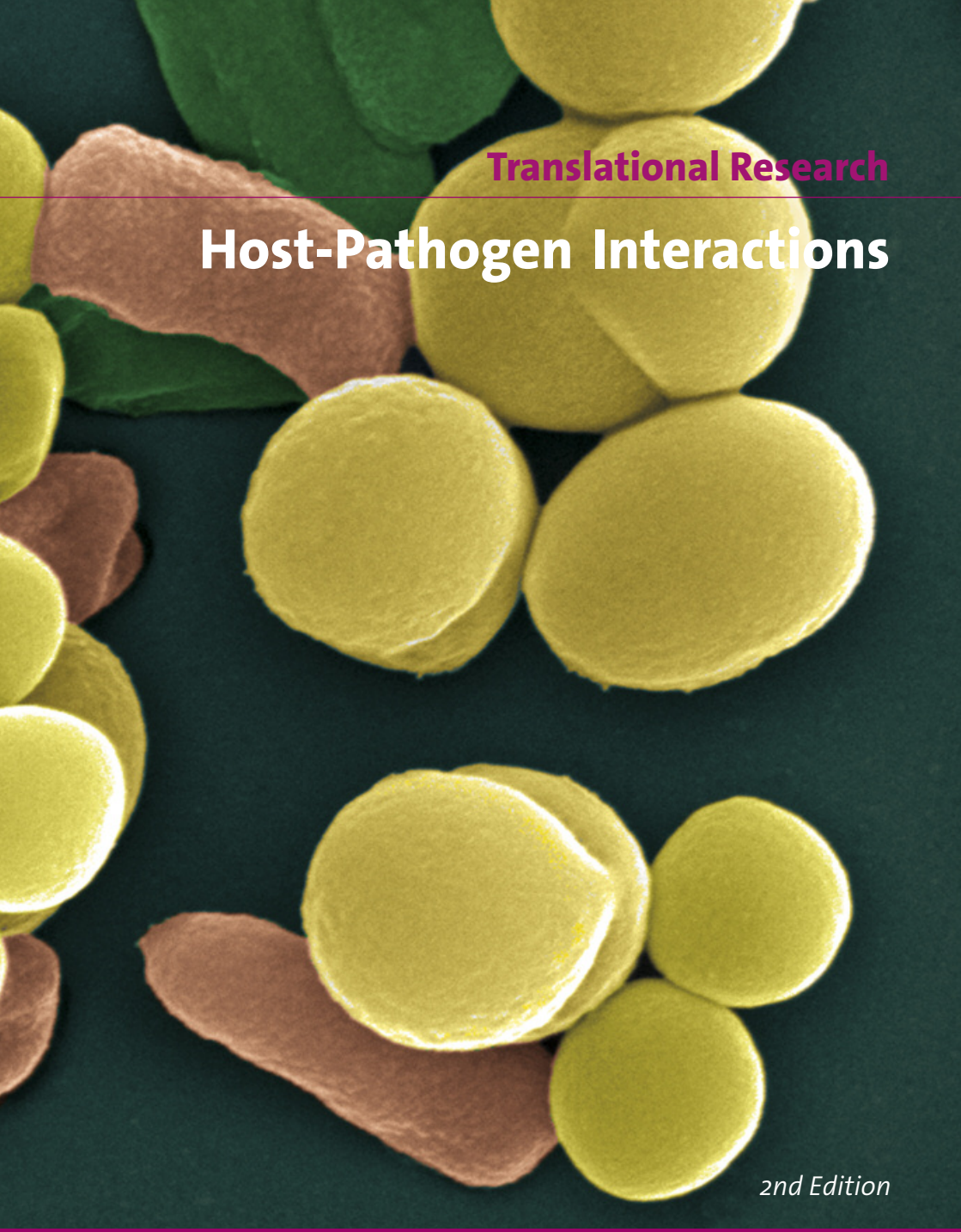


Translational Research

Host-Pathogen Interactions

2nd Edition

FACULTÉ DE MÉDECINE

UNIVERSITÉ DE GENÈVE

Microbiology and Immunology at the Faculty of Medicine of the University of Geneva

Microbes are not visible to the naked eye. Nevertheless, they represent approximately 98% of the total biomass and it is 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 this Microbiological universe. To coexist with these ubiquitous microbes, the human body has developed a sophisticated immune system, not only to defend itself against harmful organisms, but also to tolerate the presence of an astonishingly large number of bacteria. Indeed, the healthy human body requires the presence of a highly diverse microflora to digest certain nutrients, produce vitamins, stimulate the immune system, and defend itself against invading pathogens. The genetic heritage of human beings, the environment, and the ever-present microorganisms therefore shape our health. Thus, the threat of infectious diseases may vary from individual to individual and, at a larger scale, presents very different pictures in the industrial and the developing world.

Several years ago, the Faculty of Medicine of the University of Geneva made research on "Host-Pathogen Interactions" to one of its priorities. Research in microbiology and immunology encompasses a very broad field, from basic to clinical research, including the development of new powerful and rapid diagnostic tools. In addition to fostering translational research amongst clinical and fundamental research groups, the Faculty of Medicine has been renowned for its strength in humanitarian medicine, a field that also faces many challenges related to microbes.

Research at our Faculty includes a variety of microorganisms studied in different contexts: several bacteria, different classes of viruses, as well as two apicomplexa parasites and yeast are actively investigated from different perspectives. Several research groups approach the subject from the side of the host, either in fundamental research or in a clinical context. Inherent to this diversity, researchers use a wide range of approaches, from classical genetics to molecular techniques, including state-of-the-art nucleic acid analysis, proteomics and imaging.

Prof. Patrick Linder
Vice-President of the Fundamental Medicine Section

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

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. Our Faculty 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 (SMD). Research in microbiology is carried out in all of them as well as in many different departments. Host-pathogen interactions are thus studied through, a variety of techniques and from very different angles, which provides 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 emplois 1'810 people who contribute to first-class treatment of patients at the University Hospitals of Geneva, excellent research and pioneering teaching.

- 235 professors
- 994 staff in research and teaching
- 581 administrative and technical staff
- 1223 pre-graduate students (2011-2012)
- 880 post-graduated students (2011-2012)

An important reorganisation will take place in 2016, when research groups of the clinical section will be relocated to a new building next to the existing "Centre médical universitaire". In addition, diagnostic laboratories will move to the new HUG "Bâtiment des Laboratoires". Both these new facilities and the restructuration will create exciting possibilities for new interactions and new research programmes, involving basic and clinical research groups. Moreover, the Section of Pharmaceutical Sciences (Faculty of Sciences) will also move in these new facilities, extending even further the possibility of innovative interactions.

Host-Pathogen Research at the Faculty of Medicine and at the University Hospitals of Geneva

Fundamental Medicine

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

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 Anaesthetics, Pharmacology and Intensive Care (APSI)
- Department of Community Health and Medicine
  Division of Tropical and Humanitarian Medicine (HUG)

Dental Medicine

- Division of Parodontology
- Division of Cariology and Endodontics

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 microbology 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 and several optional courses and practical work are offered during second and third years .
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 Faculty of Medicine of the University of Geneva

Bacteriology

Virology

Parasitology

Mycology

Host Response

Bioinformatics

Vaccinology

Dental Bacteriology

Hygiene and Infection control

Dominique Belin

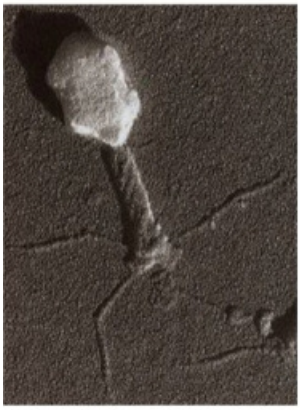
Department of Pathology and Immunology

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.

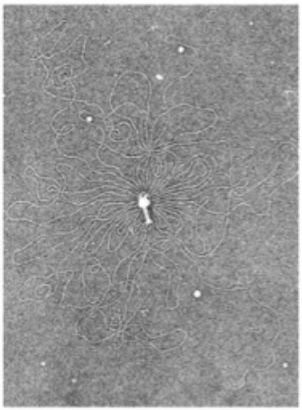
Genetic analysis of the translocation machinery in *E. coli* and of unknown genes of T4 bacteriophages

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.

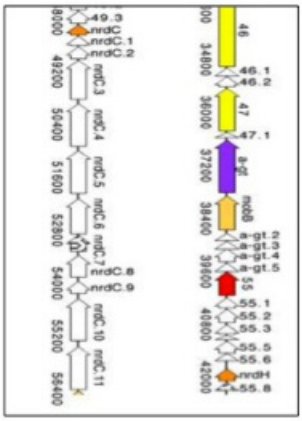
We are currently investigating the potential functions of phage T4 unknown genes. We have identified inserts that are toxic when expressed from inducible plasmids, and are concentrating our efforts on gene 55.1 and 55.2. High expression of 55.1 prevents growth while low expression confers a high sensitivity 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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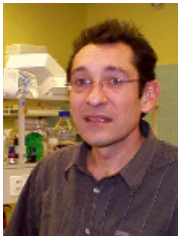
Keywords: Bacteriophage, phage T4, ORFans, E. coli genetics

Contact: Dominique.Belin@unige.ch



Patrice François

Department of Internal Medicine Specialties
Division of Infectious Diseases

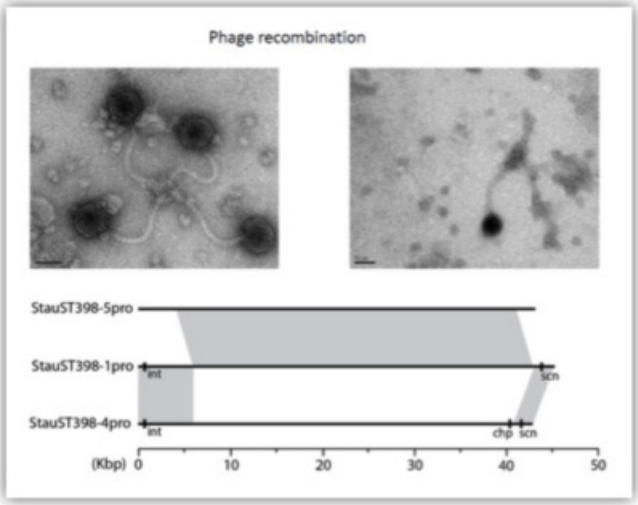
Patrice François obtained his PhD degree at the University of Paris XIII in 1996. In 2000, he was involved in the creation of the Genomic Research Laboratory at the University Hospitals of Geneva. His primary research interests are mechanisms of *S. aureus* adhesion to foreign body and roles of small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

Deciphering the virulence of *S. aureus* infections

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 the study the bacterium at the genome scale, we identified bacteriophage content as the basis of different features of this pathogen; adaptation against environmental stresses, host specificity and spreading as well as virulence and protection of genome integrity. Our main efforts target genomic regions that remain poorly explored to date, namely the segments considered as intergenic regions as well as mobile elements, in order to unravel the reasons responsible for "the success of *S. aureus*" in clinical or epidemiological settings in human and in veterinary infections. We are now characterizing small RNA molecules that we have discovered in *S. aureus* for their potential roles as regulatory RNA during infection. We are also studying mechanisms triggering their metabolism, their processing and their expression under specific conditions.

Expression of mobile elements is also one of our fields of interest as we recently identified bacteriophages as important mediators of genome plasticity and host specificity. These elements contain also important virulence factors and appear involved in the capacity of this important pathogen to invade non-phagocytic cells.

The aims of our research projects are to describe the molecular mechanisms responsible for these bacterial properties, which are crucial in the pathogenicity and virulence of *Staphylococcus aureus*.



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

Contact: patrice.francois@genomic.ch

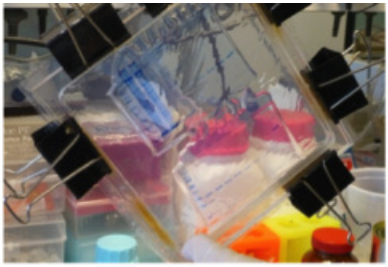
William L. Kelley

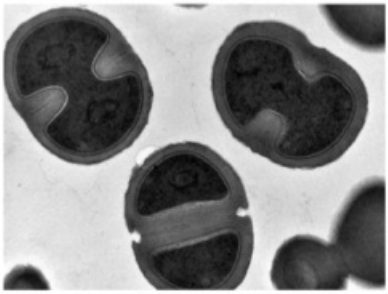
Department of Microbiology and Molecular Medicine
Department of Internal Medical Specialties
Division of Infectious Diseases

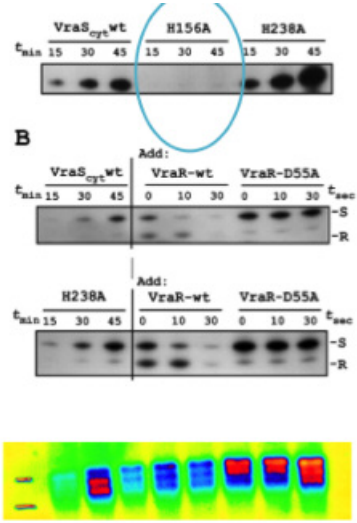
William L. Kelley graduated in 1981 from Williams College (USA), with a BA in Biology. In 1991 he obtained a PhD in microbiology-immunology with supplemental specialisation from the University Program in Genetics, Duke University Medical Center(USA). Following postdoctoral studies with molecular chaperones 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. 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.

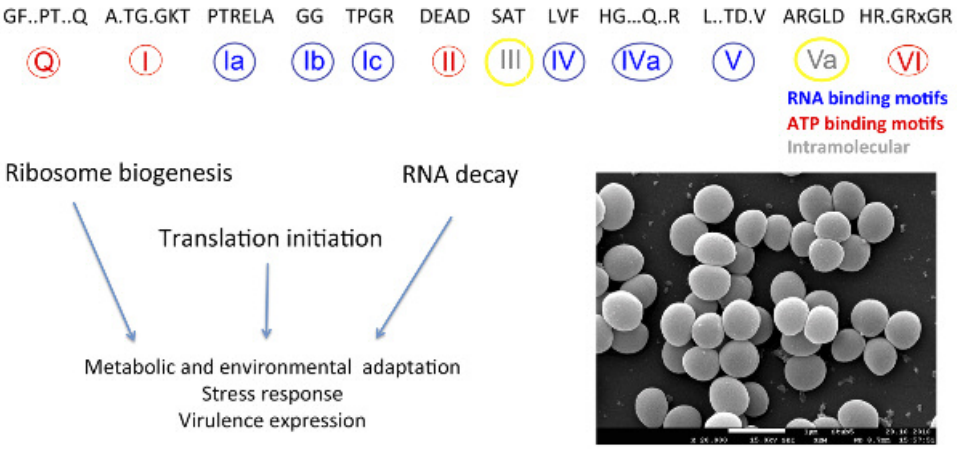
RNA metabolism and control of gene expression in *Staphylococcus aureus*

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. After studying DEAD-box proteins in yeast for many years, our group is at present analysing RNA helicases in the opportunistic pathogen *S. aureus*. Our main focus is the analysis of two RNA helicases, CshA and CshB, and their role in virulence expression and adaptation to different growth conditions.

One of the helicases is required for mRNA turnover of certain RNAs, including the agr mRNA encoding a quorum sensing system. RNA deep-sequencing shows that approximately 5% of the RNAs are stabilised in absence of the helicase. 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.

As an extension of this analysis, we are exploring the activities of the *S. aureus* RNases, that collaborate with CshA to degrade RNA. We have shown that RNase J1 and J2, which can cleave RNA both endonucleolytically and 5' exonucleolytically, are crucial at sub-normal growth conditions. Apart from their role in RNA decay, these enzymes are also responsible for maturation of essential factors, such as 16S rRNA and RNase P RNA.

In parallel to the analysis of RNA metabolism, our laboratory is continuously developing or improving methods to genetically tackle this opportunistic pathogen. Doing so, we have inactivated a restriction system to allow efficient transformation in our clinical strain. We also developed a selection/counter-selection system that is very useful in creating deletions or gene-replacements, even of genes that confer a very slow growth phenotype if inactivated.



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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* corresponding author; "Editors choice" in Science, selected by the Faculty of 1000 Biology.

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

Contact: Patrick.Linder@unige.ch

Adriana Renzoni

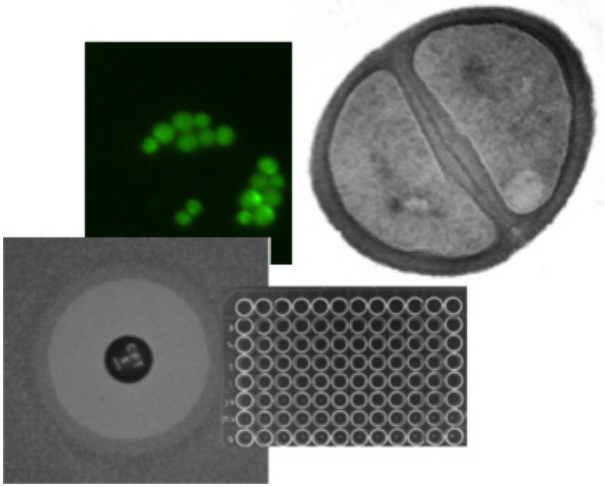
Department of Internal Medicine Specialties
Division of Infectious Diseases

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

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.

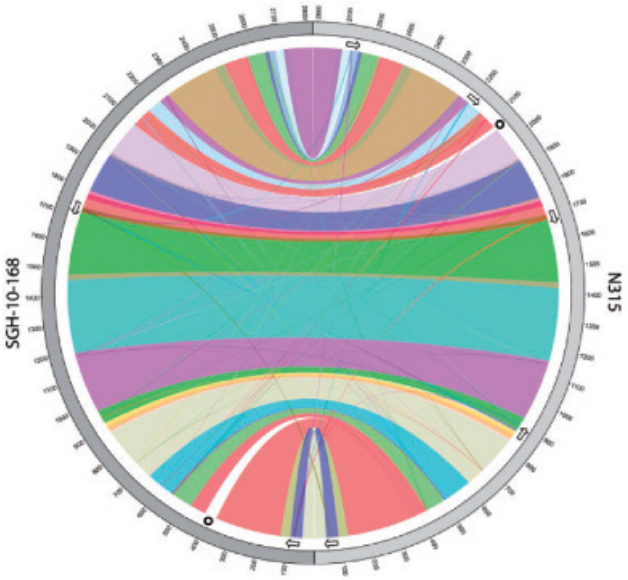
Persistence and virulence in *Staphylococcus aureus* infections

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 defences. 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. This explains the creation of our own bioinformatics group and the more recent development of research topics 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 high-throughput sequencing, 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 as evidenced by modifications in spreading, virulence and pathogenicity. Our main efforts involve genomic regions that remain poorly explored to date, namely the segments considered so far as intergenic regions, in order to unravel genomic elements responsible for "the success of *S. aureus*" in clinical or epidemiological settings. We are now characterising small RNA molecules that we have discovered in *S. aureus* for their potential roles as regulatory RNA during infection.



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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.

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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.

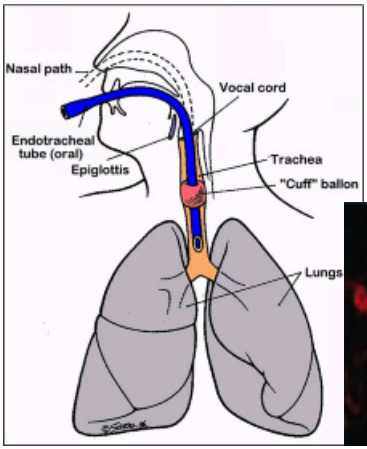
Thilo Köhler obtained his PhD in 1990 at the University of Geneva. After a two-year post-doctoral fellowship at the University of Berkeley, he returned to Geneva, and co-leads since 2003 a research laboratory in the Department of Microbiology and Molecular Medicine. He focuses his research on bacterial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

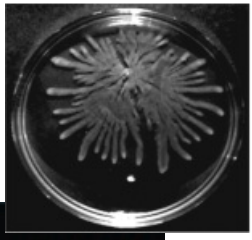
New approaches to combat *Pseudomonas aeruginosa* Infections

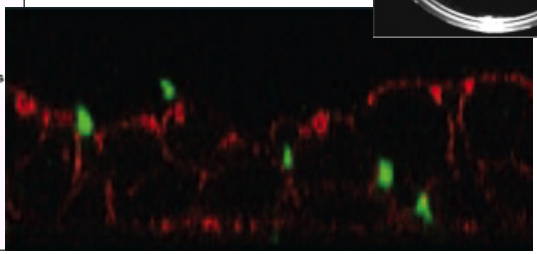
Our approach is translational, bringing clinical hypothesis and samples into the laboratory, and using metagenomics and molecular microbiology for both "*in patient*" and "in *vitro*" studies. With this approach we characterized the development of resistance upon therapy and identified Quorum-Sensing (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 (Roche Organ Transplant Research Foundation)
- 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

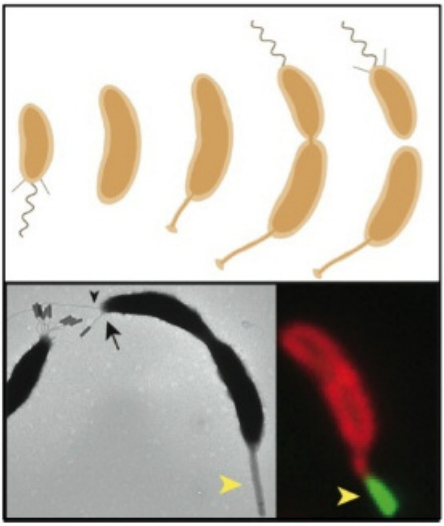
Departement. of Microbiology and Molecular Medicine

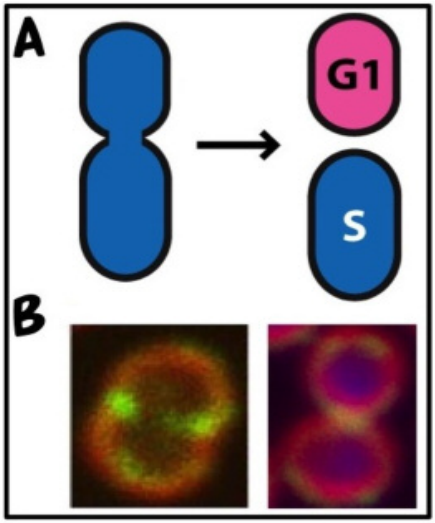
Patrick Viollier graduated in 1999 with a PhD in microbiology from the Biozentrum University of Basel (CH). After a four-year postdoctoral stage at the Stanford University School of Medicine (USA), he joined the Case Western Reserve University School (USA) of Medicine as assistant professor in 2004. 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.

Role of cell cycle control and polarity in virulence gene expression and antibiotic resistance

We study how cell cycle and polarity control virulence gene expression and antibiotic resistance mechanisms in Alpha-proteobacteria using the synchronizable and polarized bacterium *Caulobacter crescentus* as model system. Our comprehensive forward genetic and genomic approaches revealed that conserved transcriptional regulators of virulence/smybiosis gene expression in Alpha-proteobacteria can control a conserved cell cycle transcriptional switch from S-phase to G1-phase specific transcription during asymmetric division (A). We also explore bacterial polarization mechanisms and recently showed a polarity factor that protects aganist antibiotic sensitivity.

Lately, we have started investigating how strict intracellular pathogens from the *phylum Chlamydia*e assemble a division machine (B, immunolabeling false colored in green) in the absence of the conserved cell division organizer FtsZ and we are dissecting the role of the chlamydial cell wall in driving cell constriction.





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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 activites

The research projects conducted by the HIV/AIDS team are diverse. They 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 HAART.

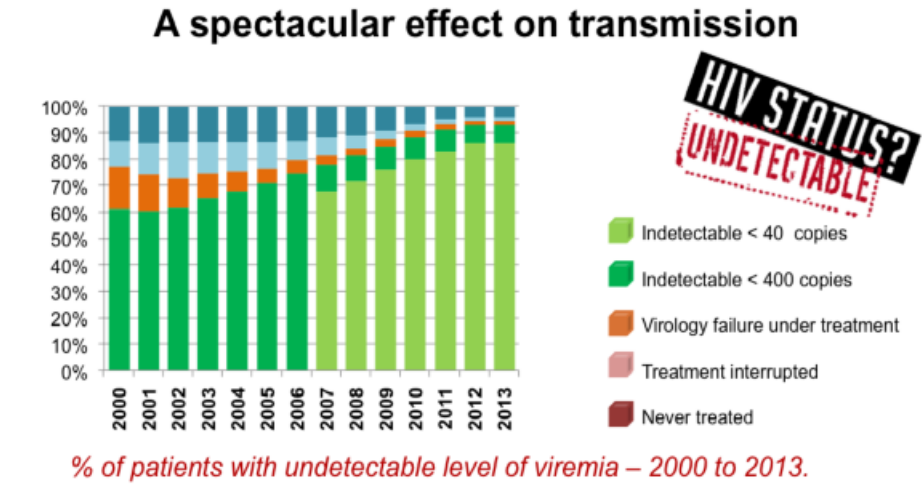
The clinical trials initiated by the research team focus on 1) progression of atherosclerosis in HIV patients under HAART after 48 weeks of lipid lowering drug intervention and 2) a Swiss multicenter trial designed to assess the need for a statin prescription in patients whose antiretroviral treatment was changed.

We are also interested in the early detection of bone anomalies with the use of a high resolution scanner for the analysis of the bone microstructure.

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. The center also participates actively in all the projects initiated by the Swiss cohort study.

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.

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). These partnerships allow us to study different epidemics and patient management systems; it also offers training opportunities and a large variety of study fields.



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 : acalmy@gmail.com

Dominique Garcin

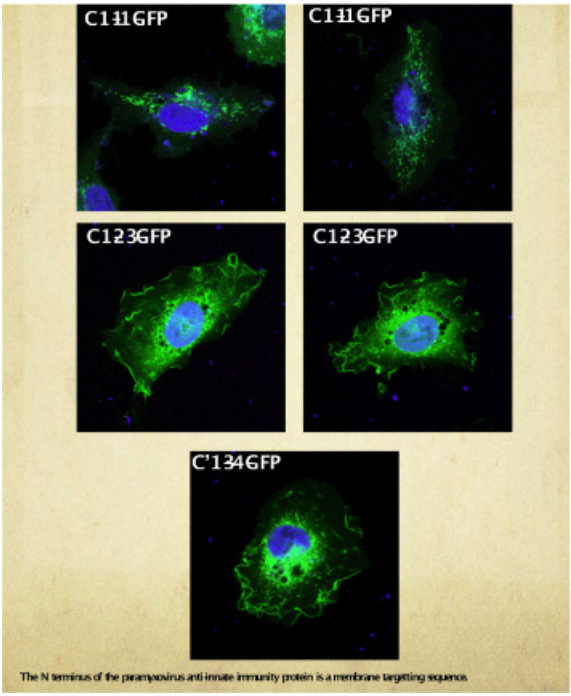
Department of Microbiology and Molecular Medicine

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.

RIG-I activation and regulation, and viral escape strategies.

Viral infections are responsible for extensive human and animal suffering and death, resulting in heavy human and economic costs. 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. Recent developments in this field now hold the promise of fighting viral infections by enhancing the innate immune response.

One of the perennial paradoxes of our studies is that the main determinant of the specific detection of an RNA virus infection is probably the molecule that is most abundant in a cell; i.e. RNA. The discrimination between self and viral RNA is based on specific features present only on these viral RNAs. Ipso facto these RNAs are central in the detection, the activation and also in the regulation of these processes. They also represent major players in viral escape strategies to escape innate immunity. Our studies focused on the cytoplasmic Pattern Recognition Receptors (PRR) member of the RIG-I Like Receptor (RLR) family, RIG-I, MDA5 and LGP2, their activation and regulation. On the other hand, our laboratory has long experience in studying negative strand virus (NSV) RNA synthesis, replication and their interactions with their host, in particular in the viral strategies to escape or counteract cellular innate responses.



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

Contact: Dominique.Garcin@unige.ch

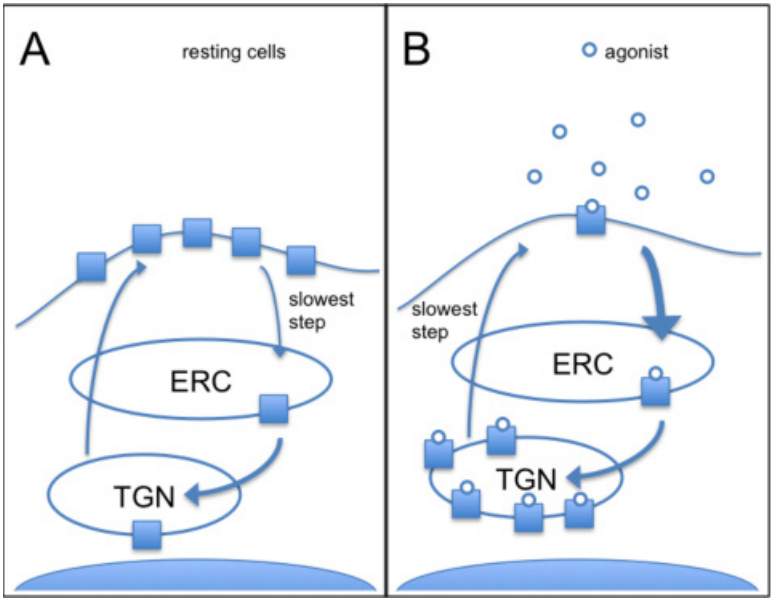
Oliver Hartley

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, and joining the Department of Pathology and Immunology in 2012.

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. A first clinical study of our best molecule is scheduled to take place at the HUG in 2014. 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

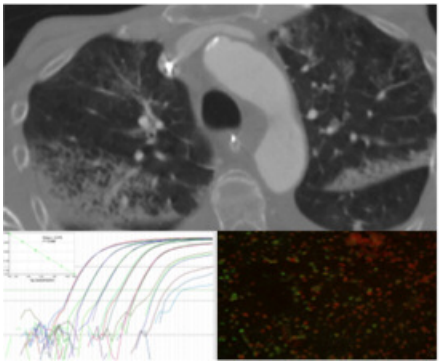
Laurent Kaiser
Department of Internal Medicine Specialties
Division of Infectious Diseases

Laurent Kaiser obtained his medical degree from the University of Geneva in 1987. He completed a full training in internal medicine and is board-certified in infectious diseases and clinical microbiology. He spent two years as Research Associate at the University of Virginia, Charlottesville, USA. Associate Professor at the Faculty of Medicine since 2006, he is the Director of the Laboratory of Virology at University Hospitals of Geneva. In 2013, he was appointed Full Professor and Head of the Division of Infectious Diseases.

Division of Infectious Diseases
The division provides high quality clinical care appropriate to a large university teaching hospital. Several staff members have developed an enhanced expertise in different fields of the speciality, such as general infectious diseases, transplant infections, joint-bone infections, clinical virology, and HIV-AIDS. All group leaders have their own research group (A. Calmy, J. Schrenzel, C. Van Delden). The division has established several close national and international collaborations with other divisions of infectious diseases and is recognized as one of the leading centres in Switzerland for the completion of a fellowship in infectious diseases or clinical microbiology.

Clinical virology
Based within University Hospitals of Geneva, the Laboratory of Virology performs more than 140,000 diagnostic procedures annually. It runs a complete panel of virological tests adapted to a large university centre caring for immunocompromised patients and transplant recipients. The goal of the team is to integrate the activities of a routine laboratory with the latest clinical developments, new diagnostic assays, and basic research in the field of virology. The laboratory also integrates and provides technical support to two national reference centres funded by the Swiss Federal Office of Public Health. It conducts influenza surveillance in Switzerland, including basic diagnostic capacities for unusual and rare viral diseases.

Clinical virology research includes all viruses with a special emphasis on respiratory infections. The latter group aims to investigate the clinical impact and epidemiology of respiratory viruses by using appropriate molecular assays. In particular, investigations have focused on the impact of respiratory viruses in immunocompromised hosts and European or African children. Close collaboration with basic research group, allows the investigation of unusual clinical observations in the field of clinical virology and promotes translational projects. The group also conducts investigations in the field of general clinical virology.



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

Contact: Laurent.Kaiser@hcuge.ch

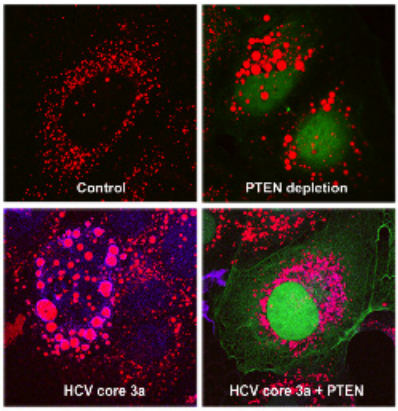
Francesco Negro

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 in Georgetown, University School of Medicine, Rockville, Maryland, USA from 1986 to 1989, and Guest Researcher at the Laboratory of Infectious Diseases at the National Institute of Allergy and Infectious Diseases, NIH, Bethesda, Maryland, USA in 1989. After having spent some time back in Turin, he joined the HUG in 1994. He was appointed Associate Professor of the Faculty of Medicine in 2006 and Full Professor in 2014.

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; factors/mechanisms of liver disease progression and resistance to interferon alpha-based antiviral therapy (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 and peripheral blood mononuclear cells), taken in the setting of various observational and interventional clinical trials.



PTEN-dependent large lipid droplet formation in HCV core 3a expressing Huh7 cells

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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

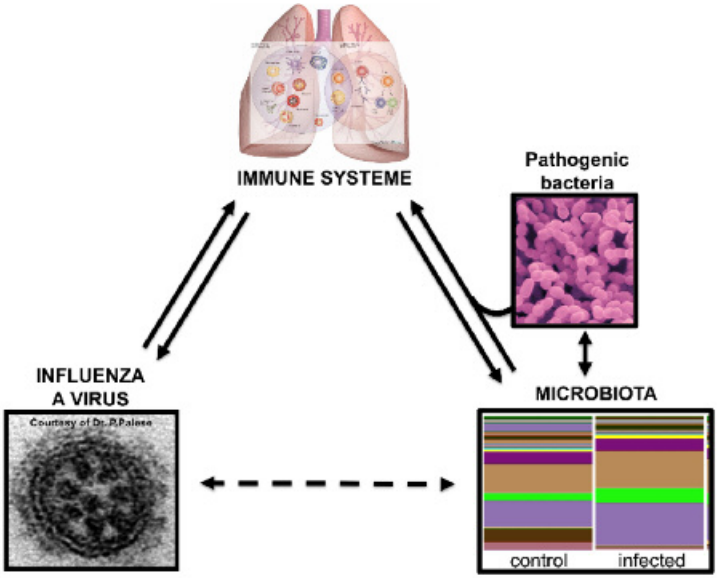
Mirco Schmolke obtained his undergraduate training in Biochemistry at the University of Münster in Germany and his PhD on "Mechanism of action of broadly neutralizing antibodies against the transmembrane protein gp41 of HIV" at the Robert Koch Institute in Berlin. He then spent five years as a postdoc 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.

Modulation of microbial communities in virus infected hosts

We use animal models to determine viral and host factors that influence bacterial super infections.

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. But viruses not only interact with their host, they also change replication condition for other microbes in the respiratory tract. This changes composition of commensal ("healthy") microbes and lays ground for invasion of bacterial pathogens. Bacterial super infections pose a serious problem in public health and the underlying molecular mechanisms are still matter of debate. Using influenza A virus in established mouse models we are investigating the triangular relationship of virus, host and bacteria.

In a second branch of research, we focus on immune-modulatory RNAs, which we are aiming to use as novel vaccine platforms. Systematic vaccination against infectious diseases was probably the main contribution to extension of life expectancy and increase of life quality since the late 18th century. Successful vaccines led to eradication of smallpox virus and quasi eradication of polio, being now endemic in only three countries worldwide. However, against other globally relevant diseases like HIV successful vaccine strategies are still missing or require continuous annual revaccination, as in case for influenza A viruses. New vaccine platforms are urgently needed to develop alternative strategies.



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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.

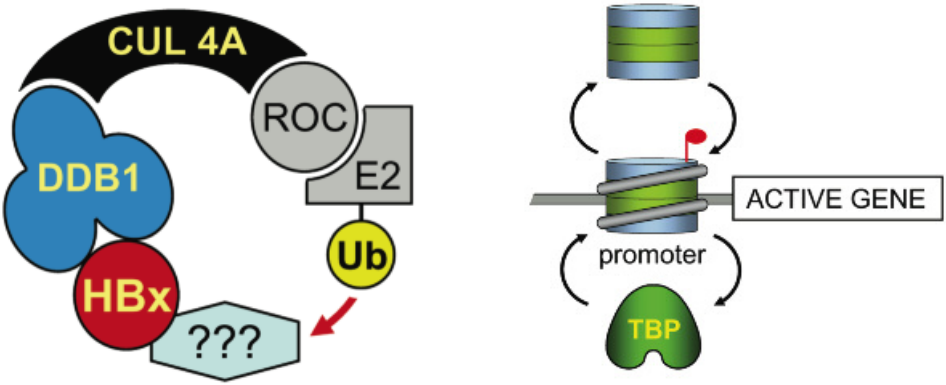
The HBx protein of Hepatitis B Virus and Regulation of Gene Expression

The HBx protein of hepatitis B virus

Chronic infection by hepatitis B virus (HBV) affects 350 million people worldwide and is a leading cause of liver cancer. The virus encodes a small protein, known as HBx, whose primary role is to promote transcription of the viral genome, which exists as an extrachromosomal DNA circle in the infected cell. We found that HBx accomplishes this task by triggering degradation of an as yet unrecognized cellular antiviral factor that somehow senses the viral DNA circle and blocks its transcription. We now aim to understand mechanistically how this newly discovered factor can act selectively on extrachromosomal DNA templates and why its destruction by the HBx protein is essential for HBV gene transcription. Because of its uncommon property and key role in the HBV life cycle, HBx may represent an attractive target for new antiviral therapies.

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.



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

Contact: Michel.Strubin@unige.ch

Caroline Tapparel Vu

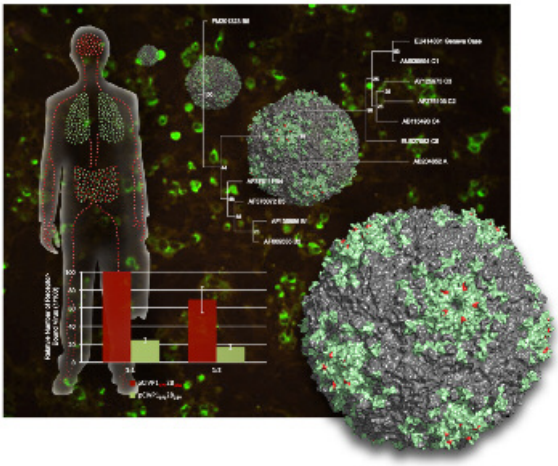
Department of Microbiology and Molecular Medicine
Department of Internal Medicine Specialties

Caroline Tapparel Vu obtained her PhD in Molecular Virology in 1998 at the Faculty of Medicine in Geneva. After a postdoctoral training in human genetics and bacteriology, she has set up basic research on rhinoviruses and enteroviruses in 2005 and is pursuing her investigations in this field since then. In 2014, she obtained the prestigious Sandoz Family Professor Fellowship, to pursue her work at our Faculty.

Identification of key viral and host factors modulating rhinovirus and enterovirus pathogenicity

Rhinoviruses (RV) and enteroviruses (EV) are leading causes of infections in humans. Although closely related within the *Enterovirus* genus of the *Picornaviridae* family, they are characterized by an important genetic variability, illustrated by the existence of more than 250 different types. This genetic heterogeneity is paralleled by an important phenotypic diversity. RV infection is mostly restricted to the respiratory tract, whereas EV can cause viremia, spread to multiple body sites, and have been associated with over 20 clinically recognized syndromes, ranging from common cold to encephalitis.

Our research group explores the pathogenic diversity of RV and EV. Using molecular, cellular and biochemical tools, we aim to determine and characterize the genetic factors that underlie clinically relevant phenotypic traits, such as virulence and neurotropism. Furthermore, we use three-dimensional human airway epithelia as models to study interactions between RV and hosts, or between RV and other respiratory pathogens. This area of research is essential in the perspective of development of antivirals and/or vaccine against these highly common infectious agents.



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Keywords: rhinovirus, enterovirus, diversity, adaptation, pathogenesis

Contact: Caroline.Tapparel@unige.ch

François Chappuis

Department of Community Health and Medicine
Division of Tropical and Humanitarian Medicine
Médecins sans Frontières

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 leishmaniasis and 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.

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

Contact: Francois.Chappuis@hcuge.ch

Dominique Soldati-Favre

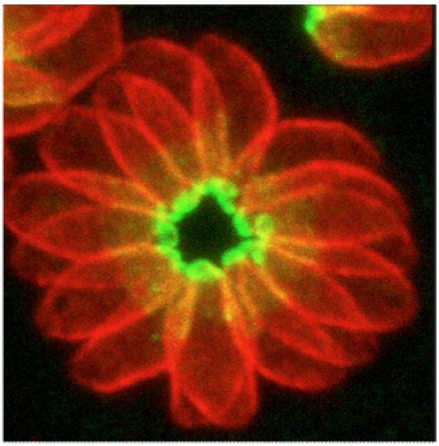
Department of Microbiology and Molecular Medicine

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 apicomplexan parasites. Gliding motility is a unique attribute of the Apicomplexa, 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 and the action of proteases on the components of the glideosome and other key factors 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 and central carbon metabolism as well as on the subversion of host cellular functions by effectors molecules that are critical to ensure successful infection.

Active host cell entry Intracellular replication



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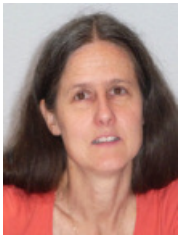
Keywords: Apicomplexa, Motility and Invasion, Metabolism, Organelles Biogenesis, Palmitoylation

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.

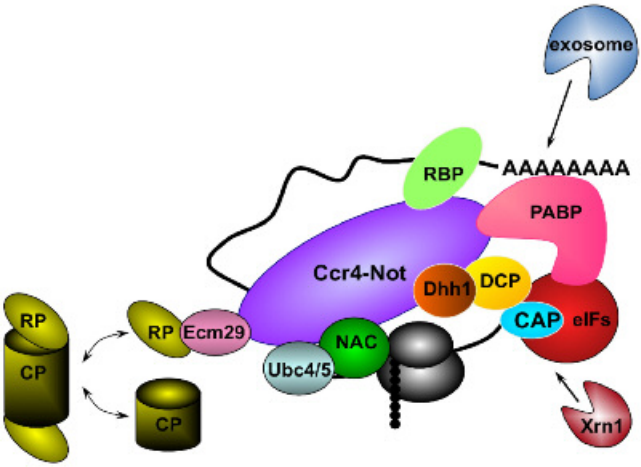
Genetic and Biochemical characterisation of the conserved Ccr4-Not complex in yeast

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

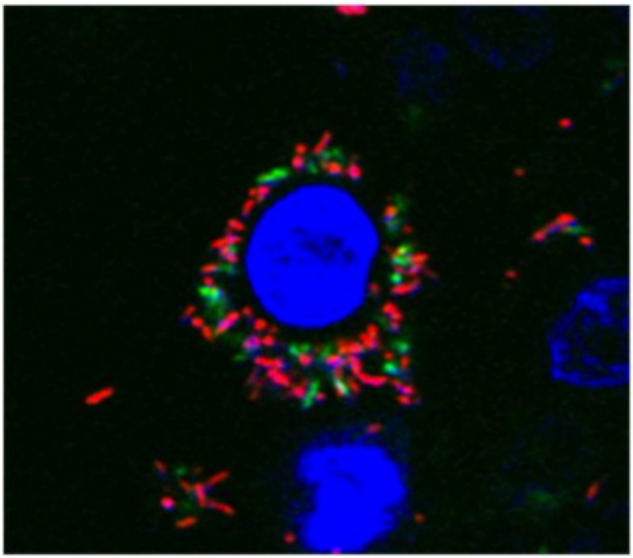
Marc Chanson

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

We are studying the regulation and function of gap junction channels in normal and inflamed lungs. Gap junctions interconnect ciliated airway epithelial cells that constitute the physical barrier between the host and the environment. In cystic fibrosis (CF), mutations of the cystic fibrosis transmembrane conductance regulator (CFTR), which is expressed in ciliated cells, alters the airway epithelium barrier. This impaired defence is associated with chronic infection and inflammation of the lung, leading to progressive loss of respiratory function. However, the links between the genetic defect in CF and initiation of the chronic infection of the airways are poorly known. We have found that CFTR regulates the activity of gap junction channels and that gap junctional intercellular communication contributes to the defence mechanisms of airway epithelial cells to infection. Thus, gap junctional intercellular communication induced by Toll-like receptor 5 activation in airway epithelial cells modulates the apoptosis/inflammation balance in a CFTR-dependent manner. More recently, we have observed that quorum sensing molecules produced by *Pseudomonas aeruginosa* (an opportunistic pathogen in CF) interfere with the function of gap junctions in airway epithelial cells. Further studies aim at the analysis of the underlying mechanisms and at understanding the consequence of gap junction channel deregulation in the pathogenesis of CF.



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

Pierre Cosson

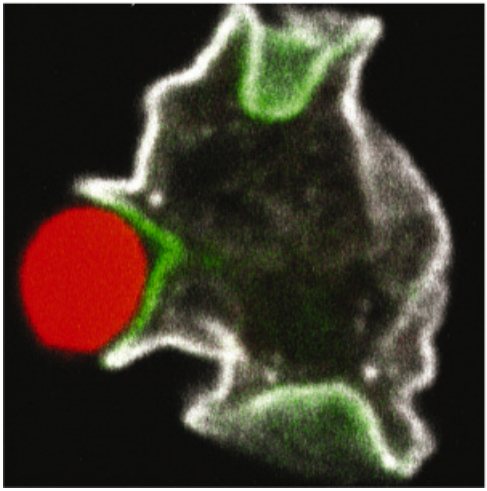
Department of Cell Physiology and Metabolism

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

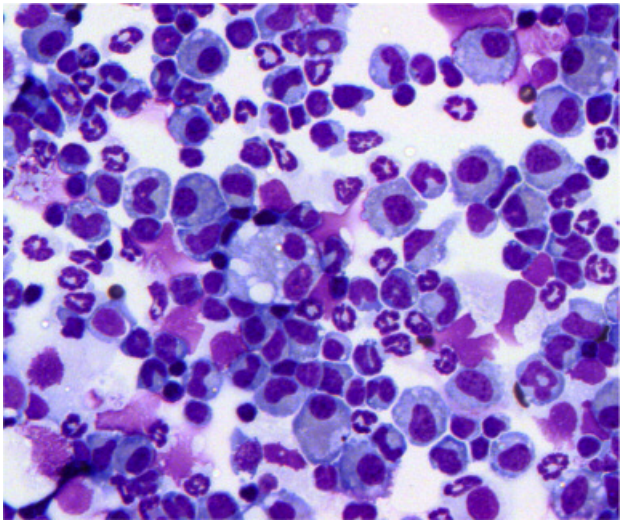
Irène Garcia-Gabay

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 Senior Lecturer at the Department of Pathology and Immunology.

Host defence mechanisms against mycobacterial infections

Our laboratory is interested in host resistance to *Mycobacterium tuberculosis* and *M. bovis* BCG infections. We are working on cellular mediators such as cytokines involved in innate and adaptive immunity to control these intracellular pathogens. We have long experience of Tumor Necrosis Factor (TNF), a pro-inflammatory cytokine activated by mycobacteria in phagocytes and T cells, which plays a critical role in granuloma formation and protection against mycobacteria. On the other hand, TNF is a main target for the treatment of inflammatory diseases and its inhibition may reactivate latent tuberculosis. We are evaluating the activity of the different TNF molecules and interactions with soluble and membrane-bound TNF receptors, to define the regulatory mechanisms involved in both host protection and inflammatory disorders in order to dissociate these two activities and propose new strategies of intervention in inflammation and infection. We are also evaluating how regulation of TNF and receptors can be manipulated during tuberculosis chemotherapy to improve bacillus elimination.



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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.

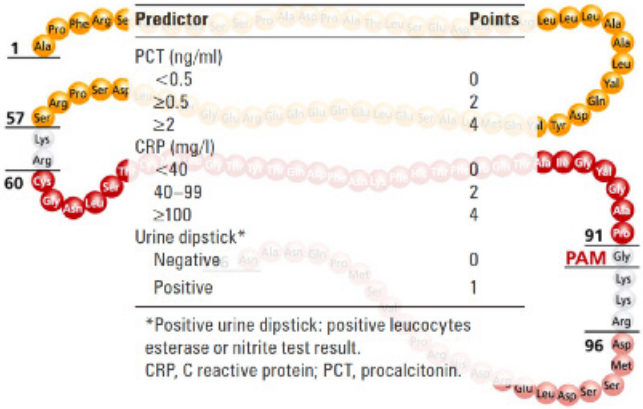
Streptococcus pneumoniae

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

Karl-Heinz Krause

Department of Pathology and Immunology

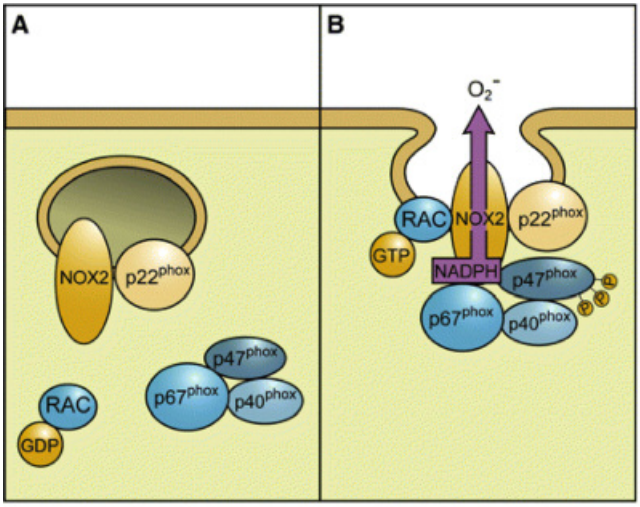
Karl-Heinz Krause obtained his medical degree in 1982 at the University of Munich, where he also trained in internal medicine. After Fellowships at the University Hospitals of Geneva (1984-87) and the University of Iowa Hospitals, USA (1987-89), he was recruited as a junior faculty member in Geneva. 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 (genetic NOX2 deficiency), diseases characterized by the concomitant occurrence of immune deficiency and hyperinflammation.

Neural differentiation of pluripotent stem cells

A second focus of the Krause laboratory is neuronal differentiation of pluripotent stem cells. Such differentiation protocols can be used to generate in vitro human neural cells and tissues. This is particularly relevant for the creation of human model systems for diseases of the central nervous system. Among others, we are using the system to study viral infection of the human CNS. Also, we are working on the response to tumor invasion of human neural tissues, which in many respects can mimic antiviral responses.



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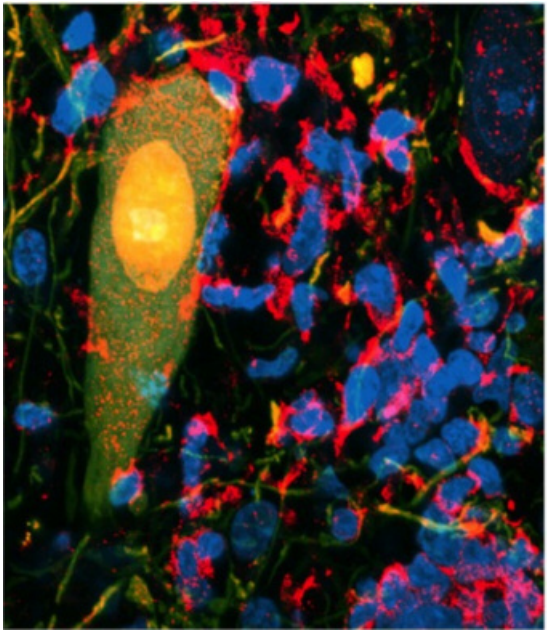
Keywords: NADPH oxidase, reactive oxygen species, infection models, pluripotent stem cells, neurons

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 (organized by J. Zapf) and worked as Postdoctoral Fellow at the University Zurich (Prof. ME Schwab). He continued his medical education to become a licensed neuropathologist at the University Medical Center Göttingen (Germany) and worked as research Fellow at the Institute of Experimental Immunology in Zürich (Profs. Zinkernagel and Hengartner). In 2010, he was awarded a SNSF Professorship Grant. He is also working as consultant in neuropathology in the division of clinical pathology (Department of Pathology and Immunology) 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 an experimental model system the role of viral infection early in life for the precipitation of CNS autoimmunity. For this purpose we are exploring a reverse genetics system for lymphocytic choriomeningitis virus (LCMV) that was established in our laboratory. Using this technology, 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 following viral CNS infection and how these effector pathways can mediate neuronal alterations that will cause neurological deficits. Furthermore, to confirm the translational implication of our experimental observations, similar investigations are performed on human brain biopsies from patients with inflammatory CNS diseases. These studies are of relevance for the development of new 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 intensive trainings in paediatrics at the HUG, she followed from 2001 to 2004 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, where she was appointed Senior Clinical Associate in 2004 and Consultant in 2009. In 2011, she obtained her Privat-Docent. She is currently Head of the Paediatric Infectious Diseases Unit in the Department of Paediatrics.

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.

We also have several clinical research projects running, in collaboration with other groups. For example, we followed a cohort of patients with Chagas disease in Switzerland and Spain, and reported their treatment and outcome. 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. 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. A similar multicenter study is performed with babies with severe RSV infections. We continue our involvement in the Swiss Mother-Child HIV Cohort Study, and the Swiss Transplant Cohort Study by contributing to new research projects.

Comparison of whole-genome maps of *Bordetella holmesii* (left) and *Bordetella pertussis* (right). Red dots show the position of the IS481,

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Keywords: children, antibody, immune response, vaccine, immunosuppression

Contact: Klara.PosfayBarbe@hcuge.ch

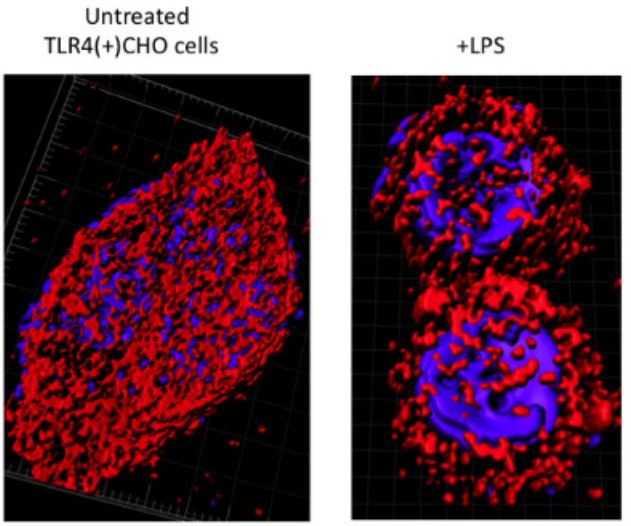
Jérôme Pugin

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.



LPS induced TLR4 clustering

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

Contact: Jerome.Pugin@unige.ch

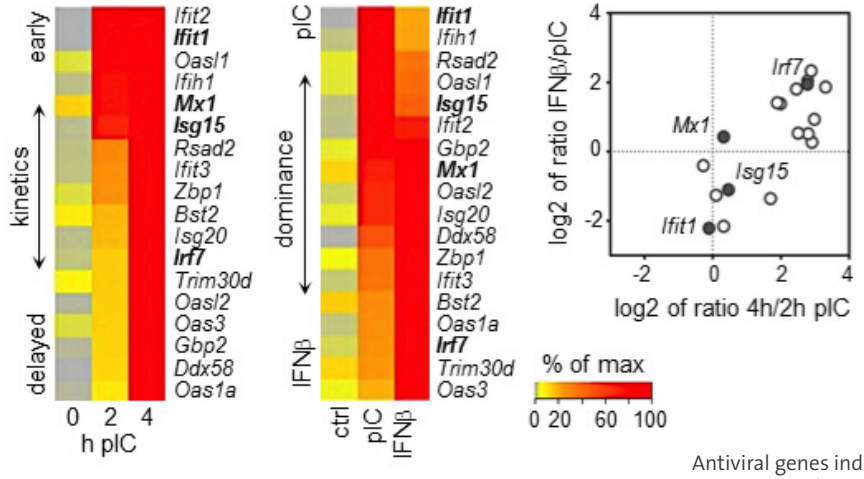
Walter Reith

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 is 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 and tumors. 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 (PAMPS) in human and mouse DCs.



Antiviral genes induced by the TLR3-agonist poly-IC and/or IFNß in lymphoid-tissue resident CD8+ DCs

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

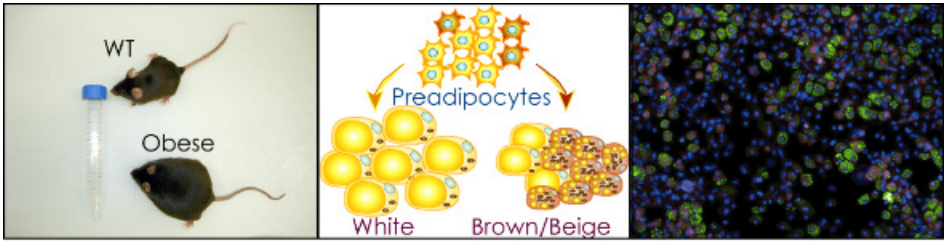
Contact: walter.reith@unige.ch

Mirko Trajkovski

Department of Cell Physiology and Metabolism
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 miRNAs in obesity and insulin resistance, which led him to be appointed Group Leader and Lecturer in Metabolism and Metabolic Diseases at the University College London (UCL) in 2012. In 2013, he was appointed Assistant Professor at the Faculty of Medicine of the University of Geneva and was awarded with a SNSF Professor Grant, still remaining affiliated to the UCL as Honorary Lecturer. In 2014 he obtained a prestigious ERC Starting Grant.

Adipose tissue plasticity and gut microbiota in obesity and insulin resistance.
Main interests of our lab are the molecular mechanisms underlining metabolic diseases, primarily obesity and insulin resistance. Promotion of increased brown fat development in humans and experimental mice leads to increased energy expenditure without causing dysfunction in other tissues, suggesting the manipulation of the fat stores as an important therapeutic objective. Our recent data indicate that miRNAs, a class of evolutionarily conserved regulatory RNA molecules, have a key role in modulating cell differentiation and metabolism of different tissue types, including adipocytes (fat cells)
The first part of our research aims at identifying metabolically active miRNAs and factors, and investigating their roles in animal models of obesity (primarily mice and rats), as well as in primary cultures of precursor cells using systems biology and targeted approaches. We also generate tools that enable us 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 (Fig. 1), and develop rational strategies to enable miRNA delivery and silencing specifically in the brown fat.
The second part of our research is focused on the role of the gut microbiota in the development of metabolic diseases, primarily dyslipidaemia and insulin resistance, and in particular the response of the host to the changes in the gut microbiota composition. A deeper understanding of these axes is a prerequisite for optimizing therapeutic strategies to manipulate the gut microbiota and the host response to combat disease and improve health.



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

Contact : Mirko.Trajkovski@unige.ch

Evgeny M. Zdobnov

Department of Genetic Medicine and Development

Evgeny M. Zdobnov obtained his PhD in 2001 from the Moscow Institute of Physics and Technology and the Engelgardt Institute of Molecular Biology RAS, Russia. He was appointed Associate Professor at the Faculty of Medicine in 2005, after his experience at the European Bioinformatics Institute (EBI) in Cambridge, UK, and, since 2006, at the European Molecular Biology Laboratory (EMBL) in Heidelberg, Germany. He is also a Group Leader at the Swiss Institute of Bioinformatics.

Comparative genomics

Genome and transcriptome sequencing is the most high-throughput and cost-effective method for comprehensive molecular interrogation of biological systems, enabling a remarkable array of subsequent studies at the molecular level. Advances in sequencing propelled the field from sequencing single genomes to sequencing all the DNA or RNA extracted directly from environmental samples (e.g. clinical specimens), revolutionizing our understanding of microbial complexity. However, raw DNA or RNA sequences are incomprehensible without comparing them to our current knowledge, and revising our knowledge from such data in the light of evolution. This is the subject of the field of comparative genomics, and the focus of our research. Genomics is unthinkable without computer data analysis, and so we mostly deal with devising computational analyses of the data and developing software to achieve our research goals.

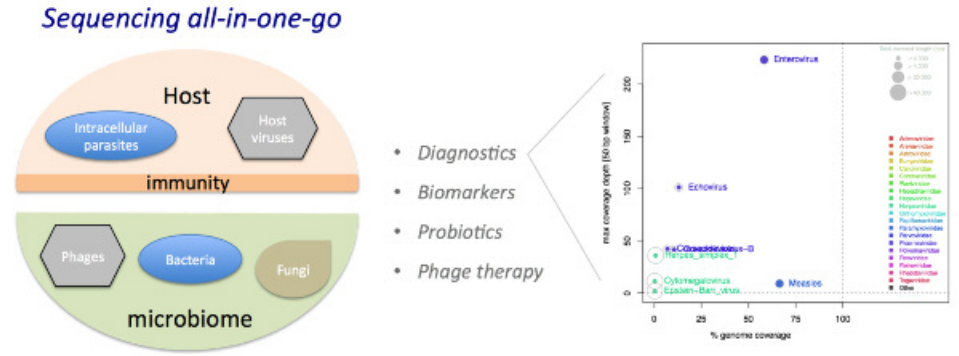
Our current research within the framework of host-pathogen interactions includes:

WGS metagenomics

- diagnostics (teaming up with L. Kaiser and O. Preynat-Seauve)
- vaginal microbiome (teaming up with D. Baud and B. Martinez de Tejada Weber)

Human innate immunity

- defining gene repertoire (teaming up with A. Telenti and J. Fellay)



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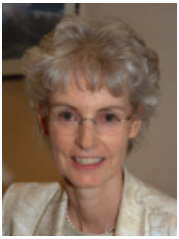
Keywords: Comparative genomics, metagenomics, diagnostics, microbiota, gene repertoire

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 focusses 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.

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

Contact: Claire-Anne.Siegrist@unige.ch

Serge Bouillaguet

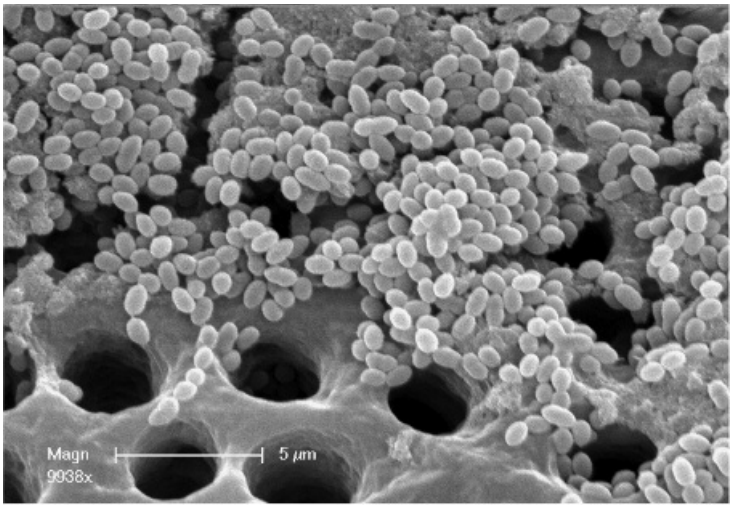
Division of Cariology and Endodontics

Serge Bouillaguet obtained his dental degree in 1983 and his Doctorate in Dental Surgery in Marseille 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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Bronnec F, Bouillaguet S, Machtou P (2010) Ex vivo assessment of irrigant penetration and renewal during the final irrigation regimen. Int Endod J. 43:663-72.

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

Contact: Serge.Bouillaguet@unige.ch

Andrea Mombelli

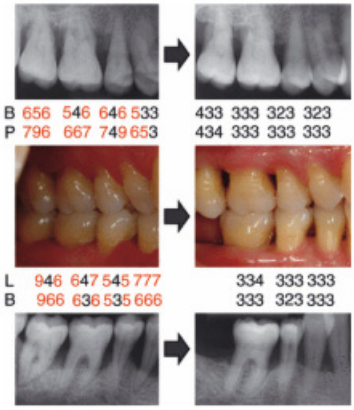
Division of Parodontology

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 FMH-certified periodontist. Before being appointed as Professor and Head of the Division of Parodontology, School of Dental Medicine of the Medical Faculty, he held the position of Head of the Laboratory for Oral Microbiology at the University of Bern School of Dental Medicine (1992-1999). Andrea Mombelli was associate Vice-Dean from 2005 to 2011.

Antimicrobial therapy as adjunct to mechanical periodontal treatment: Microbiological and systemic responses and effects on clinical outcome

Mechanical removal of bacterial biofilm and calculus from root surfaces is a well-established procedure in the treatment of periodontal disease. However, mechanical protocols alone are unable to eliminate all incriminated bacteria completely. Beneficial effects of adjunctive antibiotics on the clinical outcome of periodontal therapy have been shown, but many questions remain with regard to their optimal use and the specific relationship of benefit and risk. We study changes in the oral microbiota related to variation in clinical treatment protocols. Analyses focus on resistance development and diagnostic and prognostic utility of microbiological tests.

Does adjunctive antimicrobial therapy reduce the perceived need for periodontal surgery?



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

Contact: Andrea.Mombelli@unige.ch

Benedetta Allegranzi
Infection Control Programme
WHO "Clean Care is Safer Care" Programme

Benedetta Allegranzi obtained her medical degree in 1994 in Verona, Italy, and her post-graduate degree 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 Team Leader of the "Clean Care is Safer Care" programme at WHO HQ/PSP/IER. Dr Allegranzi spent the first twelve years of her career working as a general practioner and then became Assistant Professor in infectious diseases at the University of Verona, Italy, focusing on HIV, TB, treatment of critically ill patients, infection control and tropical medicine.

A worldwide perspective on infection control - prioritising settings with limited resources

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 Patient Safety Program "Clean Care is Safer Care", launched by WHO in October 2005. Dr Allegranzi's research activities, conducted in the context of the programme, have focused on hand hygiene, epidemiology of HAI worldwide, and HAI surveillance and infection control implementation in developing countries. In particular, through her work Dr Allegranzi has highlighted the burden of HAI in low-resource settings and has studied interventions to reduce it. She leads a global campaign on hand hygiene, which currently includes more than 15 000 healthcare settings worldwide and a network of 48 national campaigns.

Allegranzi B, Bagheri Nejad S, Combescure C, Graafmans W, Attar H, Donaldson L, Pittet D (2011) Burden of endemic healthcare-associated infection in developing countries: a systematic review and meta-analysis. The Lancet 377:228-41.

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

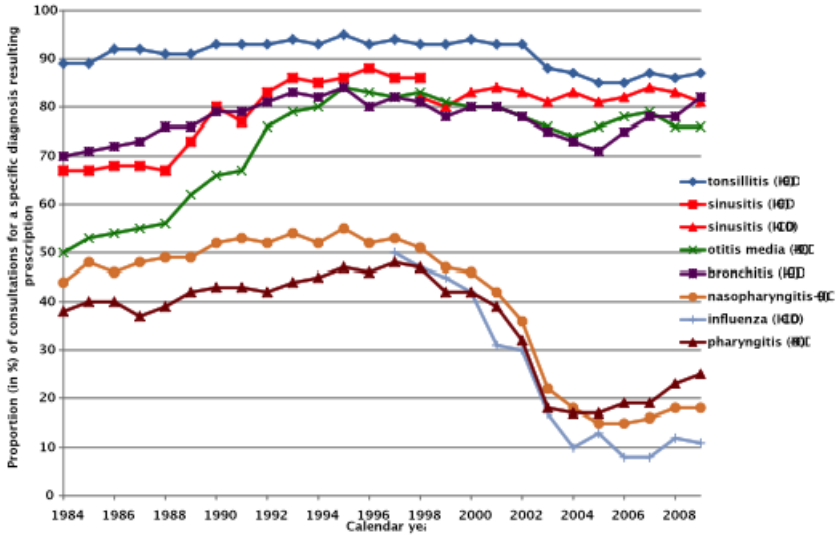
Stephan Harbarth

Department of Internal Medicine Specialties
Infection Control Programme

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 MRSA and multidrug-resistance

Over the last two decades many institutions around the globe have experienced an increase in hyperendemic multidrug-resistant microorganisms such as MRSA and ESBL-producing enterobacteriacae. 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 large-scale EU-funded studies (SATURN, R-GNOSIS, Rapp-ID, AIDA, COMBACTE) 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 burden of multiresistant microorganisms (JAC 2011, ICHE 2013), the conduct of epidemiologic studies linking patient data with molecular investigations (Clin Infect Dis 2011, ICHE 2014), the evaluation of antibiotic stewardship interventions (Lancet Infect Dis 2010, JAC 2011) and several placebo-controlled, randomised clinical trials to decolonise MRSA and ESBL carriers (JAC 2013).



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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

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 currently endorsed by two-thirds of the United Nations' Member States and currently active in 90% of countries worldwide. We have created a foundation for the prevention of healthcare-associated infection in the developing world, CleanHandsSaveLives.org (see also www.icpic.org)

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

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

Faculty
www.unige.ch/medecine

Center of Excellence in Bacteriology (CEBUG)
www.cebug.ch

Maladies infectieuses (HUG)
www.hug-ge.ch/maladies-infectieuses

Institute of Genetics and Genomics of Geneva, **iGE3**
www.ige3.unige.ch

Centre for Clinical Research
crc.hug-ge.ch

Genomic Research Laboratory
www.genomic.ch

Core Facilities
www.unige.ch/medecine/RECHERCHE/corefacilities_en.html

For citation of information within this booklet,
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or Patrick Linder

The bacteria on the cover picture are:
Bacillus megaterium, Staphylococcus aureus, Micrococcus luteus, Pseudomonas aeruginosa, Escherichia coli.
The scanning EM micrograph was colored artificially.

Dr. Karl Perron
Dr. Fanny Cavat

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