EPFL and ETH grippenet.ch, an EU funded research program on influenza-like-illness syndromic surveillance, based on a crowdsourcing approach. It produced massive open online courses (MOOCs) in various domains of global health including Zika and Ebola, and an innovative simulation prototype to train public health professionals (e.g. National Focal Point and WHO staffs) on International Health Regulations.

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Contact: Antoine.Flahault@unige.ch

Olivia Keiser

Olivia Keiser completed her PhD in Epidemiology at the University of Bern in 2009, having previously obtained Masters degrees in both Biology (University of Basel, 2001) and Statistics (University of Neuchâtel, 2004). After having worked ten years as an Epidemiologist and Research Group leader at the University of Bern, she will now join the Institute of Global Health as Assistant Professor in March 2017 (under a grant awarded by the Swiss National Science Foundation, SNF). Her research focuses on HIV and hepatitis C in high and low-income settings. She has led projects within large cohort studies including the Swiss HIV and the Swiss Hepatitis C cohort and the International Epidemiology Databases to Evaluate AIDS. She has also developed mathematical simulation models to assess the effectiveness and cost-effectiveness of interventions to combat different infectious diseases. With the interdisciplinary SNF professorship grant, her group will combine mathematical modelling approaches with advanced statistical models. She will include methods from social sciences to better understand the spatial spread of HIV and other diseases and propose interventions. She is working closely with several national and international organizations including the Swiss Federal Office of Public Health, the Bill and Melinda Gates Foundation, WHO, UNITAID and the World Bank.

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Contact: olivia.keiser@unige.ch

Francis Moussy

Francis Moussy PhD, is Professeur Titulaire (Adjunct Professor) at the Institute of Global Health, School of Medicine, University of Geneva. His main occupation is at the World Health Organization where he is leading projects to facilitate the development, access and use of diagnostics that are suitable for Low-and-Middle Income Countries (LMICs). Prior to joining WHO in 2009, Dr Moussy worked as Professor and Deputy Director in the Brunel Institute for Bioengineering at Brunel University (West London), UK working on biosensors. From 2002 to 2007, Dr Moussy held a position as a tenured Associate Professor of Chemical & Biomedical Engineering at the University of South Florida in Tampa. Dr Moussy also worked for 4 years in Canada after completing his Doctorate in Biomedical Engineering at the Université de Technologie de Compiègne, France.

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Contact: francis.moussy@unige.ch

Xavier Perret
Department of Botany and Plant Biology

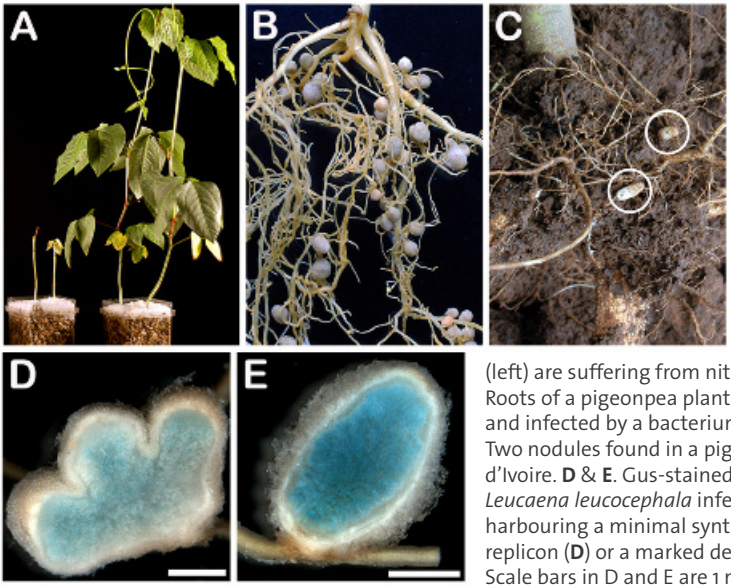
Xavier Perret graduated with a PhD in Biology from the University of Geneva in 1991. After a postdoctoral training in the laboratories of Prof. Sydney Brenner at Addensbrooke's Hospital (Cambridge, UK) and Scripps Research Institute (La Jolla, USA), he joined the group of Prof. W.J. Broughton at the University of Geneva in 1994. Appointed as a senior lecturer in 2001, he contributed in 2007 to the creation within the Department of Botany and Plant Biology of a Microbiology Unit, which he led until the end of 2013.

Molecular cues allowing soil bacteria (rhizobia) to colonize plant cells

For many years our group has been deciphering the molecular basis for symbiotic promiscuity of the soil bacterium *Sinorhizobium* (*Ensifer*) *fredii* strain NGR234. Amongst the many rhizobia that form nitrogen-fixing symbioses with leguminous plants, strain NGR234 has the unusual capacity to associate with more than 120 genera of legumes. To fix nitrogen for the benefit of host plants, rhizobia must first induce formation of root (or less frequently of stem) nodules and then form persistent intracellular colonies within nodule cells. Development of root nodules and the subsequent infection process leading rhizobia into nodule cells require the coordinated exchange of many signal molecules. Primed by flavonoids released by roots of host plants, strain NGR234 responds with a broad spectrum of symbiotic keys including a complex cocktail of nodulation (Nod) factors, effector proteins secreted by type three secretion systems (T3SS) and various surface polysaccharides which, together, fine tune the outcome of symbiotic interactions.

Currently our group follows two complementary research lines:
1. Assemble synthetic plasmids carrying the minimal number of genes required for inducing nodule formation on roots of host legumes, infect these nodules and ultimately fix nitrogen within them;
2. Screen the diversity of rhizobial solutions that exists in fields, pastures or forests to identify novel symbiotic strains to be used as bioinoculants for boosting the development of legume crops.

To expedite the screening procedure for novel rhizobial strains, we recently established protocols that bypass cultivation of nodule bacteria prior to identification by mass spectrometry. Concomitantly we also developed the spectral database that secures identification of rhizobia regardless of the species or genus they belong to. Identification of unknown nodule bacteria was successfully tested on rhizobia found inside nodules of pigeonpea (*Cajanus cajan*) collected in fields of Côte d'Ivoire.



A. Promiscuous strain NGR234 provides to cowpea plants (right) the fixed nitrogen required to grow. Non inoculated plants (left) are suffering from nitrogen starvation. **B**. Roots of a pigeonpea plant with nodules formed and infected by a bacterium from Côte d'Ivoire. **C**. Two nodules found in a pigeonpea field in Côte d'Ivoire. **D** & **E**. Gus-stained sections of nodules of *Leucaena leucocephala* infected with a strain harbouring a minimal synthetic symbiotic replicon (**D**) or a marked derivative of NGR234 (**E**). Scale bars in D and E are 1 mm.

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Contact: xavier.perret@unige.ch

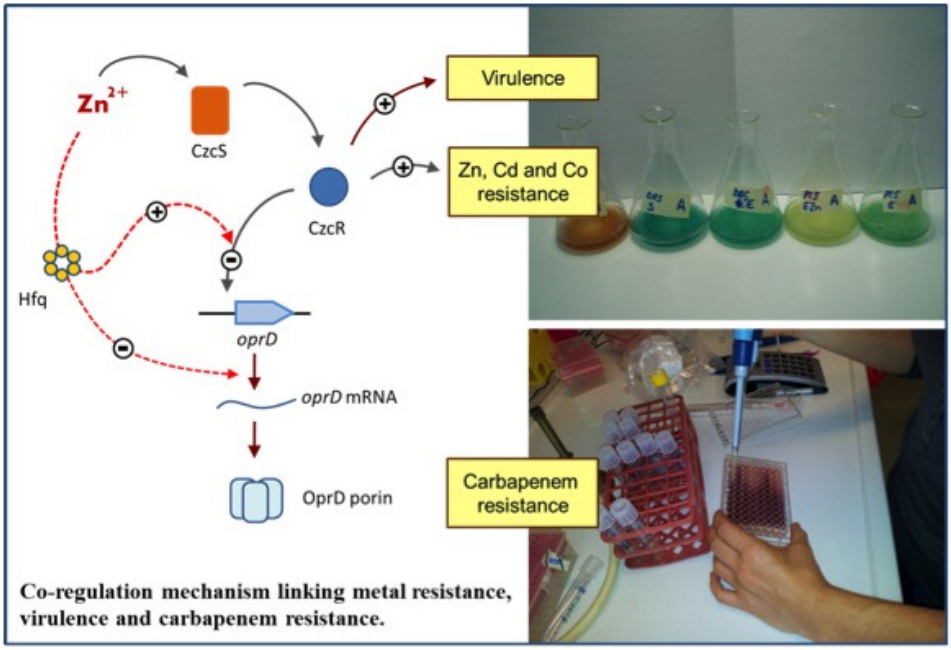
Karl Perron

Department of Botany and Plant Biology

Karl Perron obtained his PhD in Molecular Biology in 2000 at the University of Geneva. Then he spent eight years as post-doc and senior post-doc at the CMU (Geneva) in different groups in bacteriology. During this period he set-up BiOutils, a platform of life sciences communication of the University of Geneva. In 2008 he was appointed scientist and then lecturer at the Sciences Faculty (Biology and Pharmaceutical Sciences). Since then he is responsible of a research laboratory of bacteriology at the Microbiology Unit, in charge of bacteriology teaching for students in pharmacy and co-responsible of the BiOutils interface.

Pseudomonas aeruginosa: from a common environmental bacterium to a severe opportunistic pathogen.
Our group is working on the adaptation of *Pseudomonas aeruginosa* to environmental challenges such as the presence of metals. We found that an excess of Zn or Cu, induces the expression of the metal-inducible CzcRS two-component system (TCS) that activates the expression of a metal efflux pump CzcCBA and down-regulates the expression of the OprD porin. Since this porin is the route of entry of carbapenem antibiotics, bacterial cells become in presence of Zn or Cu resistant to this major family of anti-Pseudomonas compounds, often used as the last line of treatment. Additionally the CzcRS TCS modulates the expression of virulence factors by controlling the las quorum sensing system. These results are of primary importance since trace metals are not only present in the environment, but also within the body and are included in the composition of numerous medical treatments. We are currently deciphering the pathways linking metal export and antibiotic import. Moreover, we are partner of the Swisstransmed platform to study the behavior of *P. aeruginosa* during burn wound infections and to improve biological bandages used in burn patients. Finally, in collaboration with research laboratories of the Pharmaceuticals Sciences, we are strongly involved in the discovery of new antibacterial compounds and developing new screens for fighting against Gram-positives and Gram-negatives pathogens.

Education
Funded in 2007 as an interface between STEM biology educators and academic environment, BiOutils is the life sciences communication platform of the UNIGE. It is fully integrated within our laboratory and it offers a wide range of activities that are spacing several disciplines as microbiology, molecular biology and biochemistry (www.bioutils.ch).



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Keywords: Pseudomonas aeruginosa, virulence, two-component system, carbapenem, zinc

Contact: karl.perron@unige.ch

Thierry Soldati

Department of Biochemistry

Thierry Soldati studied Biochemistry in Geneva and then carried out his doctoral work at the Institute for Cell Biology of the ETH in Zurich, before being a postdoctoral fellow at Stanford University Medical School. In 1995, he joined the Max Planck Institute for Medical Research in Heidelberg as independent Group Leader. In 2001, he was appointed Lecturer at the Department of Biological Sciences of Imperial College London. In 2004, he joined the Department of Biochemistry, University of Geneva, as a Senior Lecturer. Since 2012 he is an Associate Professor.

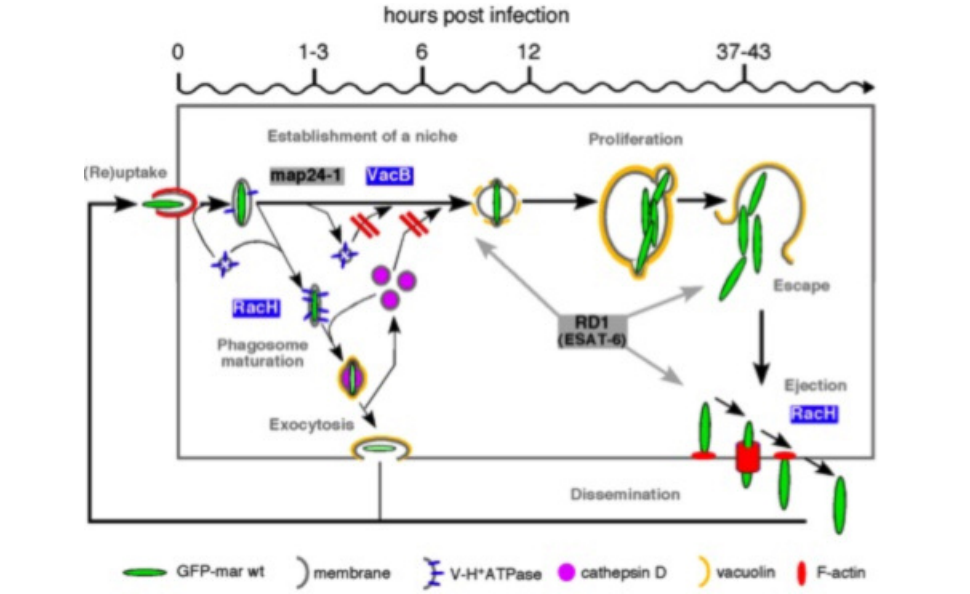
Cellular and molecular mechanisms of phagocytosis and cell-autonomous defences against mycobacteria infection.

The major aim of the Soldati group is to understand the integration, the cooperation of signalling, cytoskeleton and membrane trafficking in phagocytosis and its relevance to host-pathogen interactions. To this end, we use the social amoeba *Dictyostelium* as a model organism as it is a professional phagocyte very similar to mammalian phagocytes of the innate immune system in morphology and behaviour, but is genetically and biochemically tractable.

Phagocytosis is an ancestral eukaryotic process that allowed key innovations during evolution, and mechanisms of recognition, signalling and killing are surprisingly conserved throughout evolution. We study phagosomal components and mechanisms using a combination of genetics, proteomics and cell biology, for example dissecting the role of cytoskeleton, WASH, Rab GTPases, the excocyst, EHD and Dynamin in the formation and closure of the phagocytic cup, and in the flux of membrane during maturation and recycling from endosomes/phagosomes.

On the other hand, intracellular bacterial pathogens, and among them pathogenic mycobacteria such as *Mycobacterium tuberculosis* and *M. marinum*, evolved specific mechanisms to modify the bactericidal environment of the phagosome and proliferate within phagocytes. In particular, we discovered that both *M. marinum* and *M. tuberculosis* can escape from their vacuole into the cytosol, and are then ejected from the cell through an F-actin structure, we named the ejectosome.

Finally, the experimentally versatile Dictyostelium – M. marinum infection model provides a powerful and ethically un-concerning system to study mycobacteria pathogenicity, and we have recently used it in medium-throughput phenotypic screens to identify anti-infective compounds exhibiting no or little antibiotic activity.



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The full publication list can be found at: http://archive-ouverte.unige.ch/authors/view/1802

Keywords : phagocytosis, amoebae, mycobacteria, infection, host-pathogen interactions

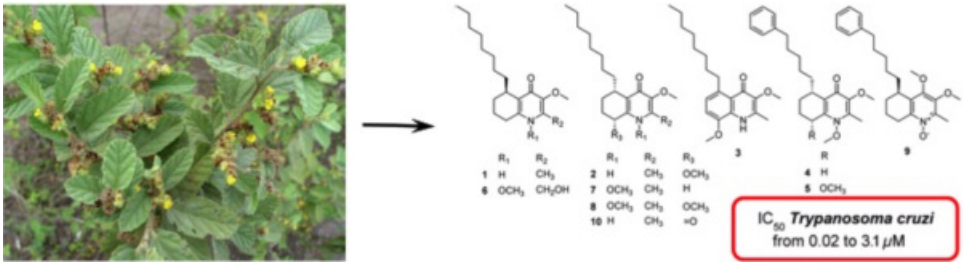
Contact : Thierry.Soldati@unige.ch


Muriel Cuendet / Philippe Christen

Pharmacognosy research unit

Muriel Cuendet earned her PhD in pharmaceutical sciences in 1999 from the University of Lausanne. From 1999 to 2003, she was a research associate at the Department of Medicinal Chemistry and Pharmacognosy, University of Illinois at Chicago, USA. She then became research assistant professor at the same institution until 2005, followed by 4 years at Purdue University, West Lafayette, IN, USA. In 2009, Dr Cuendet went back to Switzerland where she started her research unit as associate professor in the School of pharmaceutical sciences at the University of Geneva.
Philippe Christen obtained his PhD in pharmaceutical sciences in 1986 from the University of Geneva. Following postdoctoral studies at the School of pharmacy of the University of London, he was appointed senior lecturer in 1990 at the School of pharmaceutical sciences of the University of Geneva. His primary search interest is the discovery of new antiparasitic and antifungal natural products from plants used in traditional medicine.

Natural products as antimicrobial and antiparasitic compounds
The pharmacognosy research unit is focused on the discovery of bioactive natural products. As established by ample precedent, nature provides broad chemical diversity. Most antiparasitic drugs available on the market (when available) have a limited efficacy and strong side effects. Some plant extracts having shown good in vitro and in vivo activity are currently being investigated to uncover the compounds responsible for the activity and their mechanism of action. The absorption and the metabolism of pure compounds and phytopreparations are also being evaluated in vitro and in vivo



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Contact: muriel.cuendet@unige.ch / philippe.christen@unige.ch

Jean-Luc Wolfender

Phytochemistry and bioactive natural products

Jean–Luc Wolfender is a chemist, who completed a PhD in pharmacognosy with Prof. Kurt Hostettmann in 1993 on the metabolite profiling of bioactive constituents from the Gentianaceae. He performed his postdoc in UCSF in San Francisco on identification of conotoxins in venoms. He was appointed associated Professor at the University of Lausanne in 2000 and is now full Professor at the University of Geneva since 2009 and presently president of the School of Pharmaceutical Sciences.

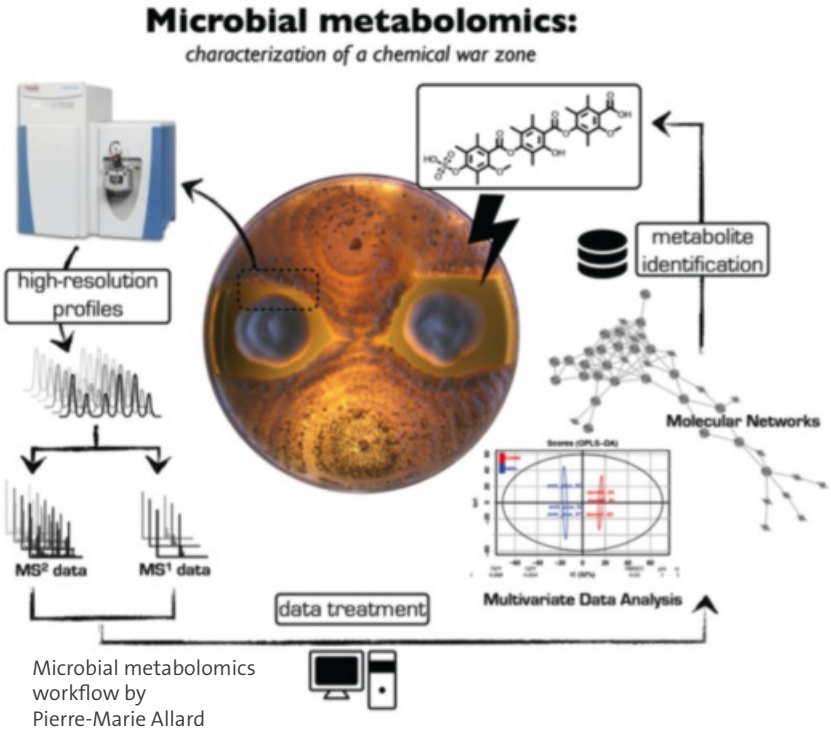
Development of innovative strategies for deciphering the composition of fungal and microbial metabolomes and study of their interactions by metabolomics

The identification of secondary metabolites in crude natural extracts at the analytical level represents a challenge because of their high chemical diversity. This is true for the dereplication of natural products (NPs) at the early stage of a bioactivity-guided phytochemical investigation to avoid the tedious re-isolation of known compounds. This is also strongly needed in metabolomics for the identification of biomarkers, key to better understand fundamental biological processes.

Our group has developed analytical strategies for high-resolution metabolite profiling of complex natural extracts from plant or microbial origin. For deep metabolome analysis, extracts are profiled by ultra-high performance liquid chromatography coupled (UHPLC) to high resolution mass spectrometry (HRMS), and tandem MS experiments are automated in a data dependent manner. This provides thousands of high quality HRMS/MS spectra that are used for automated peak annotation. In parallel we have developed a library of more than 300'000 MS spectra calculated in silico based on a structural database of all NPs reported today. The combination of the library with data mining methods, allowing to cluster together MS/MS spectra that share similar structural elements (molecular networks), allows extensive metabolite annotation. When new NPs are highlighted in this way, their targeted isolation monitored by MS at the preparative level is performed and full de novo identification is achieved with sensitive micro NMR methods.

Using metabolomics we are studying microbial interactions for the search of stress-induced compounds, key for a better understanding of their interactions. We have developed co-culture experiments that allow mimicking natural fungus-fungus confrontation. We have studied metabolites from the genus Fusarium, a frequent plant pathogen and major opportunistic fungus in patients with severe immunosuppression. This has led to the discovery of novel induced antifungal metabolites.

We are presently screening many fungal and bacterial strains of medical or ecological interest and study their interactions at the molecular level for identifying novel class of antifungal and antimicrobials to provide in depth fundamental knowledge of their interactions.



Microbial metabolomics workflow by Pierre-Marie Allard

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Contact: Jean-Luc.Wolfender@unige.ch

Faculté de Médecine
Université de Genève
1, rue Michel Servet
1211 Genève 4

Faculty of Medicine
www.unige.ch/medecine

Center of Excellence in Bacteriology (CEBUG)
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Cover:
Indirect immunofluorescence confocal microscopy image of human foreskin fibroblasts (not visible) infected with Toxoplasma gondii tachyzoites forming intravacuolar rosettes.

In red TgIMC1, a marker of the parasite inner membrane complex and in green TgMyoI, a myosin mother implicated in cell cell communication.

Karine Frenal

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