Message from the SCCL Leadership

Welcome to the Swiss Cancer Center Lausanne!

In spite of great advances in knowledge and in the practice of cancer medicine, cancer remains a devastating problem. One in two men and one in three women will be affected by cancer in their lifetime, and for far too many we still have no enduring therapies. The complexity of the cancer problems requires innovative approaches, bold investments and effective clinical translation.

The new Swiss Cancer Center Lausanne was created to respond to the challenge of improving the treatment of human cancer. We are bringing together fundamental, translational, and clinical cancer researchers from the Swiss Federal Institute of Technology Lausanne (EPFL), the Ludwig Center for Cancer Research of the University of Lausanne, the ISREC Foundation, the University of Lausanne (UNIL), the Swiss Institute of Bioinformatics (SIB), and the University Hospitals of Canton Vaud (CHUV), along with our Geneva partners, the University Hospital of Geneva (HUG) and the University of Geneva (UNIGE), and other Swiss institutions. Our agenda is to create a highly integrated, multidisciplinary, and collaborative cancer research community, aimed at solving urgent cancer problems and ultimately developing exceptional care and innovative solutions for our cancer patients.

We bring together highly talented clinicians and nurses, clinical investigators, basic and translational biomedical researchers, chemists, biomaterial engineers and cell engineers, imaging experts, geneticists, mathematicians and bioinformaticians to foster innovative cancer research, with the intertwined goals to elucidate mechanisms of cancer and to apply such knowledge to the development of breakthrough therapies. We are building on decades of investment in research and clinical infrastructure in the region, to create one of the few integrated cancer centers in continental Europe.

We aim at bringing scientific discoveries to the clinic in record time, to improve detection, prevention and therapy of
cancer. In other words, we seek to reduce the burden of cancer, urgently, through team science.

We are a new organization, a work in progress, of transformation and change, and much still needs to be done. The Department of Oncology at the CHUV was launched on January 1, 2013, while the SCCL was officially announced on January 15, 2013. We are very proud of what has been accomplished already. Of course, many of the elements of the SCCL pre-existed its creation. For that, we are extremely grateful to our founding institutions and our supporters for the extraordinary investments they have made, and continue to make, to support our mission and our vision.

This report, the first we produce since the SCCL’s inception, summarizes our activities to date. It is by no means exhaustive, but we believe that it provides a clear view of our spirit, our direction, and most importantly of our potential.

We are excited to be part of this rare opportunity to build a new comprehensive cancer center and are enthusiastic to be engaged with such a diverse group of talented colleagues, in an era where technology and knowledge are coming together to advance progress in cancer medicine, presaging a future where oncology miracles will no longer be such rarities.

Professor George Coukos  
Director, SCCL

Professor Douglas Hanahan  
Vice-Director, SCCL
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1. **DISCOVER THE SCCL**

1.1. **WHAT IS THE SCCL?**

In January 2013, the CHUV, UNIL, EPFL and the ISREC Foundation unveiled their partnership plans for the creation of the Swiss Cancer Center Lausanne (SCCL). A letter of intent was signed by the leading institutions, laying down the common vision for outstanding cutting edge cancer research to offer the most innovative approaches to cancer sufferers.

The SCCL is an integrated research community resulting from a new partnership between CHUV, UNIL and EPFL, which will integrate their multidisciplinary cancer research programs with a common focus, to solve urgent cancer problems. The Ludwig Institute is envisaged to become a founding partner in 2015. In addition, we are building strong partnerships with the University of Geneva, its hospital HUG, and other Swiss institutions, and with our clinical colleagues in the Western region of Switzerland through the creation of the Swiss Romande oncology regional network. The combined strengths and complementary environments of the founding partners and our collaborators are central to the creation of unparalleled opportunities for discovery and clinical development.

Formative multidisciplinary interactions and collaborative efforts between clinicians, researchers and bioengineers in the SCCL will result in synergies and integration between cutting-edge basic, translational and clinical cancer research, paving the way for the development of innovative technologies and research programs, to allow direct translation of science to the clinic. SCCL’s global approach aims at boosting innovation and cutting-edge research to significantly improve patient longevity and quality of life.

At the heart of the Western Switzerland’s Health Valley, home to 450 biotechs, 300 medtech companies, 500 biomedical research laboratories, and 8 incubators, the newly created SCCL will play a catalytic role in fostering innovation in cancer medicine in the BioAlps network, the Life Science cluster of Western Switzerland.
1.2. KEY GOALS OF THE SCCL

The SCCL’s mission is to become an elite cancer center recognized worldwide for innovative technologies applied to cancer detection, prevention and cure, combining cutting-edge basic cancer research to rapid and effective translation to the clinic. The SCCL is therefore set to achieve the following goals:

**Cancer Detection and Prevention**

Cancer prevention by understanding and reducing environmental, behavioral or genetic risk factors and by boosting immunity, as well as developing methods for early tumor detection, including genetic testing and imaging approaches, is an important mission of the SCCL.

**Multidisciplinary Research**

The SCCL aims to set up an interactive and co-operative multidisciplinary environment that fosters synergy and integration across basic, translational and clinical cancer research frontiers, involving clinicians, scientists and bioengineers from multiple backgrounds, organized in focused thematic programs of excellence, to elucidate the molecular mechanisms underlying different forms of human cancer.

**Therapeutic Innovation**

The SCCL aims to develop new anticancer technologies in the areas of precision radiotherapy, immunotherapy, and targeted molecular drugs, and to test new mechanism-guided cancer therapies through clinical trials, with clear prospect of prolonging patients’ lives and improving quality of life.

**Inspirational Training**

The SCCL aims to train, mentor, support, and inspire the career development of future generations of cancer research scientists, cancer bioengineers, and cancer clinicians.
1.3. THE AGORA BUILDING – THE NUCLEUS OF THE SCCL

The ‘AGORA‘ Translational Cancer Research Building will become the SCCL’s flagship and a focal point of its operations, when it is inaugurated in early 2018.

Located on the CHUV campus, this visionary building, with its «open » architecture aimed to foster collegial interactions throughout, will gather up to 300 cancer researchers and bio-engineers as well as clinical researchers into thematic ‘neighborhoods’, facilitating ‘bumping’ intersections in a 9,000 m² space under one roof, as a community of experts united in the fight against cancer. The building will comprise three research lab floors, a mouse hospital, as well as imaging and molecular analysis facilities.

The “agora”, the public level of the building, is designed to create frequent daily interactions, where researchers meet by plan or by chance, as they sit at the café or transition through the building. The building offers also a visionary atrium fostering reflection, communication and planned or accidental encounters. The laboratory floors have comfortable spaces for informal meetings and interactions through the workplaces, and its design facilitates horizontal interactions within a given floor, as well as vertical interactions across floors, through ample transparent staircases. Open, continuous lab spaces eliminate barriers among groups, and give ample flexibility for constantly reshaping research. Offices are clustered to enhance interactions among leading investigators, and generous space is dedicated to clinicians and bioinformaticians.
“Both interdisciplinary and disciplinary communication as the central element of successful research will be evident in the organization of the floor plans. Communication plays a central role both inside and outside the entire building” commented prize-winning architect, Stefan Behnisch, at the opening of the competition exhibition on CHUV premises in January 2013.

The ISREC Foundation is funding the construction of the building, the cost of which is estimated to be 80 million CHF.
1.4. FOUNDING INSTITUTIONS - AND KEY INSTITUTES AND CENTERS

UNIL - University of Lausanne

The University of Lausanne was founded in 1537. Today, it hosts more than 14,000 students and over 4,000 collaborators, and has an annual budget of CHF 458 million. Through its various faculties, UNIL dispenses top-quality pre- and post-graduate training and enjoys an international reputation as a research institution. In 2013, the CWTS Leiden Ranking ranked the University of Lausanne 45th globally and 22nd for Citations per Publication, while the Shanghai ranking classified it as 40th institution globally.

The Faculty of Biology and Medicine (FBM) is home to a top-level medical and life sciences research center. It is driven to foster creativity and innovation in the fields of basic and clinical research as well as synergies between biology and medicine in favor of fundamental sciences, medical sciences and the benefit of the community.
The Ludwig Institute for Cancer Research is an international non-for-profit organization with a 40-year legacy of pioneering cancer discoveries by the world’s leading cancer scientists. The Ludwig Institute conducts its own research and clinical trials, making it a bridge from the most basic questions of life to the most pressing needs of cancer care. The Institute has an expansive research presence through its branches and collaborative laboratories around the world and is a part of a broader community that includes six US-based Centers. Together the Institute and the Centers comprise Ludwig Cancer Research.

The Lausanne branch was created in 1975 under the direction of Jean-Charles Cerottini devoted to the study of the interactions between the immune system and cancer, particularly the immunobiology of cytolytic immune cells such as CD8 T lymphocytes and NK cells. Since its inception in the Lausanne scientific environment, the branch has steadfastly nurtured world-class research in tumor immunology and cancer immunotherapy. During the 70’s and 80’s, scientists in the Lausanne branch made major discoveries on the molecular events underlying CD8 T cell recognition of antigens and in the understanding of their role in anti-tumor adaptive immune responses.

Following key strides in the field of T cell immunity, the branch launched a translational research program in the early 90’s devoted to the study of human T cell responses in cancer patients with a specific focus in the immunotherapy of malignant melanoma. This was followed by a series of phase I clinical trials of peptide immunization using novel immunomonitoring assays and aiming at the optimization of vaccination via the testing of molecularly defined vaccine adjuvants. The Lausanne branch was the first to prove the great value of viral mimetic compounds such as Toll-like receptor 9 agonists associated with peptide vaccine emulsions in advanced melanoma patients.

In 2011, the Faculty of Biology and Medicine of the University of Lausanne entered an agreement with the Ludwig Institute to jointly support a Lausanne Ludwig Center, as part of the integration of the branch to the University (LICR@UNIL).
EPFL - École Polytechnique Fédérale de Lausanne

The modern era of EPFL as a Swiss Federal Institute of Technology began in 1968, when the federal government acquired and reinvented a regional polytechnical school. Today, nearly 14,000 people study or work on campus, about 9,900 of these beings Bachelor, Master or PhD students. More than 125 nationalities are present on campus, with 48% of the student population being foreign nationals.

EPFL is considered to be among the world’s most prestigious universities in technology. The three most influential and widely observed international university rankings ranked EPFL No. 1 (Academic Ranking of World Universities) or No. 2 (QS World University Rankings, and Times Higher Education World University Rankings) in the field of Engineering and Technology in continental Europe in 2013–2014. QS World University Ranking 2014 ranked EPFL world’s No. 10 in engineering. Academic Ranking of World Universities 2014 ranked EPFL world’s No. 19 and Europe’s No. 3 in the Engineering, Technology and Computer Sciences subcategory, behind Cambridge and notably ahead of Caltech, Princeton and ETH Zurich.

EPFL
(figures from 2014 Annual Report)

- EPFL No. 1 in the field of Engineering and Technology in continental Europe in 2013–2014 (Academic Ranking of World Universities)
- 9,921 students, 3,894 collaborators
- 616 million CHF annual budget
Swiss Institute for Experimental Cancer Research (ISREC) at EPFL

The Swiss Institute for Experimental Cancer Research (ISREC) was created in 1964 as an independent cancer research foundation. Initially located at the CHUV campus and later in Epalinges, ISREC was integrated into the School of Life Sciences at EPFL in 2008, relocating to the newly constructed life science building at EPFL’s lakeside campus.

The ISREC faculty investigates a spectrum of fundamental biological systems that are variously co-opted or disrupted during the development of cancer. Prominent amongst the research topics are signaling pathways that normally regulate aspects of embryogenesis and organogenesis, and mechanisms orchestrating the cell division cycle and the maintenance of genomic integrity during cell proliferation.

Increasingly, genetically engineered mouse models of human cancer are being used to elucidate the roles of such signaling circuits and regulatory mechanisms in tumors, as well as the complex interplay of cancer cells with ostensibly normal cells in their collective "tumor microenvironment". ISREC is developing a novel strategic plan to directly study mechanisms of cancer in model systems and in human tumors, notably involving outreach to the medical oncology community in the region.

Prof. Douglas Hanahan assumed the direction of ISREC in 2009. ISREC, with 15 research groups engaged in cancer and cancer-related biomedical research, positioned EPFL – along with its Institute of Bioengineering – to become a major force in cancer research in Switzerland, and an important component of the SCCL. In 2014 ISREC celebrated its 50th birthday. Over 2,000 articles have been published by ISREC researchers in various scientific journals, notably in Cell, Nature and Science.
The Institute of Bioengineering (IBI) at EPFL

The Institute of Bioengineering sits at the interface of the life sciences and engineering. With over 40 research groups, led by faculty members with backgrounds in cellular, molecular or computational biology, chemical or mechanical engineering, medicine, physics or physical chemistry, immunology, or materials science and engineering, the IBI addresses questions in basic life sciences as well as their implications in human biology in health, disease, diagnostics and therapeutics.

Areas of research include systems ad computational biology; systems physiology and immune engineering; molecular, cell and tissue engineering; bio-optics and bio-imaging; and micro- and nano-bioengineering. Many of the IBI faculty members are focused on various basic biological questions related to cancer biology and medicine. Their dual affiliation allows application of the most advanced technologies to the biological and biochemical sciences, focused on translation into therapeutics and diagnostics.

The activities of IBI have contributed to the ranking of EPFL at the very top of bioengineering programs in the world.
The University Hospital of Lausanne has its origins in the early 1200’s. It became University hospital in 1890, linked to UNIL. Today, it is a highly technologically advanced 1,500-bed quaternary medical center employing over 9,000 people, with 1,350 doctors and over 3,000 nurses, and an annual budget of CHF 1.5 billion (2013 Annual Report data). Gathering together under one roof all types of medical specialties, equipment and state-of-the-art technologies, as well as internationally recognized research skills, the CHUV conducts both applied and clinical research in the field of cancer.

The CHUV has three key missions: Care, Research and Training.

**Care.** The CHUV offers specialized treatments in all medical areas. Patient care is at the heart of the hospital’s concerns. The CHUV aims to provide patients with the most adapted and successful treatment programs.

**Research.** The CHUV conducts clinical, translational and fundamental research activities in close collaboration with the Faculty of Biology and Medicine at UNIL. Such activities are developed in the field of cancer, among other fields, and include all types of cancer disease specialties under multidisciplinary centers equipped with state-of-the-art technologies. CHUV also develops research partnerships with EPFL, other Swiss University Hospitals and Medical Schools, and various Swiss and international institutions.

**Training.** As a university hospital, the CHUV participates in pre- and post-graduate training programs for clinicians, nurses and other health professionals, in close collaboration with the Faculty of Biology and Medicine at UNIL, with academic societies and the University of Applied Sciences of Western Switzerland (HES-SO) and its canton Vaud health academy (Haute Ecole de Santé Vaud), an important site for education in healthcare.
ISREC Foundation

The ISREC Foundation is a private non-profit foundation, established on 18 June, 1964, on the instigation of its president, Rodolphe Stadler, and its director and co-founder, Professor Henri Isliker. The ISREC Foundation began its operations by setting up the Swiss Institute for Experimental Cancer Research (ISREC). Since 2008, ISREC has been divided into two separate, independent entities. On the one hand, there is the ISREC@EPFL research institute, now integrated into EPFL, and on the other hand, there is the ISREC Foundation, recognized for its continuing visionary support of cancer research, most notably its lead role in the design, funding, and construction of the Agora Translational Cancer Research Building. 2014 marked ISREC’s 50th anniversary and over those years more than 150 Swiss and foreign personalities, including 4 Nobel prize winners, have sat on the foundation or scientific councils.

Today, the Foundation continues to make a significant contribution to the landmarks in the development of our understanding of cancer. Its mission is focused on three avenues:

- the AGORA Translational Cancer Research Building
- faculty development for the SCCL in the form of “ISREC Chairs” granted to ISREC@EPFL and CHUV-Oncology
- the provision of grants for the encouragement of biology or medical students participating in PhD programs on cancer research

In the period 2008-2014 the ISREC Foundation has invested over CHF 19 million in cancer research in the region. In addition, the commitment to build the Agora building corresponds to CHF 80 million.
The SCCL scientific neighborhood in and around Lausanne

Together, the founding institutions of the SCCL and the multidisciplinary research environment which they create, offer a reservoir of unique and complementary competences for the identification of key discoveries and the development of therapeutic breakthroughs.
1.5. GOVERNANCE OF THE SCCL

A Director and a Vice-Director, one from UNIL-CHUV and the other from EPFL, will lead the SCCL. The founding appointments are:

Professor George Coukos of UNIL-CHUV as Director, and Professor Douglas Hanahan of EPFL as Vice-Director.

The Leadership of the SCCL will be overseen and advised by a Board of Directors (BoD), which will initially include the Presidents of the three Institutions (or their designated representatives), the Deans of the Faculty of Biology and Medicine at UNIL and of Life Sciences at EPFL, and the Chairman of the ISREC Foundation.

The Director and Vice-Director will assemble an Executive Leadership Team (ELT) composed of faculty from the three institutions to assist them in guiding and operating the SCCL and its initiatives, including overseeing the operations in the Agora translational cancer research building and its essential connections to the other distributed sites of the SCCL. Additionally, the ELT will make recommendations to the stakeholder institutions on strategic planning and institutional investments, to maximize synergisms.

The SCCL will convene a Scientific Advisory Board (SAB) composed of internationally prominent cancer scientists and cancer clinicians to review the progress, near-term and mid-term strategic plans for the SCCL, adding scope and experience to complement that of the leadership team. The SAB will also advise the ELT on the initial and continuing occupancy of the Agora building.
1.6. **KEY NUMBERS 2013-2014**

**RESEARCH**

CHUV  
LICR@UNIL  
EPFL  
UNIL

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Over **CHF 2.5 billion** annual operating budget  
(CHUV, UNIL and EPFL collectively)

**CHF 70 million** annual budget for cancer research

Over **60** cancer research lab groups
1,500 new **oncology patients** (each year)

30,000 **outpatient visits** (each year)

20,000 **chemotherapy preparations** (each year)

127 open **clinical and translational studies**
NEW CLINICAL
AND
CLINICAL RESEARCH
SPACE
Planned 2015-2016

2,000 m² new outpatient clinical unit
1,400 m² new outpatient phase I space
1,150 m² new bone marrow transplant and cell immunotherapy units
700 m² GMP facility for immune cell manufacturing
NEW LABORATORY SPACE

Planned 2015-2016

8,000 m² laboratory space in Agora
3,500 m² laboratory space in Biopôle 3
750 m² new tumor analytical facility in CHUV
2. HIGHLIGHTS

2.1. KEY 2013-2014 HIREs

Professor Eric Raymond was recruited in 2014 through a highly competitive international search to the new position of chief of the medical oncology service at the CHUV. Candidates included leading clinicians and investigators from Harvard, MD Anderson, U Chicago, and many prominent European institutions.

Professor Raymond has over 200 scientific publications and is recognized as a world-class leader in first-in-human and early-phase drug development and a leading European medical oncologist. He has been responsible for the clinical development of oxaliplatin for colorectal cancer and Sunitinib for neuroendocrine tumors of the pancreas, from preclinical studies to registration. He also has extensive experience in translational research. Professor Raymond was appointed Full Professor at UNIL.

Professor Raymond initially developed his interests in pharmacology and participated in the development of many novel treatment protocols during his clinical research training with Professor Aimery de Gramont at the University Hospital of Saint-Antoine (France). He then joined Professor Daniel Von Hoff in San Antonio, Texas, to work on new drug molecules.

Back in France, he conducted several years of research in the Department of Medical Oncology at Gustave Roussy Institute, as head of early drug development clinical trials. In 2003, Eric Raymond succeeded in creating, *ex nihilo*, a department of oncology within both Beaujon and Bichat hospitals in Paris.
Professor Jean Bourhis, previously Chair of Radiation Oncology at the Gustave Roussy Institute in Paris, was recruited as the new chief of the CHUV Radiation Oncology Service in fall 2012.

Professor Bourhis has over 350 publications, and is one of the most prominent radiation oncologists internationally and an expert in radiation therapy of head-and-neck cancer. He brings world-class expertise in clinical radiation oncology, along with a strong sense of clinical innovation, and an advanced research program in radiotechnology and radiobiology. Professor Bourhis was appointed Full professor at UNIL.

Professor Bourhis became Professor of Radiation Oncology at the University of Paris in 1999 and was appointed Head of the Radiation Oncology Department at the Gustave Roussy Institute in 2002. He has been principal investigator of a number of clinical trials in Head and Neck Oncology, including several multicentric randomized trials. He coordinated several large-scale international collaborative meta-analyses, whose contributions have been recognized worldwide. He is also co-founder and co-chair of the GORTEC group, dedicated to conducting clinical trials in head and neck cancers.

Beside his clinical activities, he has a major interest in Laboratory and Translational Research. He spent a year at the Gray Laboratory in London and obtained a PhD in Molecular Oncology in 1992 at the University of Paris. Professor Bourhis was also scientific director of the research and development project ARCHADE in Caen (France) on Hadrontherapy (development of a cyclotron for proton and carbon ions acceleration) from 2008 until 2011.

From 2009 to 2011, Professor Bourhis held the position of President of the European Society for Therapeutic Radiology Oncology (ESTRO).
Dr Lana Kandalaft, was recruited in 2013 from the University of Pennsylvania, where she was Assistant Professor and Clinical Operations Director of the Ovarian Cancer Research Center, to head the new Center for Experimental Therapeutics, an integrated structure of clinical services and laboratory facilities in the Department of Oncology, which supports clinical and translational research at the CHUV and the Swiss Cancer Center Lausanne.

Dr Kandalaft has strong expertise in translational research and regulatory policies. She is interested in moving biologically-focused cancer research ideas into clinical trials, with the identification of novel translational cancer immunotherapies, including cancer vaccines, cell-based immunotherapy and genetically-modified cell therapy.

At the OCRC, Professor Kandalaft played a crucial role in the development and implementation of clinical protocols originating from laboratory discoveries. She submitted successfully to the FDA several IND applications for investigator-initiated clinical trials, including cell-based and gene therapy for cancer, working with researchers in the laboratory to conduct late-stage pre-clinical work required for the IND submission and with the regulatory team to assemble the applications. She also supervised the regulatory and clinical teams, to ensure compliance with regulatory authorities, and coordinated clinical trial conduct with the business team, the clinical team of nurses, sub-investigators, clinical fellows and core directors, to ensure a seamless clinical operation.
Professor Sandrine Faivre was recruited in June 2014 as Professor of Medical Oncology at the Department of Oncology at CHUV and joined the department in November 2014. She was Professor of Medical Oncology at the University Paris VII (Denis Diderot) and Head of the Clinical and Translational Research Unit in the Department of Medical Oncology at Bichat-Beaujon University Hospitals in Paris.

Prof. Faivre graduated and was board certified in medical oncology in 1998. Working on cell signaling associated with heterotrimeric G-proteins and their role in cellular invasion, she obtained her Ph.D. in cellular and molecular biology in 2002. After a post-doctoral fellowship at the Cancer Therapy and Research Center & Institute for Drug Development at the University of Texas in San Antonio, she spent 6 years at Gustave-Roussy Institute in Villejuif working on clinical and translational research in phase I-II clinical studies on early drug development. She has been investigator of a more than 100 phase I/II studies. More specifically, she developed trials with novel anticancer agents in head and neck cancers. She is a member of the American Association for Cancer Research, American Society of Clinical Oncology, European Society of Medical Oncology, and International Liver Cancer Association. She has published more than 140 peer-reviewed papers.

Prof. Faivre’s research includes clinical trials with novel molecules targeting cancer signaling pathways (including VEGFR, mTOR, MET, TGF-beta, CXCR4 inhibitors), the study of alternative imaging criteria of response to anticancer agents (including antiangiogenic compounds), to translational research investigating patient tumor and blood biomarkers of sensitivity to anticancer agents and to molecular pharmacology exploring sensitivity and resistance to anticancer agents using in vitro, in vivo, and ex vivo models of cancer.
Professor Lorenzo Alberio moved to the University of Lausanne and CHUV in April 2014, where he was appointed Associate Professor and Chief Physician in charge of the clinic of general hematology and the hemostasis laboratory at the CHUV. Lorenzo Alberio obtained his MD degree in 1990 at the University of Bern, Switzerland. He underwent training in internal medicine in Lugano, Locarno and Bern and went on to complete his education in hematology at the Department of Hematology and Central Hematology Laboratory, Inselspital, Bern University Hospital. He performed research at OU-HSC, Oklahoma City, USA, at the Theodor Kocher Institute, Bern and at the EFS, Strasbourg, France. In 2004 he was given the Venia Docendi and since 2009 he has been an Associate Professor at the Faculty of Medicine, Bern University.

Prof. Alberio’s research interests focus on the study of procoagulant COAT platelets and of heparin-induced thrombocytopenia (HIT).

Current research focuses on the signaling mechanisms underlying COAT platelet generation and the role of COAT platelets in hematological diseases, such as paroxysmal nocturnal hemoglobinuria, myelodysplastic syndromes, and myeloproliferative neoplasms. In addition, over the years, Lorenzo Alberio’s group has investigated mechanistic, diagnostic, and therapeutic aspects of heparin-induced thrombocytopenia (HIT), which represents a fascinating hemostatic paradox and a challenging diagnostic problem. He has particularly developed a Bayesian diagnostic approach in order to reach a rapid exclusion or confirmation of suspected HIT. Current interests are the development of a rapid functional assay for HIT and the dissection of platelet intracellular signaling events induced by anti-PF4/heparin-antibodies.
Professor Christine Sempoux was recruited in March 2014 as Professor of Pathology and Chief Physician at the CHUV Institute of Pathology, and started her new activities in the fall 2014.

She graduated as a MD at the Catholic University of Louvain (Belgium) in 1990, and obtained a PhD degree in Biomedical Sciences in 2002. She spent one year at Memorial Sloan Kettering Cancer Center and Mount Sinai Medical School in New York City (NY, USA) to increase her pathologist experience in digestive oncology and hepatology. From 1998 to 2014, she was a senior member of the Pathology Department at the “Cliniques Universitaires Saint Luc” (Catholic University of Louvain, Brussels, Belgium) and became Professor in 2005. She has authored more than 160 scientific publications. She is a member of the Laennec Liver Pathology Society, the Hans Popper Hepatopathology Society and the European Society of Pathology.

Prof. Sempoux has strong expertise in digestive pathology. Her research interests focus on three different topics, namely endocrine pancreas, colorectal cancer and liver. In endocrine pancreas, she studied congenital hyperinsulinemia, a rare disease affecting mostly neonates. In colorectal cancer, she showed the existence of a particular subgroup of patients with a peculiar p53 expression, mostly correlated with microsatellites instability but not always. In addition, her clinical group assessed the pathological response and impact on survival of several original clinical trials and she led, during several years, a central pathology review for the national program for the quality of care of rectal cancer (PROCARE). In liver, she is currently studying liver fibrosis in children after transplantation, intra-hepatic cholangiocarcinomas and other primary liver carcinomas phenotypes. In close collaboration with other pathology teams worldwide, she is also trying to understand and define malignancy in hepatocellular adenoma.
Professor Massimo Bongiovanni was recruited in February 2014 as Associate Professor and Chief Physician at the CHUV Institute of Pathology. He started his new role in July 2014.

Prof. Bongiovanni obtained his M.D. degree at the University of Turin (Italy) in 1996 and received the certification in Anatomic Pathology at the same university in 2002. He underwent trainings to improve his pathologist experience in neoplastic and non-neoplastic lung/pleural diseases at the University of Graz (Austria), and in thyroid cytology and histology at Massachusetts General Hospital (Boston, MA, USA). From 2003 to 2010 he was staff pathologist at the University of Geneva in Clinical Pathology, where he became Privat-Docent in 2010. From 2011 to 2014, he was Associate Director of the Institute of Pathology in Locarno. He is a member of several Pathology Societies and of the SwissNET.

His diagnostic expertise and clinical research activities are focused on thyroid lesions and the possibilities to apply molecular test to routine thyroid fine-needle aspirates. In particular, laser capture microdissection applied to routine cytological specimens has been proved to provide high quality material (DNA & RNA) for next-generation sequencing techniques. He is author of more than 80 scientific publications.
Dr. Elisa Oricchio joined the ISREC@EPFL in November 2014 as a tenure track Assistant Professor, supported by a career development award - sponsored chair - from Fondation-ISREC. She was previously a postdoctoral fellow at Memorial Sloan Kettering Cancer Center in New York (USA).

Her research focuses on the cancer genetics and its translation into new therapies. She combines genomic analyses of human tumors with functional in vivo studies to assess the role of genetic lesions in tumorigenesis, disease progression, and relapse under treatment. In particular, she uses mouse models to study the oncogenic action and therapeutic implications of key altered pathways in lymphomagenesis.

In September 2008, Elisa joined the lab of Dr. Hans-Guido Wendel at Memorial Sloan Kettering Cancer Center (MSKCC) as postdoctoral fellow and focused on the genetics of follicular lymphoma (FL). She developed a new mosaic mouse model of follicular lymphoma and she identified a new secreted tumor suppressor, the ephrin receptor A7 (EPHA7). In a subsequent work, using genomic analyses, she identified a more aggressive type of FL and she proposed a new combination therapy for high-risk FL patients. Recently, Elisa expanded her research beyond follicular lymphoma, she examined the risk of malignancy associated with stem cell therapies and she proposed to use a new cancer-specific failsafe mechanism in stem cell derived tissues.

Elisa Oricchio graduated in Genetics with highest honors in 2004 at University of Rome “La Sapienza”. During her PhD, she investigated the role of retro-elements in melanoma and prostate cancer and graduated in 2008 at the National Italian Institute of Health in Rome Italy.
Dr. Bruno Correia joined the EPFL Institute of Bioengineering in the fall 2014 as a tenure-track Assistant Professor in Immunoengineering. He was previously a postdoctoral fellow at The Scripps Research Institute, La Jolla (USA).

At the Scripps Research Institute, Dr Correia worked in the laboratory of Prof. Benjamin Cravatt on the development of chemoproteomics strategies to profile the druggable proteome. His main scientific interests lie in computational protein design and also in merging experimental in vitro evolution with theoretical techniques to engineer protein-based therapeutics. He is an expert in molecular modeling, structure-based protein design, immunogen design and algorithmic development for protein design.

Bruno Correia was trained as a biological chemist at the Universidade de Coimbra – Portugal, where he got his bachelor in 2004. He then obtained a PhD in Computational Biology at the ITQB-Universidade Nova de Lisboa and Instituto Gulbenkian Ciência. From 2007 to 2012, he was a PhD student in the laboratories of David Baker and Bill Schief at the University of Washington, Seattle, where he developed several novel algorithms for protein design with structural flexibility. He then used these algorithms to design novel immunogens for vaccine engineering. Notably, he was able to create the first computationally-designed immunogen which elicited potent neutralizing antibodies against the Respiratory Syncytial Virus (RSV) for which there is no vaccine available against RSV. This work provided the proof of concept for epitope-focused immunogens and their potential for the development of new vaccines.
Dr. Raffaele Renella joined the CHUV in January 2015 to serve as Attending Staff Physician in the Pediatric Hematology-Oncology unit and as the Director of its research laboratory. Since 2010, he has been active as a physician-scientist at the Boston Children’s - Dana Farber Cancer and Blood Disorder Center, Harvard Medical School, Boston (USA) where he was promoted to Faculty in 2013.

Dr. Renella attended medical school at the University of Geneva and completed training in Pediatrics at the CHUV in Lausanne (board certification in Pediatrics in 2007). After further training in Pediatric Hematology-Immunology and Stem Cell Transplantation at Hôpital Necker-Enfants Malades in Paris (France), he returned to the CHUV as Chef-de-Clinique before joining the MRC Molecular Hematology Unit at the Weatherall Institute of Molecular Medicine of the University of Oxford (UK). He was awarded a Lord Florey-Berrow Scholarship in Biomedical Sciences and obtained a PhD (DPhil) in Molecular Hematology for his work on the Congenital Dyserythropoietic Anemias in 2009. During his time in Oxford, he also held the position of Honorary Clinical Specialist Registrar at the Pediatric Hematology-Oncology Unit of the John Radcliffe Hospital. Subsequently, he joined the Boston Children’s - Dana Farber Cancer and Blood Disorder Center and Harvard Medical School in Boston (USA) where he completed a Clinical & Research Fellowship in Pediatric Hematology/Oncology and performed translational research within the laboratory of Professor David A. Williams. After a fellowship, he joined the Faculty of Harvard Medical School as Instructor of Pediatrics and was promoted to Attending Physician at both Boston Children’s Hospital and Dana-Farber-Cancer Institute.

Dr Renella’s main scientific interests are the study of the anomalies affecting hematopoietic stem cells along their differentiation, and the translation of discoveries in this field into therapeutic approaches for children with inherited and acquired blood disorders.
Dr. Steven Dunn joined the Department of Oncology, UNIL-CHUV, in February 2014 as Research Leader and Director of the Antibody Engineering Laboratory in Prof. Coukos’ group.

Dr. Dunn received his bachelor’s degree and Ph.D. in Plant Biochemistry from Exeter University (1988, 1992). After two post-doctoral projects and a period in the agrochemical industry as a Senior Scientist and Team Leader in plant and fungal target research, he switched to biologics drug discovery and spent time at Cambridge Antibody Technology (2001-2003) and Immunocore (2003-2009), in Oxford, UK, before joining Merck Serono in Geneva (2009-2013) as a Principal Scientist heading the Phage Display antibody platform. Dr. Dunn has developed expertise in the discovery and optimization of novel biomolecules with potential therapeutic, diagnostic and high-impact research utility, as well as the conception and design of novel molecular and cell-based engineering strategies for targeting solid tumors. He is also interested in understanding how best to assess the off-target and ‘danger’ potential of immune cells expressing engineered receptors.

Dr. Alexandre Harari joined the Department of Oncology, UNIL-CHUV, in November 2013 as Director of the Immune Development and Monitoring Core at the Center for Experimental Therapeutics.

Dr. Harari obtained his Master’s degree in Biology from UNIL in 1997. After a 3-month training period at the Burnham Institute in San Diego USA, he started his PhD in Lausanne with Prof Giuseppe Pantaleo on immune correlates of virus control. He then became the scientific chief of the Vaccine and Immunotherapy Center’s lab. In parallel, he also led the TB research unit. As main scientific achievement, Dr Harari was a pioneer in the association between T-cell polyfunctionality and immune signatures and effective control (e.g. Harari, Nature Rev Immunol, 2006). He also established a certified immune monitoring facility allowing robust analyses of vaccine-induced immunity (e.g. Harari, J Exp Med, 2008), which also led to the development of new immune-based diagnosis tools (Harari, Nature Med, 2011). To date, Dr. Harari is author of more than 60 peer-reviewed publications and the recipient of several awards.
Mrs. Kim Ellefsen joined the Department of Oncology, UNIL-CHUV, in December 2013 as Director of Operations at the Center for Experimental Therapeutics.

She obtained her master’s degree in Biochemistry from Montreal University, Québec, Canada. She has worked the past 15 years within public institutions and pharmaceutical companies. Her experience and competencies have been acquired in various activities especially at the international level, and in complex and demanding environments. She has developed strong expertise in the field of vaccine immunity in clinical trial and immunological assays. She has a large experience in clinical phase I and II vaccine trials, combined to management and coordination roles. For more than a decade, during her research period, she has been working in the field of antiviral and vaccine immunity and has developed a strong expertise in immunology and biochemistry. She has especially developed several assays to measure, characterize, quantify and monitor virus-specific and vaccine-induced T-cell responses.

Dr. Armand de Gramont joined the Department of Oncology, UNIL-CHUV, in September 2014 as Director of the new Drugs Evaluation Laboratory at the Center for Experimental Therapeutics.

Dr. de Gramont obtained his Master’s degree in Structure, Function and Protein Engineering from the Pierre et Marie Curie University in Paris in 2001. He did his PhD in the same university followed by a postdoc at the National Institutes of Health in Bethesda (USA) on cell cycle control. In parallel he was formed in translational research in oncology and biotechnology business development. He then became the head of a small biotechnology/service company in France until 2014. His main scientific interests are experimental pharmacology, tumoral and microenvironment heterogeneity, therapeutics and biomarkers development (de Gramont, Nature Rev Clin Oncol, 2015). Dr. de Gramont is secretary of the GERCOR IRC cooperative group dedicated to early drug development and translational research in oncology. He also serves as member of foundation and pharmaceutical company scientific boards.
2.2. AWARDS AND DISTINCTIONS

As well as its draw amongst high-caliber international research leaders, recognition of the newly formed SCCL is measurable through the attribution of several prestigious awards to many of its researchers, in support of their outstanding scientific contributions and multiple inter-laboratory collaborations to cancer research advancement.

Distinctions

The Honorific Lifetime Achievement in Cancer Research Award of the *American Association for Cancer Research* was awarded to **Prof. Douglas HANAHAN. 2014**

Professor Hanahan was at the same occasion elected:

**Fellow of the AACR Academy, 2014**
American Association for the Advancement of Science, Wachtel Cancer Research Award (Honorable Mention)

was awarded to Prof. Michele de Palma. 2013

American Society of Neuro-Oncology, Victor Levin Award

was awarded to Prof. Monika HEGI and Prof. Roger Stupp for their paradigm-changing discoveries and the continued impact of their discoveries on the treatment of patients with brain tumors. 2013

Member of German National Academy of Sciences, Leopoldina

Election as; Prof. Gian-Paolo Dotto. 2013

Pfizer Research Award

one of the main biomedical research awards in Switzerland, to Prof. Tatiana Petrova and her postdoctoral fellow, Dr. Amélie Sabine, for the excellence of their work in understanding lymphatic vessel formation in development and cancer, and in lymphedema. 2013

Doctor Honoris Causa, Universidad Nacional de Colombia

was bestowed upon Prof. Pedro Romero. 2013

Swiss Society of Thoracic Surgery Prize for the best clinical publication

to Dr Jean Yannis Perentes. 2013

The Ellsworth Lecture in Ghent, Belgium

to Prof. Francis Munier. 2013
Highly Cited Researcher, *Thomson Reuters*

Selection as; **Prof. Vincent Mooser. 2014**

*Swiss Society of Thoracic Surgery* Prize for the best clinical presentation

 to **Dr Thorsten Krueger. 2014**

*Swiss Society for Visceral Surgery* Award for best publication

 to **Dr Martin Hübner. 2014**

*Swiss Society for Research in Surgery* Award for best publication

 to **Dr Olivier Dormond’s group. 2014**

*Swiss Society of Urology* Award for best poster at the 70th Annual Assembly

 to **Dr Laurent Derré’s group. 2014**

*CIMT* Prize for best abstract at the 13th Annual Meeting

 to **Dr Nathalie Rufer’s group. 2014**

*European and Swiss Congress of Internal Medicine* Award for best poster

 to **Prof. Chantal Csajka, Prof. Laurent Decosterd, Prof. Chin Eap and Dr. Khalil Zaman. 2014**
Faculty of Biology and Medicine of Lausanne Award for clinical research

to Dr Solange Peters. 2014

New Grants

SCCL Investigators have won numerous highly competitive grant awards recently. The total amount of new grant contracts from the EU or from the Swiss federal government initiated in the period January 2013-June 2014 was collectively over CHF 20 million.

European Research Council (ERC) Advanced grant

to Prof. George Coukos to develop vascular-disrupting lymphocyte therapy for tumors (Antivessel T-cells). 2013-2018 (2.5 million €)

to Prof. Douglas Hanahan to study the mechanisms of and interplay between invasion and angiogenesis, leading to develop new strategies for cancer therapy. 2013-2018 (2.5 million €)

to Prof. Pierre Gönczy to study the mechanisms governing centriole formation. 2013-2018 (2.5 million €)

to Prof. Gian-Paolo Dotto to investigate the genetic/epigenetic basis of ethnic differences in cancer predisposition. 2013-2018 (2.5 million €)

European Research Council (ERC) Starting grant.

to Prof. Dietmar Zehn to study and identify the molecular mechanisms that enhance T cell-mediated immune responses in infectious diseases and malignant tumors. 2013-2018 (1.5 million €)

to Prof. Fabio Martinon for a research program entitled ER inflammation and dedicated to elucidate the molecular mechanisms and pathways emerging from the endoplasmic reticulum (ER) that regulate inflammatory and innate immune responses. 2012-2017 (1.5 million €)
EU FP7 grants (2 grants)

awarded to Prof. Pedro Romero, as work package leader on research related to cancer immunotherapy. 2013 (1 million €)

Horizon 2020 – Research and Innovation FP - Marie Skłodowska-Curie Actions

awarded to Prof. John Prior and Prof. George Coukos, as co-initiators of project on new personalized treatments using radioisotope beams, notably for treating ovarian cancer (consortium of 8 EU and 3 Swiss members). 2014-2018 (2.8 million €)

Eurostars-2 Eureka

awarded to Prof. John Prior, as co-principal investigator on project on new high-resolution, high sensitivity dedicated breast positron emission tomography scanner (5 EU partners). 2014-2017 (2.2 million €)

European Innovative Medicines Initiative grant

to Prof. Cathrin Brisken to develop new models for pre-clinical evaluation of drug efficacy in common solid tumors. 2011-2016 (650,000 €)

European Organisation for Research and Treatment of Cancer grant

*to Prof. George Coukos, Dr. Lana Kandalaft and Dr. Fernanda Herrera* for a phase II randomized clinical trial combining vaccination with chemo-radiotherapy in locally advanced cervical cancer. 2013-2017 (1.8 million CHF, amount granted to EORTC by INOVIO)

*to Dr. Anna Dorothea Wagner* (Principal Investigator) for a randomized clinical study on targeted treatment for early HER-2 positive gastric cancer, involving fifty European centers and seven Korean centers. 2014-2022 (6.8 million CHF, amount granted to EORTC by Roche)
Swiss National Science Foundation TransMed grant

to Prof. Douglas Hanahan, Prof. George Coukos, Prof. Olivier Michielin, Dr Krisztian Homicsko, Prof. Daniel Speiser, Dr Emanuela Romano, and Prof. Melody Swartz to conduct translational research projects including co-clinical trials multi-targeting oncogenic drivers, angiogenesis, and the tumor-promoting lymphatic microenvironment in melanoma. 2013 (1.9 million CHF)

Swiss National Science Foundation Sinergia grant

to Dr. Carlo Rivolta and Prof. Yvan Arsenijevic to develop a synergistic approach for the analysis and gene replacement therapy for FAM161 deficiencies. 2013-2016 (1.2 million CHF)

to Prof. Margot Thome-Miazza, Prof. Georg Lenz and Prof. Francesco Bertoni to investigate the molecular mechanisms underlying the development of aggressive B-cell lymphomas in order to develop new approaches for the therapy and diagnosis of these lymphomas. 2014-2016 (1.6 million CHF)

Swiss National Science Foundation professorship grant

to Prof. Dietmar Zehn to study and identify the molecular mechanisms that enhance T cell-mediated immune responses in infectious diseases and malignant tumors. 2013-2017 (1.5 million CHF)

Swiss National Science Foundation grant and FBM-UNIL

to Prof. John Prior, Prof. George Coukos, Prof. Jean Bourhis and Dr. Marie-Catherine Vozenin for the acquisition of a MicroPET/SPECT/CT equipment for preclinical molecular imaging. 2014-2015 (977,000 CHF)

Gateway Award, Rising Tide Foundation

to Dr. Solange Peters (Principal Investigator) for a Phase IB/II Study of Combination Treatment with Carboplatin/Paclitaxel and the Copper Chelator, Tetrathiomolybdate in Patients with Advanced Solid Tumors. 2014 (400,000 €)
The Lake Geneva area is home to numerous foundations with long tradition of funding cancer research.

Notable among them, are the ISREC and the Medic foundations, which collectively have invested over CHF 38 million in the period 2008–2014 in cancer research grants awarded competitively to SCCL members.

Another important foundation that issues highly competitive grants for biomedical research is the Leenaards foundation. Proposals must integrate scientists and medical doctors from Lausanne and Geneva. The Leenaards Foundation has invested over CHF 5 million in cancer research in the period 2004-2014. Several awards were won for cancer research in the period 2013 – 2014.

Leenaards Foundation Awards

to Prof. Michele De Palma (EPFL) and Prof. George Coukos (UNIL-CHUV) to develop effective combinations integrating antiangiogenesis therapy and immunotherapy for breast and ovarian cancer. 2013 (750,000 CHF)

to Dr. Anita Wolfer (CHUV), Prof. Elena Dubikovskaya (EPFL) and Prof. Yann Seimbille (UNIGE) for their work on targeted cancer therapy and the development of efficient tumor-specific chemotherapeutic agents. 2014 (750,000 CHF)

to Prof. Olivier Michielin (UNIL-CHUV), Prof. Douglas Hanahan (EPFL), Dr Krisztian Homicsko (CHUV) and Prof. Pierre-Yves Dietrich (UNIGE) for their work in understanding the role of cancer-associated fibroblasts in the development of resistance to malignant melanoma treatments. Nested Project 2014 (750,000 CHF)
3. SIGNATURE RESEARCH PROGRAMS

Integrating cutting-edge basic and clinical research, with the development of effective translational research, will allow the SCCL to accelerate transfer of innovation towards patient care and offer our cancer patients innovative and personalized treatments.

Our recent activities have focused on building four signature programs:

- Immune Therapy
- Molecular Oncology & Targeted Therapeutics
- Precision Radiotherapy
- Nuclear Medicine and Molecular Imaging

3.1. IMMUNE THERAPY

Background

Research on thousands of cancer patients over the past decade has shown that the body’s immune system can naturally recognize and attack tumors. Patients with spontaneous antitumor immune response can in some cases live much longer. Boosting this intrinsic immunity against cancer is now producing remarkable results for patients with certain cancers.

The Ludwig Center for Cancer Research of the University of Lausanne has decades of expertise in tumor immunotherapy. Ludwig Lausanne investigators were among the first to develop and test vaccines in melanoma and analyze reliably immune responses to tumors. Building on this expertise, our aim is to develop the new generation of effective immunotherapies using the most advanced technologies in protein and cell engineering.
Recent advances in understanding, on the one hand, how tumors can evade immune attack, and on the other hand, clarifying the requirements to elicit effectively antitumor immunity, along with major breakthroughs in antibody development, immune cell engineering, and immune cell culture systems, have collectively allowed the clinical development of potent immunotherapies that have produced major clinical benefit in a subset of cancer patients. However, important challenges remain. Many patients do not respond, while other respond partially or transiently.

Our immunotherapy program takes a systematic approach to the problem. Over 25 collaborating research laboratories of biomedical scientists, immunologists, bioinformaticians and bioengineers are working to understand fundamental mechanisms and to develop effective solutions, asking: Why can some tumors be attacked by the immune system, while others cannot? How do killer T cells differentiate, signal and function? Why does their killing ability become exhausted/enfeebled in tumors? What are the key factors involved in T cell suppression in tumors, and how can they be overcome? The Lausanne environment offers world-class expertise in immune and molecular analytical assays, advanced systems biology – both experimental and mathematical, along with computational biology, and bioengineering infrastructure to support groundbreaking initiatives.

Advanced protein and cell immune engineering labs are developing tomorrow’s molecular drugs, vaccines and cell therapies.

Thanks to the creation of one of the largest centers for T-cell manufacturing in an academic setting worldwide, and to visionary investments in hospital infrastructure, these therapies will be taken rapidly to the clinic in Lausanne.

**Therapy using genetically engineered T cells**

Genetic engineering techniques are now enabling the construction of designer T cells for new therapeutic applications affording unprecedented potency against human tumors.
Patients’ T cells are removed from the blood, processed in the laboratory, endowed with powerful new properties to recognize, invade and destroy tumors, and then infused back into the same patients (so called ‘personalized medicine’).

Genetic engineering entails introducing new receptor genes that allow T cells to recognize tumor-specific targets. Following adoptive transfer, a large proportion of circulating T cells are tumor-specific, a condition that has never been possible before, for example with vaccines. Taking advantage of deep expertise in T cell receptor cloning and optimization, as well as in antibody engineering and optimization, the Ludwig and other SCCL labs are developing promising receptors to be engineered into T cells with specificity against different tumor targets. Of particular interest are strategies that target mutated or highly specific tumor antigens, since these are expected to have increased specificity, sparing normal tissues. In addition, approaches that target the cancer stem cells or the tumor vasculature are being developed and tested, since if successful, they could have transformative effects as universal cancer therapies.

In addition to better recognizing human tumors, molecular and cell engineering is also presenting unprecedented opportunities for improving T cell function, endowing T cells with appropriate receptors to home to tumors and attack them; with fortified stimuli to allow them to kill limitless numbers of tumor cells. In addition, T cell regulatory programs can be rewired in the laboratory to make the cells more resilient, resistant to the adverse conditions of the tumor microenvironment. Additionally, T cells can be engineered to carry molecular “switches” making them amenable to regulation by innocuous drugs administered to patients. Several of these approaches are pursued in the laboratories of SCCL, and the best will be moved to the clinic.
Adoptive therapy using natural anti-tumor T cells

In addition to generating antitumor T cells through de novo engineering, many patients exhibit natural anti-tumor T cells in blood or in their tumors. The discovery that a proportion of solid tumors, from all tumor types, contain T cells that naturally exhibit antitumor activity presents important opportunities to activate this ‘natural’ immune response to eliminate a patient’s tumor. One approach entails isolating tumor-specific T cells from tumors and expanding them in the laboratory for adoptive therapy in which the cells are infused in vastly expanded
numbers back into the patients from which they originated. This approach has generated important results in melanoma, but has not been tested in other solid tumors.

We are developing methodologies that allow for the precise identification of tumor-specific T cells from tumors or from blood and their optimal expansion. Thus far, we have been able to demonstrate that powerful anti-tumor T cells can be expanded out of ovarian and breast cancers, melanoma, glioblastoma, and other solid tumors.

In addition, multi-antigen cancer vaccines can dramatically expand populations of tumor-specific T cells, which can be harvested from blood or tumors and expanded in the laboratory to produce billions of tumor-specific activated T cells for infusion back into the patient (adoptive therapy), amplifying the anti-tumor immune response.

The genetic engineering opportunities described above, aimed at enhancing the functional properties of T cells during adoptive therapy, can also be employed to genetically manipulate naturally arising anti-tumor T cells to render them hyperactivated and tireless. This offers the potentially important advantage that such ‘super endurance’ T cells continue to recognize and attack tumors via their naturally selected recognition of tumor but not normal tissue antigens, having been selected for such specificity in the patient’s body, thus enhancing safety.

**Cancer vaccines**

The successful development of powerful immunomodulatory antibodies and other compounds that reduce the immunosuppressive microenvironment of tumors has renewed interest in cancer vaccines. Since vaccines expand the pool of endogenous T cells attacking cancer, combinations with immunomodulators appear very attractive.

The Ludwig Lausanne environment has contributed pioneering work in vaccine development in the last three decades. Building on this excellence, we continue to pursue development of cancer vaccines, seeking to optimize the choice of targets, their pharmacological formulation, the delivery platforms and the
therapeutic combinations that help maximize the anti-tumor immune response.

To date cancer vaccine efficacy remains modest. We strive to combine basic immunology research and clinical testing to increase therapeutic efficacy in cancer patients. One of the challenges with developing cancer vaccines is to choose optimal tumor antigens to target, much as it is important to select the right targets in conventional warfare. One promising class of vaccine targets are mutated proteins created by the hallmark chromosomal instability that results in DNA damage to genes, in some cases altering the structure and composition of encoded proteins. These mutated proteins are perceived by the immune system as foreign substances, similar to pathogens, and thus potent immune responses can be raised, in contrast to the self tolerance of their unmutated counterparts. Furthermore, cancer vaccines are more effective if they involve multiple targets, especially if these targets are proteins involved in the oncogenic transformation process. Unfortunately, most of the mutated and many of the unique non-self cancer antigens are also “private”, i.e. they may be present in an individual tumor, but are not shared by tumors of other patients.

In collaboration with other SCCL laboratories the Ludwig Center is developing methodologies that will pave the way for a new generation of molecular cancer vaccines, by integrating deep proteomic and genomic analyses, bioinformatics.
assimilations and sophisticated immune analyses. These methodologies aim at identifying shared as well as private tumor-specific genes, and deducing relevant sequences from the target antigens they encode to identify those that are displayed on the surface of cancer cells. The deep expertise in immune analyses at the Ludwig Center, and the rich data handling resources of the Swiss Institute of Bioinformatics, make Lausanne an exceptional environment for the development of robust methodologies and algorithms for identifying unique tumor specific target sequences, which will be used to develop high throughput individualized vaccines, specific to any given tumor.
Complementary approaches in preclinical or clinical vaccine development at the SCCL include the optimization of delivery platforms, a critical issue in cancer vaccinology. For example, we are testing special stimulatory peptide adjuvants (fragments of proteins visible to the immune system and which can be chemically synthesized) or tumor lysates admixed with various compounds isolated from specialized immune cells that potently increase one’s ability to induce the desired anti-tumor immunity. The latter include compounds that mimic foreign molecules uniquely found in microbial pathogens; nanoparticles that resemble in size bacteria or viruses; or dendritic cells, which are the primary cells that orchestrate T cell attacks against foreign invader pathogens or cancer cells. The unique research and clinical resources gathered in the SCCL provide the means to rapidly transfer new knowledge from our research teams into early phase clinical trials testing new vaccine designs. These projects will help us determine which platform is suitable for the clinical development of personalized cancer vaccines, potentially customized for different forms of human cancer, with their particular strengths and vulnerabilities.

**Clinical Immuno-Oncology program**

Our clinical immuno-oncology program is developing rapidly to offer the most advanced immunotherapy approaches, developed by industry or internally at the SCCL. T cell therapies and vaccines developed at the SCCL will be taken to the clinic using the most rigorous approaches of good clinical practice (GCP) and good manufacturing practice (GMP) recognized internationally. We are preparing clinical trials with genetically engineered T cells for melanoma, cervical and oropharyngeal cancer driven by the human papilloma virus (HPV), and other solid tumors. In addition, we are preparing adoptive therapy using naturally occurring tumor infiltrating lymphocytes (TILs) for melanoma, breast, ovarian and lung cancer. Finally, dendritic cell vaccines for solid tumors will be introduced using whole tumor antigens.

To support this advanced program, we are building a state-of-the-art facility for cell manufacturing, compliant with forward-thinking GMP guidelines. In addition, in the hospital we are
building a state-of-the-art unit for T cell therapy, along with a dedicated apheresis unit.

In addition to cell-based immunotherapy, we are pursuing testing of combination immunotherapy with checkpoint blockade antibodies such as CTLA-4 and PD-1/PD-L1 antibodies in combination with vaccines, chemotherapy, targeted molecular therapy (e.g. PARP, BRAF inhibitors) or radiation. Finally, we are pursuing the clinical development of new immune therapy agents developed by pharma. Examples include first in human or phase-I studies with cytokine-antibody conjugates, bi-specific antibodies, antibodies against new immune checkpoints, DNA vaccines, and radio-immunotherapy.
### 3.2. MOLECULAR ONCOLOGY & TARGETED THERAPEUTICS

**Delivering the right therapy at the right time to the right patient**

The Molecular Therapeutics program is based on the integration of preclinical and clinical cancer research disciplines as a continuum from bench experiments to bedside patient care, paving the way for therapeutic innovations aimed at circumventing therapeutic resistance and enhancing treatment options for patients.

**Background**

Development of new drugs and drug delivery methods requires world-class teams and facilities for fundamental, translational and clinical cancer research, integrated with world-class systems biology, bioinformatics, pharmacology, and molecular and chemical bioengineering infrastructure as well as state-of-the-art imaging facilities. Clinical translation requires modern research platforms for pharmacokinetic/pharmacodynamic evaluations and real-time molecular pathology, as well as research laboratory facilities that can address specific cellular and molecular pharmacodynamic effects of drugs at the tumor site, to better understand drug response and resistance.

Recent data has shown that tumor heterogeneity is a major reason that many targeted therapies fail; this heterogeneity is dependent both upon genetic and/or epigenetic drifts of sub-populations (clones) of cancer cells (i.e. cells in distinct tumor locations harboring divergent genetic and epigenetic abnormalities) and upon plasticity of the tumor ecosystem (involving stroma cells such as fibroblasts, angiogenic cells, macrophages, and other immune cells).

At a cellular level, cancer and stroma cells depend upon multiple signal transduction and metabolic molecules that could serve as targets for therapeutic interventions.

Deep sequencing has revealed the most common gene mutations that drive oncogenesis in most tumors, identifying many important therapeutic targets. However, parallel progress in epigenomics and proteomics has revealed the enormous complexity and plasticity of the mechanisms regulating gene
pathways, and protein expression and post-translational regulation, with additional levels of complexity but also opportunities for therapy. The complexity of the tumor biology remains a real challenge for drug development in the clinic.

Detection of specific drug targets and biomarkers in real-time, at critical stages of tumor progression, will be central to the identification and delivery of the most accurate personalized therapies throughout the progression of a patient’s disease. Such close molecular monitoring of tumor requires analysis of successive biopsies guided by molecular imaging and performed at essential time points to understand genetic and phenotypic drifts, and reveal mechanisms of drug resistance or sensitivity to therapy.

Another source of biomarker discovery and monitoring will come from the study of materials carried over in the bloodstream, such as proteins, nucleic acids, tumor-emitted vesicles, or circulating cancer cells. The analysis of these biomarkers will indeed be crucial to disclose parameters reflecting biological interaction between the host and the tumor.

Moreover, the expanding use of novel imaging technologies will provide non-invasive, real-time functional information about tumor characteristics, offering repeated live snapshots of tumor changes at multiple sites, and the ability to monitor drug delivery and its effects to the site of tumors.

Goals

In order to efficiently target the tumor with accurate drugs and combination treatments, the Molecular Oncology & Targeted Therapeutics program intends to:

- Translate discoveries from the SCCL laboratories to the clinic. This may include validation of mechanisms of disease and biomarkers on human tumor tissues, clinical translation of therapeutic combinations, or clinical development of imaging, analytical diagnostic or therapeutic technologies developed by SCCL laboratories and our collaborators
- Develop an integrated platform for comprehensive molecular and cellular interrogation of tumors using
archived and fresh human tumor tissues collected and processed at the Swiss Cancer Center’s affiliated University Hospital (CHUV), using multiple cellular phenotypic and molecular analysis methods, including single-cell analyses and next-generation high-throughput sequencing technologies

- Address treatment sensitivity/resistance issues related to tumor heterogeneity and to dynamic tumor-stroma interaction by developing fresh and live ex-vivo tissue cultures and single cell analyses
- Develop a drug testing platform using primary human cancer cell cultures and patient-derived xenografts
- Develop a word-class first-in-human phase I clinical trial program for new drugs and novel drug delivery methods, supported by a state-of-the-art clinical pharmacology group and by a real-time molecular pathology and biomarker laboratory infrastructure
- Conduct co-clinical trials in mouse and man, which will allow the parallel investigation of mechanisms of therapeutic sensitivity and resistance, and the iterative development of combinations to address resistance and improve therapeutic efficacy
- Develop organ-targeted therapies and in-vivo molecular imaging in collaboration with the Department of Medical Imaging at CHUV

The integrated program

This project can be developed by the integration of the following four programs:

- Preclinical drug development
- Molecular targets and biomarkers program
- Early phase clinical and co-clinical trials
- Molecular imaging

Preclinical drug development

SCCL laboratories are investigating various aspects of cell regulation, cell-autonomous mechanisms of oncogenesis as well as extrinsic mechanisms of disease including cancer stem cell regulation and function, angiogenesis, and tumor
microenvironmental regulation of drug resistance and metastasis. Based on the understanding of new mechanisms and the identification of new therapeutic targets, novel therapeutic combinations with existing drugs are being tested, while several laboratories are actively involved in the development of new small molecule drugs, therapeutic macromolecules, predictive biomarkers of drug response, or molecular analytical/diagnostic technologies and molecular imaging to capture drug biodistribution and effects in vivo. The SCCL has set its highest priority to foster the clinical translation of these new developments, to benefit patients.

In parallel, we aim to acquire a broad understanding of mechanisms of sensitivity and resistance to novel anticancer entities, including within-patient tumor heterogeneity as well as between-patient variability in tumor characteristics and behavior. This requires significant investments in real-time tumor analyses at a systems level, to capture various cell populations using phenotypic and molecular parameters, which could be correlated with functional parameters, including response to standard of care and new experimental drugs in patient and/or ex vivo in “organotypic” cultures reproducing the tumor microenvironment. The development of a tumor analytical core facility comprising a drug testing unit and sophisticated cellular analytical technologies as part of the Center for Experimental Therapeutics (CTE), in collaboration with many of the analytical platforms of UNIL, CHUV and EPFL, will afford us this unique opportunity.

**Molecular targets and biomarkers program**

Targeted therapies require the discovery of specific predictive biomarkers for patient screening. Monitoring of these biomarkers is also essential to evaluate treatment efficacy. Biomarkers identification will be initiated early, while compounds in testing are progressing through their first steps of clinical development. This side-by-side evaluation of drug with companion biomarkers will require accurate knowledge of drug target and mechanisms of action. The Molecular Oncology Platform, developed as collaboration between the Institute of Pathology and the Center for Experimental Therapeutics, will
include a Biomarker Lab and a next generation Onco-Sequencing Unit, which will support molecular oncology therapeutics in the clinic.

**Early Phase clinical trials and co-clinical trials**

Drug safety validation and drug activity evaluation are performed in early phase clinical trials. First-in-human trials are phase 0/I studies evaluating the safety, pharmacokinetics, pharmacodynamics and preliminary biological or clinical activity of a new molecule. Such crucial evaluations require world-class facilities and teams trained to deliver safe care, collect high-quality data, and acquire clinical experience with drugs that may have never been tested before (first in class).

The SCCL aims at developing a high-quality translational research program assessing the effects of drugs using sophisticated tumor imaging as well as molecular assessment of drug effects on tumor biopsies performed at repeated time points from baseline to progression, guided by molecular imaging information. Parallel investigation of various blood parameters, including circulating cancer cells, nucleic acids, and proteins will allow clinical validation of the companion biomarkers.

The use of animal models, including genetically engineered immunocompetent mice or human tumor xenografts (cell line-derived and patient-derived xenografts), will allow further testing the effects of new drugs. When run in parallel, drug testing in human and in appropriate tumor models in mouse (co-clinical trials) can be a powerful approach to investigate mechanisms of drug resistance and identify response biomarkers. The integrated analysis of co-clinical trial results can greatly accelerate the design of new combinations in subsequent clinical trials.
3.3. PRECISION RADIOTHERAPY

Radiotherapy is, after surgery, the second contributor to cancer cures. The exceptional progress in physics and imaging has now enabled the development of more efficient and better-tolerated radiotherapy, with an increasing proportion of patients who become free of tumors and with significantly reduced side effects. In the domain of Radiation Oncology, the CHUV is at the forefront of the fight against cancer. In the past two years, one of the most important achievements of Radiation Oncology at CHUV has been the broad implementation of high precision radiotherapy for most tumor types.

Recently, specific programs have been launched in order to implement high precision stereo-radiotherapy for targeting tumors in the lung, the spine or the liver, thereby broadening its therapeutic indications. The clinical needs are important and the CHUV has made major investments to markedly increase its capacity to develop this “total body stereo-radiotherapy”, notably through the purchase of a CyberKnife, a sophisticated robotic radiotherapy device specifically dedicated to treating particular tumor types, with increased precision (less than one millimeter), intensity and efficiency.
These developments have been carried out in the context of a partnership between the CHUV and Accuray, world leader in high-precision radiotherapy with international headquarters locally, in Morges (Vaud). This outstanding collaboration has resulted in the CHUV radiation oncology site being designated an Accuray International Flagship Reference Site, with two Tomotherapies and one CyberKnife. Furthermore, two key research programs have been launched in collaboration with Accuray to develop new tools to automatically implement the dose of radiation in 3D and to further improve the treatment of moving targets treated with large volume by tomotherapy.

**New research developments**

**Experimental radiotherapy**

The Radiation Oncology service at the CHUV has developed an ambitious research program in radiation oncology. An unprecedented experimental radiotherapy platform has been established, which includes a new device that integrates 3D CT imaging and tomotherapy for mouse experiments, as well as a prototype enabling the delivery of ultra-intense “Flash-beam” irradiation. The platform has also been integrated with the functional and molecular imaging platforms for mouse models of cancer being developed at the CHUV with the support of the Center for Molecular Imaging, which will enable radiotherapy guided by the functional and molecular characteristics of the tumors.
All the relevant models for tumor and normal tissues have been established, and the facility is now fully operational. The main focus of this new platform is translational research, bench to bedside testing of new combinations of targeted molecular drugs with radiotherapy.

The laboratory has also established joint research programs combining immunotherapy and radiotherapy so as to understand the immunomodulatory effects of radiation therapy, optimize dose and schedule, and to develop the next generation of immuno-radiotherapy combinations.

**Flash-beam radiotherapy**

Flash-beam irradiation is a totally new type of radiotherapy that delivers electrons at a density over 1,500 times higher than conventional machines. This results in fewer side effects and greater anti-tumoral efficacy. Following comprehensive preclinical testing in mice, a worldwide first human prototype has been installed at the CHUV, in partnership with the Alcen group, a pioneering company specializing in technological innovation in aeronautical and medical engineering.

The goal of the whole research program is to transfer the exciting observations about flash beam IR obtained in laboratory animals to patients, from bench to bedside, and to define the optimal setting for clinical trials, to ultimately treat patients (starting in 2016) with cancers that have not been cured with conventional treatments.

All these new and complex developments in Radiation Oncology at the CHUV will benefit from an internal collaboration with the Institute of Radiophysics, which is an international reference site for medical physics and metrology, integrating experts in all the fields of medical physics for radiotherapy, imaging, metrology, and radioprotection.
3.4. NUCLEAR MEDICINE AND MOLECULAR IMAGING

Background

The Nuclear Medicine and Molecular Imaging program at the CHUV is part of the integrated Center for Biomolecular Imaging (CIBM), a partnership involving a consortium of Lake Geneva institutions (UNIL, CHUV, EPFL, UNIGE and HUG), and is equipped to support projects in preclinical and clinical diagnostics and therapeutic research and development.

PET and SPECT are impacting patient care as safe, fast, and reliable techniques to obtain in vivo, quantitative, high-sensitivity (nano/pico molar) and non-invasive information about tumor biology and anatomic distribution. These technologies provide an opportunity to interrogate tumors for cell surface receptors, signal transduction pathways, apoptosis, proteolytic enzymes or extracellular matrix targets. Applied to both pre-clinical and clinical settings, there is evident potential to revolutionize personalized drug development. For example, image-guided biopsies and treatments are increasingly needed to personalize therapies. Whole-body imaging allows the assessment of tumor heterogeneity non-invasively, so as to direct biopsies towards the site(s) identified as most representative of the targeted process.

Molecular imaging can also stratify patients for clinical trials to enrich proof-of-concept studies with defined imaging phenotypes, to aiming at shorter, smaller and more efficient clinical trials. There is also the potential for clinical imaging to serve as surrogate end-points that could speed up the registration of new drug therapies and to stratify patient population to lower the cost of drug development. Finally,
target-specific radioligands will play an important role in drug development and managing therapy. They can enable detection of drug biodistribution or therapeutic response early, increasing the probability of success in late phase clinical trials.

“Theranostics” — a combination of therapeutics and diagnostic imaging — is playing an increasingly important role in radiation-based targeted therapies using radiopharmaceuticals. In this approach, radiation is administered to cancer using peptides, proteins or antibodies labeled with therapeutic radionuclides ($^{90}$Y, $^{177}$Lu, $^{131}$I, $^{149}$Tb, $^{161}$Tb, etc.) under the guidance of the same ligand labeled with PET ($^{18}$F, $^{68}$Ga, $^{89}$Zr, $^{64}$Cu, $^{86}$Y) or SPECT radioisotopes ($^{99m}$Tc, $^{123}$I, etc.).

Preclinical molecular imaging and therapy offer unique opportunities to expedite clinical applications by validating drug targeting (proof-of-concept) in small animals models, studying biodistribution, pharmacokinetics/pharmacodynamics, toxicity, and its combination with distinctive therapeutic agents such as chemotherapy, antiangiogenic or gene therapy agents, as well as external radiation therapy. The Nuclear Medicine and Molecular Imaging Department at the CHUV has state-of-the-art equipment for performing pre-clinical (micro-PET/SPECT/CT) and clinical imaging (latest-generation time-of-flight PET/CT and SPECT/CT) using commercially cyclotron-produced or in-house generator-produced radiopharmaceuticals. Collaborations with universities or research cyclotrons (USZ, ETH Zurich, PSI and CERN) provide exciting opportunities to participate into first-in-human studies and phase 0 (micro-dosing) to phase I Swissmedic-approved/GCP clinical trials, expanding from a foundation set over the past two decades.

The following sections will describe a few selected projects as illustration of our translational and clinical research program.

**Translational Program in Molecular Imaging**

Direct imaging of angiogenesis has not been extensively investigated in the clinical setting. After developing and validating peptides targeting the $\alpha_v\beta_3$ integrins in a first-in-human trial, we are now conducting the first large-scale clinical trial in 120 patients aiming at establishing the utility of $^{68}$Ga-NODAGA-RGD in 12 different tumors, including gliomas.
Cancer cells can acquire resistance to signals initiating apoptosis and its imaging could be very insightful during therapy. We are also conducting a phase I study to study the ability of $^{99m}$Tc-rhAnnexin V-128 to detect **in vivo** apoptosis and its safety in human patients.

In a collaborative study with the Paul Scherrer Institute, ETH Zürich, University of Zürich and the CHUV, we are pursuing $^{18}$F-AZA-folate to study for the first time the detection of folate receptor in women affected by ovarian cancer.

In a CHUV-led study conducted within a European consortium and funded by FP7 EU grant, an endoscopic PET probe coupled to ultrasound has been developed to guide biopsies; initial tests in pigs are planned in 2015, as a precedent to possible clinical trials.

A “Science-to-market” grant is supporting the development of wireless pure $\beta^+$ (positron) probes for radio-guided oncological surgery, which are now being tested in oncological surgery for melanoma, head and neck and lung cancer.

Understanding tumor heterogeneity is crucial, and hybrid PET-assisted biopsies can help in identifying the sites of biologically relevant tumor cells. A system has been developed to verify the adequacy of sampling directly at the bedside during biopsy, which will greatly enhance biopsy accuracy aiming at understanding tumor microenvironment.

**Translational Program in Theranostics**

We have previously conducted a radioimmunotherapy pilot study in non-Hodgkin indolent lymphoma using $^{131}$I-labelled rituximab (CD20 antibody) at the CHUV. We observed remarkable long-term progression-free survival in patients treated with this hybrid immuno/radioimmunotherapy, with some lasting 8+ years. A prospective study is currently being planned.

In the context of a collaboration involving CERN, ISREC, HUG and CHUV, we are developing novel radioisotopes for medicine (MEDICIS), capitalizing on the construction of a new CERN building (ISOLDE) with a separate beam line and a physical isolation facility. In this context, we are assessing novel neurotensin analog peptides for targeting neuroendocrine
pancreatic cancer. Initial experiments are being conducted in mice, and clinical translation is foreseen.

The bombesin receptor family comprises the gastrin releasing peptide receptor (GRPr), which is over-expressed in prostate and breast cancer. Bombesin is a 14-amino acid amphibian homolog peptide, which binds with high affinity to the GRPr. A preclinical study has established the feasibility and dosimetry of a GRPr antagonist $^{68}$Ga-NODAGA-RM6 in mice and a clinical study targeting prostate cancer clinical study has already included 5/60 patients with prostate cancer. A breast clinical trial is currently in planning. Peptide-targeted radiation therapy with alpha-emitters using bombesin receptor antagonist ($^{149}$Tb) is also being developed using a prostate cancer xenograft mouse model.

Personalized dosimetry for selective interstitial radiation therapy (SIRT) has been used with success to increase the overall survival and quality of life of patients with inoperable liver tumor/metastases who cannot undergo chemotherapy. Personalized patient dosimetry enhances the radiation dose delivered to tumor tissue while minimizing toxicity. The efficacy of this approach will be tested and compared against the current standard of care.
4. THE CENTER FOR EXPERIMENTAL THERAPEUTICS

The Center for Experimental Therapeutics (CET) is a new clinical-translational platform in the Department of Oncology of UNIL-CHUV, working at the interface of basic and clinical research and responding to the ever-changing landscape of cancer therapeutics. Its mission is to bring the latest in treatment innovation to CHUV oncology patients. This center collaborates with different CHUV entities to build an integrated environment that supports clinical innovation and patient-oriented translational research. Headed by Dr. Lana Kandalaft, the CET comprises several cores, platforms and facilities, and is divided into a clinical and a translational research subdivision, which work under one organization to bring innovation from bench to bedside. Quality and safety assurance are amongst our key concerns. The CET operates according to a Quality Management Program in compliance with ISO 9001, and is aiming to obtain ISO 9001 certification by the end of 2015.

4.1. CLINICAL RESEARCH STRUCTURES

New Clinical Research Spaces

The CHUV is making significant investments to expand its capabilities for clinical research in oncology. New spaces are created for the conduct of early-phase drug studies and for immunotherapy cell product infusions in the outpatient as well as the inpatient setting.

An ambitious outpatient phase I unit is being created of overall 1,200 m² to meet the needs of the oncology drug development and immuno-oncology programs. This comprises an initial construction of the Outpatient Early Drug Development Unit, a 550-m² space dedicated to support first-in-human and early-phase drug clinical trials. It is slated for completion by May 2016. It will include eight infusion beds; a dedicated investigational pharmacy; consultation rooms; a biopsy room; lab space for specimen processing, packaging and shipment; and dedicated space for the clinical research staff of nurses, coordinators and clinicians. In addition, an Outpatient Cell
Therapy Unit will be built by Q3 2016, to support outpatient infusions of cell-based therapies. This 650-m² unit will be contiguous to and integrated with the Early Drug Development Unit, and will comprise space for a dedicated apheresis unit and a cell therapy infusion unit (up to 5 beds each).

Kim Ellefsen
Director of Operations CET and Head of Tumor Processing Facility

« My everyday job is multifaceted. It involves the set up and coordination of clinical studies including the establishment of all the guidelines and processes underlying the proper running of the trial, to meet Good Clinical Practice requirements. In parallel, within the Translational Core, I am responsible for the fresh tumor collection, processing and cryopreservation activities.

What I really enjoy is my involvement with diverse teams. I work in collaboration with many different CHUV services, interact on a daily basis with professionals from various backgrounds and fields of expertise such as researchers, medical specialists (oncologists, surgeons, pathologists, anesthetists), research nurses, administrative officers, human resources managers etc... Being part of the SCCL community will not only give greater visibility to the CET activities but also federate teams around major cutting-edge research projects. »

Complex cell therapy studies will require a sophisticated inpatient setting with continuous monitoring and intensive care capabilities. A new, state-of-the-art Inpatient Cell Therapy Unit will support phase I studies requiring hospitalization for prolonged infusions, monitoring or laboratory studies (completion in Q3 2016). This hospital unit will have 10 beds with intermediate-intensive care and cardiorespiratory monitoring capabilities and a small laboratory for biospecimens.
Cell Manufacturing GMP Facility

This Good Manufacturing Practice (GMP) facility aims at providing cancer patients with access to new cell-based treatments in the area of cancer immunotherapy. Slated for opening in two stages, a small facility will be operational by Q4 2015, while the final facility will be open by Q1 2017. Once completed, this will be a multi-faceted facility with the capability to manufacture autologous cell-based therapeutics in support of Phase I/II clinical trials for a variety of tumor indications. This will be the largest academic manufacturing facility for cell-based immunotherapy in Europe. The facility will have the capacity to manufacture over 300 cell products annually, including:

- autologous tumor-infiltrating T lymphocytes (TILs)
- autologous, non-engineered T cells
- genetically engineered T cells
- dendritic cell vaccines

With the exception of the tumor-infiltrating lymphocytes, the starting material for GMP manufacturing processes is peripheral blood mononuclear cells harvested through apheresis. TILs are isolated from sterile fresh tumor material.

The GMP facility will comprise two independent ISO 8 Production Suites for the manufacture of engineered (genetically modified, GMO) and non-genetically modified (non-GMO) products, respectively. Production suites will feature state-of-the-art closed-system cell processing equipment as well as custom isolator technology for aseptic activities. Each suite will be outfitted with a separate personnel entry/exit, materials entry and pressure-controlled transfer hatches for waste and final product exit. An independent Media Preparation Suite will support both production areas. A fully equipped Process Development Suite will provide clinical scale-up capabilities and process optimization. The Quality Control Suite is divided into four distinct areas for efficient in process and final product release testing. Support areas include Materials Receipt/Quarantine/Release, Cryo-storage/Shipping, Administration and Archives. An independent, validated Environmental Monitoring System will monitor, record and alert the functional status of the facility and equipment.

The facility will be supported by a Quality Assurance unit responsible for the implementation and maintenance of the Quality Management System reflective of the most current
regulatory directives and guidelines. This includes a science and risk-based approach to quality as defined in Quality by Design (QbD) to identify effective control strategies for the consistent production of safe and high quality products for patients.

The Oncology GMP Facility has been designed to support the manufacturing of Advanced Therapeutic Medicinal Products (ATMPs) in compliance with local, national and EU regulatory requirements. Quality risk management principles are applied throughout the development of each stage of the project including facilities, utilities, equipment and processes, in order to minimize variability and reduce the risk of contamination or cross-contamination. In addition, the need for flexibility to accommodate the diversity of products and evolution of the technology has been taken into consideration as early as the concept stage. The facility design incorporates flexibility while maintaining GMP regulatory requirements for the manufacture of quality, safe and effective cell-based products.
Clinical Trials Unit (CTU)

The CTU comprises three distinct groups: The Regulatory Office provides the necessary support for protocol and Investigational Medicinal Product Dossier (IMPD) development, for submission to and regulatory dialogue with the Swiss Agency for Therapeutic Products (Swissmedic), the European Medicines Agency (EMA), the Food and Drug Administration (FDA), and local Ethics Committees (EC).

The Clinical Operations Unit provides the coordination and day-to-day management of protocol implementation, subject coordination, and data handling. The Research Nursing Unit provides patient care, supports the informed consent process, administers the study agent(s) or intervention(s), and monitors responses to therapeutics and interventions.

Over the past ten years, the CTU has acquired expertise in the design, implementation and conduct of clinical trials in various fields of cancer. The CTU has developed infrastructures and capacity to conduct phase I/II and III clinical trials, with the main goals being the assessment of the safety, pharmacokinetics and pharmacodynamics/biological effects of investigational products. The CTU’s staff (total of 17 employees presently) works according to strict ethical regulations and internationally

Stéfania Manciana
Chief Nurse of the Ambulatory Oncology Care Unit and Research Nurses Team Coordinator, CHUV

« On the one hand, I supervise a clinical team of at least 30 nurses and assistant nurses who deliver standard treatments to ambulatory oncology patients. This implies that I make sure everyday that each incoming patient receives the proper treatment from the designated nurse to guarantee care quality and patient security. The team will grow to at least 40 caregivers by the end of 2015. On the other hand, I coordinate a team of 4 research nurses. Working in close collaboration with the CET and the clinical research associates, this team is dedicated to optimizing the patient’s multi-step clinical research day. Team activities range from inclusion of the patient in a clinical trial, to consent form presentation to the patient for signature, medical examination assistance for a specific treatment, treatment delivery and follow-up. Importantly, the SCCL will support the creation of a new research nurse training program.

My work allows me to reach out to and communicate with numerous healthcare and research professionals including Pharmas, CET, clinical research nurses, clinical research associates. I am thrilled to meet the great challenge of introducing new treatments to patients such as immunotherapies. The SCCL is an outstanding initiative for gathering efforts and key expertise to propose and deliver innovative therapies and exceptional care quality to patients, to provide them with new solutions and bring real hope to them. »
recognized Good Clinical Practices (GCP). The CTU clinical activities are governed by a manual of operating procedures (MOP). This manual is in compliance with national regulatory requirements.

The CTU has daily interactions with the CHUV Pharmacy, the CHUV Institute of Pathology, and certified laboratories in order to conduct clinical trials in accordance to GCP.

In 2014, the CTU managed 127 clinical trials and translational studies. Among these 127 clinical trials, 59 were open to accrual (including 4 phase I trials, 6 phase I/II trials, 15 phase II trials, 1 phase II/III trials and 17 phase III trials, and 16 translational/biomarker/registry studies). In these, more than 525 patients underwent treatment and follow up (clinical trials and translational studies. The unit has an excellent track record of high quality data.
Open Clinical Trials in 2014

Clinical innovation through early phase clinical trials is a prime focus of the SCCL. In 2014, we received accreditation as a first-in-human phase I designation site from Novartis and Roche. Four phase I studies with new molecular oncology drugs and 4 phase I studies in immunotherapy-radiotherapy or immuno-chemotherapy combinations are planned in the course of 2015. Over the past year, four CHUV Oncology faculty members have been approved as principal investigators for European randomized phase-III clinical trials, a reflection of the international profile of the SCCL members.

Following are representative clinical trials presently open at the CHUV.

David Bonnet
Clinical Research Associate, Clinical Trial Unit of the CET

“My work in the field consists in coordinating clinical trial-related activities between various involved professional entities including care team, medical team, trial sponsors or contract research organizations. In other words, I am responsible to coordinate and ensure a proper daily flow of study information between all trial stakeholders, whether they are external or internal to the CHUV or the Department of Oncology.

Working at the crossroads between these interdisciplinary teams is truly exciting as there is no routine in the job, everyday is different.

As a clinical research associate within the SCCL community, I am happy to be part of this whole cancer research initiative and opportunity to significantly push forward the development of innovative anti-cancer therapeutics. With the creation of the SCCL, one can realize and see the real therapeutic outcome of all research efforts, on the patient.”
<table>
<thead>
<tr>
<th>Indication</th>
<th>Title</th>
<th>Phase</th>
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<tr>
<td>Hepatocellular carcinoma, stage B et C</td>
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<tr>
<td>Hepatocellular carcinoma, stage B</td>
<td>A phase I open label/phase II randomized, double-blind, multicenter trial investigating the combination of everolimus and TransArterial ChemoEmbolisation (TACE) with doxorubicin in patients with hepatocellular carcinoma - SAKK 77/09 and SASL 30</td>
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<tr>
<td>Stomach and gastro-esophageal junction, metastatic</td>
<td>A double-blind, placebo-controlled, randomized, multicenter Phase III Study evaluating the efficacy and safety of pertuzumab in combination with trastuzumab and chemotherapy in patients with HER2-positive metastatic gastroesophageal junction and gastric cancer – BO25114 Jacob</td>
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<tr>
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<td>Multicenter registry</td>
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<tr>
<td>Colorectal cancer, advanced stage</td>
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<tr>
<td>Squamous cell carcinoma of the anal canal, stage II-IIIB</td>
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<tr>
<td>Breast, metastatic HER2+</td>
<td>A randomized phase II trial of pertuzumab in combination with trastuzumab with or without chemotherapy, both followed by T-DM1 in case of progression, in patients with HER2-positive metastatic breast cancer – SAKK 22/10</td>
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<tr>
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<tr>
<td>Male breast cancer</td>
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<tr>
<td>Breast, neoadjuvant</td>
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<tr>
<td>Breast, 3D cell culture model</td>
<td>Development of a high throughput organotypic culture system by 3D culture of primary breast cancer cells on QGel® matrix: a system to predict the efficacy of anticancerous drugs in vitro in breast cancer patients and enable personalized treatment.</td>
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<tr>
<td>Acute promyelocytic leukemia</td>
<td>A randomized phase III trial assessing the role of arsenic trioxide and/or ATRA during consolidation course in newly diagnosed acute promyelocytic leukemia (APL) – APL 2006</td>
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<tr>
<td>Acute Lymphoblastic Leukemia (ALL), &lt; 60 years-old</td>
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<td><strong>Acute Myeloid Leukemia, &gt; 65 years-old</strong></td>
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<td><strong>Newly diagnosed Ph/BCR-ABL positive patients with chronic myeloid leukemia</strong></td>
<td>Treatment optimisation of newly diagnosed Ph/BCR-ABL positive patients with chronic myeloid leukemia (CML) in chronic phase with Nilotinib vs. Nilotinib plus Interferon alpha induction and Nilotinib or Interferon alpha maintenance therapy – CML V</td>
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<td><strong>Aggressive B-cell lymphoma</strong></td>
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<td><strong>Diffuse large B cell lymphoma.</strong></td>
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<tr>
<td><strong>Newly diagnosed Multiple Myeloma and non eligibility for transplantation</strong></td>
<td>A randomized, open-label Phase III Study of Carfilzomib, Melphalan, and Prednisone versus Bortezomib, Melphalan, and Prednisone in transplant- ineligible patients with newly diagnosed multiple myeloma – Clarion 2012-005</td>
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<td><strong>Ocular Melanoma, adjuvant</strong></td>
<td>A randomized Phase 3 Study comparing Fotemustine adjuvant chemotherapy treated patients to monitored patients with choroid melanoma at high risk of recurrence</td>
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<tr>
<td><strong>Ocular Melanoma, metastatic</strong></td>
<td>Sorafenib and radioembolization with SIR-Spheres® for the treatment of metastatic ocular melanoma</td>
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<tr>
<td><strong>Advanced non operable or metastatic Melanoma with NRAS gene mutation</strong></td>
<td>The NEMO trial (NRAS melanoma and MEK inhibitor): A randomized Phase III, open label, multicenter, two-arm study comparing the efficacy of MEK162 versus dacarbazine in patients with advanced unresectable or metastatic NRAS mutation-positive melanoma</td>
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<tr>
<td><strong>BRAF-mutant melanoma at high risk for recurrence</strong></td>
<td>A phase III, randomized, double-blind, placebo-controlled study of vemurafenib (ro5185426) adjuvant therapy in patients with surgically resected, cutaneous BRAF-mutant melanoma at high risk of recurrence – BRIM-8</td>
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<tr>
<td><strong>Untreated Unresectable or Metastatic Melanoma</strong></td>
<td>Phase III, Randomized, Double-Blind Study of Nivolumab Monotherapy or Nivolumab Combined with Ipilimumab Versus Ipilimumab Monotherapy in Subjects with Previously Untreated Unresectable or Metastatic Melanoma – BMS CA 209-067</td>
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<tr>
<td><strong>Metastatic melanoma or metastatic Merkell cell carcinoma</strong></td>
<td>A Phase I, exploratory, intra-patient dose escalation study to investigate the preliminary safety, pharmacokinetics, and anti-tumor activity of pasireotide (SOM230) s.c. in patients with metastatic melanoma or metastatic Merkel cell carcinoma</td>
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<tr>
<td><strong>Solid tumors Advanced</strong></td>
<td>LDE225 in combination with Paclitaxel in patients with advanced solid tumors. A multicenter phase I trial</td>
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<tr>
<td><strong>Solid tumors CEA-positive, advanced and/or metastatic</strong></td>
<td>An open-label, multi-center, dose escalation, phase I study with an expansion phase, to evaluate safety, pharmacokinetics and therapeutic activity of RO6895882, an immunocytokine, consisting of a variant of interleukin-2 (IL-2v) targeting carcinoembryonic antigen (CEA) administered intravenously, in patients with advanced and/or metastatic solid tumors.</td>
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<td>Category</td>
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<tr>
<td><strong>Solid tumors</strong></td>
<td>Pilot study to evaluate percussive ventilation dosimetric gain for radiation therapy of lung cancers, breast cancers, or gastro-intestinal cancers with oligometastases in the liver</td>
<td>other</td>
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<tr>
<td><strong>Head and Neck, squamous cell canceroma, Advanced localized stage</strong></td>
<td>A Phase I/II randomized study to determine the maximum tolerated dose, safety, pharmacokinetics and antitumor activity of Debio 1143 combined with concurrent Chemo-Radiation Therapy in patients with locally advanced squamous cell carcinoma of the head and neck</td>
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<tr>
<td><strong>Head and Neck, oral mucositis</strong></td>
<td>A phase II, multi-centre, randomised, double-blind, placebo-controlled study comparing the efficacy and safety of clonidine lauriad® 50 µg and 100 µg mucoadhesive buccal tablet (MBT) applied once daily to those of placebo in the prevention and treatment of chemoradiation therapy induced oral mucositis in patients with head and neck cancer</td>
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<tr>
<td><strong>SCLC, with limited disease</strong></td>
<td>A randomized open-label phase II trial of consolidation ipilimumab in limited-stage SCLC after chemo-radiotherapy - STIMULI: Small cell lung cancer Trial with Ipilimumab in Limited disease</td>
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<tr>
<td><strong>NSCLC, advanced (stage IIIb) and operable</strong></td>
<td>Preoperative chemotherapy and radiotherapy concomitant to Cetuximab in non-small cell lung cancer (NSCLC) patients with IIIb disease. A multicenter phase II trial – SAKK 16/08</td>
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<tr>
<td><strong>NSCLC, first-Line Therapy for Stage IV or Recurrent PD-L1+</strong></td>
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<td>III</td>
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<tr>
<td><strong>NSCLC, locally advanced or metastatic, PD-L1 positive</strong></td>
<td>A phase-II, multicenter, single-arm study of MPDL3280A in patients with PD-L1-positive locally advanced or metastatic non-small cell lung cancer - GO28754</td>
<td>II</td>
</tr>
<tr>
<td><strong>NSCLC, advanced non-squamous (stage IV)</strong></td>
<td>Bevacizumab, pemetrexed and cisplatin, or erlotinib and bevacizumab for advanced non-squamous NSCLC stratified by EGFR mutation status. A multicenter phase II trial including biopsy at progression (BIO-PRO trial) - SAKK19/09</td>
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<tr>
<td><strong>NSCLC, non-squamous with EGFR mutations (stage IV)</strong></td>
<td>An open-label phase II trial of erlotinib and bevacizumab in patients with advanced non-small cell lung cancer and activating EGFR mutations Bevacizumab and ErLotinib In EGFR mut+ NSCLC - BELIEF</td>
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</tr>
<tr>
<td><strong>NSCLC, advanced ALK positive</strong></td>
<td>Randomized multicenter phase III open-label study of alectinib versus crizotinib in treatment-naive anaplastic lymphoma kinase-positive advanced non-small cell lung cancer – BO28984 ALEX</td>
<td>III</td>
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<tr>
<td><strong>Medulloblastoma, recurrent or refractory</strong></td>
<td>An international, randomized, open-label Phase I/II study of vismodegib in combination with temozolomide versus temozolomide alone, in adult patients with recurrent or refractory medulloblastoma presenting an activation of the Sonic Hedgehog pathway</td>
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<td><strong>Anaplastic Glioma, Anaplastic Astrocytoma, Anaplastic Oligoastrocytoma, Anaplastic Oligodendroglioma no 1p/19q deletion</strong></td>
<td>Phase III trial on Concurrent and Adjuvant Temozolomide chemotherapy in non-1p/19q deleted anaplastic glioma. The CATNON Intergroup trial.</td>
<td>III</td>
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<tr>
<td>Study Description</td>
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<tr>
<td><strong>Glioma (stage II et III), recurrent</strong></td>
<td>Randomized trial assessing the significance of Bevacizumab in recurrent grade II and Grade III gliomas. The TAVAREC trial</td>
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<td><strong>Glioblastoma, newly diagnosed, old patients</strong></td>
<td>A phase II, randomized, parallel-group, explorative, open labeled multi-center study of bevacizumab (Avastin®) in elderly subjects with newly diagnosed glioblastoma</td>
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<tr>
<td><strong>Glioblastoma, adjuvant</strong></td>
<td>A Prospective, Multi-center Trial of NovoTTF-100A Together With Temozolomide Compared to Temozolomide Alone in Patients with Newly Diagnosed GBM</td>
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<tr>
<td><strong>Glioblastoma, adjuvant</strong></td>
<td>An International, Randomized, Double-Blind, Controlled Study of Rindopepimut/GM-CSF with Adjuvant Temozolomide in Patients with Newly Diagnosed, Surgically Resected, EGFRvIII-positive Glioblastoma (The &quot;ACT IV&quot; Study)</td>
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<td><strong>Glioblastoma, recurrent</strong></td>
<td>Phase III trial exploring the sequence of bevacizumab and lomustine in patients with first recurrence of a glioblastoma.</td>
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<tr>
<td><strong>Glioblastoma, recurrent</strong></td>
<td>Phase I/II study of S 49076, a multi-target inhibitor of c-MET, AXL, FGFR in combination with bevacizumab in patients with recurrent glioblastoma multiform - CL1-49076-002</td>
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<tr>
<td><strong>Glioblastoma, recurrent</strong></td>
<td>A randomized Phase III open label study of Nivolumab versus Bevacizumab and a safety study of Nivolumab or Nivolumab in combination with Ipilimumab in adult subjects with recurrent glioblastoma - BMS CA 029-143</td>
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<tr>
<td><strong>Prostate, localized, Epstein + or Epstein extended</strong></td>
<td>Active monitoring of two patient groups affected by localized prostate cancer. Monoconic, prospective, comparative, non-randomized study - Surveillance active</td>
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<tr>
<td><strong>Prostate, localized</strong></td>
<td>A phase I-II dose escalation study of stereotactic body radiation therapy in patients with localized prostate cancer - CHUV-DO-HYPO</td>
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<tr>
<td><strong>Prostate, recurrent, hormone-sensitive or metastatic</strong></td>
<td>Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy A multi-arm multi-stage randomized controlled trial.</td>
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<tr>
<td><strong>Prostate, metastatic and hormone-resistant</strong></td>
<td>Orteronel maintenance therapy in patients with metastatic castration resistant prostate cancer and non progressive disease after first-line docetaxel therapy: A multicenter randomized double-blind placebo-controlled phase III trial</td>
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<tr>
<td><strong>Prostate</strong></td>
<td>Immune Monitoring in Prostate Cancer Patients Undergoing Radiotherapy or Chemotherapy - CHUV-IMPCR-2013</td>
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<tr>
<td><strong>Germ cell tumors, seminoma</strong></td>
<td>Carboplatin chemotherapy and involved node radiotherapy in stage IIA/B seminoma.</td>
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</table>
Support studies/other activities

<table>
<thead>
<tr>
<th>Indication</th>
<th>Title</th>
<th>Phase</th>
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<tbody>
<tr>
<td>Chronic liver disease</td>
<td>Prospective randomized controlled trial comparing response and recurrence rate between percutaneous microwave coagulation therapy and percutaneous radiofrequency ablation for the treatment of hepatocellular carcinoma in patients with a chronic liver disease</td>
<td>other</td>
</tr>
<tr>
<td>Radiology</td>
<td>Use of CT imaging reconstructions in iterative mode: how far can irradiation be reduced in kids and young adults?</td>
<td>other</td>
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<tr>
<td>Melanoma</td>
<td>MK3475 EAP</td>
<td>Compassionate</td>
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<td>Melanoma</td>
<td>MEK117341 tramatinib EAP</td>
<td>Compassionate</td>
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<td>Melanoma</td>
<td>Registry of Yervoy -BMS</td>
<td>Registry</td>
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<tr>
<td>Per os oncologic treatment - compliance</td>
<td>Oral oncologic treatments : pilot study of measure and interdisciplinary support of adhesion</td>
<td>other</td>
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4.2. TRANSLATIONAL RESEARCH STRUCTURES

Oncology Translational Core

A 760-m² facility located in the CHUV Orthopedic Hospital building, this core facility will be dedicated to fresh tumor manipulation and analysis, and will support translational research at the SCCL requiring viable primary patient tissue or blood. Its main focus is to establish approaches to cancer tissue transfer, processing, storage and analysis, which will meet the needs for personalized cancer therapy, spanning from autologous tumor-based immunotherapeutics, such as vaccines and TILs, to personalized drug screening, and patient-derived tumor xenografts (PDXs). In addition, this platform will support the tumor tissue needs of the translational and clinical cancer research community of the SCCL through the development of innovative tumor-based analytical methodologies.
The Oncology Translational Core comprises the **Tumor Processing Facility**, which has been functional since May 2014, dedicated to the fresh tumor tissue collection. Activities include tumor processing and live cryopreservation; analysis of fresh tumors; assay standardization; data management; and documentation according the GCLP compliance. After a portion of the surgical tumor specimen has been removed at the Institute of Pathology to address the routine diagnostic needs, the remainder of the specimen is transported to the Tumor Processing Facility to be used for lysate preparation, isolation and expansion of tumor-infiltrating lymphocytes (TILs) and/or *in vitro* drug and chemo sensitivity assays.

The main goal of the **Immune Development and Monitoring Core** (IMC), slated for completion by end of 2015, is a Standard Operating Procedure (SOP)-driven, quality controlled, immune-monitoring platform. The IMC is specialized in blood- and tumor tissue-based immune monitoring approaches to ensure the collection of reliable and reproducible data for the detection, quantification, and characterization of immune responses. The core offers state-of-the-art tools, assays and technologies under GLP and GCLP guidelines to provide immune monitoring.

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**Hélène Bichat**

*Lab Technician in Oncology, CET*

« I work in parallel between the Clinical Trial Unit and the Translational platform at the CET. At the Clinical Trial Unit, I am the referring person in charge of collecting patient blood samples in clinical studies to subsequently process the blood, aliquot serum, plasma and isolate the cells, before storing the materials. In addition, in a direct collaboration with the Institute of Pathology (for operating room samples) and with the Institute of Radiology (for biopsy samples), I am also responsible for collecting patient tumor tissue samples to freeze and store. Regarding the Translational platform, I work with Dr Alexandre Harari from the Immune Development and Monitoring Core where we focus on implementing optimized flow cytometry conditions, and with Kim Ellefsen from the Tumor Processing Facility where I slice the tumor specimens into lots of small samples before storing them, with the ultimate goal to culture them for Tumor-Infiltrating Lymphocytes expansion. I am very enthusiastic to work in a translational approach environment where one can see the direct application of lab results to patients. Moreover, I get to interact with many experts from diverse disciplines such as pathologists, anesthetists, research nurses etc ..., which is truly fascinating. The development of the SCCL community will definitely increase the CET visibility and will offer access to UNIL and EPFL researchers in need of patient samples to pursue their projects. »
services during discovery, pre-clinical, and Phase I-III clinical development. In addition, the IMC is dedicated to develop novel immune assays for the deep molecular and cellular characterization of immune responses and the tumor microenvironment, including single cell assays and miniaturized assays using microfluidics and nanotechnology in collaboration with EPFL.

One goal of the IMC is to capture immune events not just in blood but also in the tumor microenvironment using cutting-edge technology. To evaluate immune cell and molecular signatures in the tumor microenvironment, one approach led by Dr Periklis Foukas in the Immune Landscape Laboratory, involves multiplexed immunohistochemical staining of formalin-fixed paraffin embedded tissue sections, followed by multispectral imaging and linear unmixing. Multispectral imaging and linear unmixing offer the opportunity to analyze tumor slides in a comprehensive, spatially-oriented and quantitative fashion, each being stained with multiple antibodies, in either a bright field (up to 3-4 antibodies + counterstain) or fluorescence (up to 6-8 antibodies + counterstain + autofluorescence removal) mode. A Vectra™ Automated Multi-modal Tissue Analysis System has been installed for this project. It automates quantitative data acquisition and streamlines data extraction on up to 200 slides in

**Alexandre Harari**

*Director of the Immune Development and Monitoring Core, CTE, and Team Leader in the Coukos Laboratory*

« As director of the immune monitoring core, I supervise the implementation of standardized and robust immuno-monitoring assays for the research community. The core is therefore a service facility which is available to researchers, where we perform analyses and follow-up of immune parameters from the patient’s own tumor and blood cells to characterize immune responses. As a team leader, I carry out translational research aiming to develop strategies to identify new personalized treatments for patients. More specifically, my group is investigating novel assays to discover new tumor epitopes. These assays will then be transferred to the core facility to offer personalized vaccination solutions to patients. In other words, my job combines service providing and exploratory research. Both sides nicely complement each other. Housing state-of-the-art multidisciplinary expertise and knowledge, the SCCL does promote and facilitate strong scientific collaborations networks between its members. Regarding my work, these joint forces will allow a faster development of new valuable methods, assays or techniques. »
a single batch run. Additional molecular signatures at the RNA and protein level are developed using state-of-the-art multiplexed methodologies such as Nanostring, Meso Scale Discovery electrochemiluminescence assay, and reverse phase protein array.

The Drug Development Unit, which will start its activities in the summer of 2015, is focused on aiding the clinical and translational programs aiming to developing personalized therapy. Fresh tissue slices or 3D reconstructions will be maintained in culture media and used to test the effects of chemotherapy as well as immunomodulatory drugs in short-term cultures. These will be correlated with patient responses in vivo. In addition, following tumor digestion, tumor cells can be purified and propagated in vitro in order to derive a constant supply of primary tumor cells to perform additional assays. Panels of conventional, targeted and new experimental drugs alone or in combination can be tested in relatively simple assays. Conventional drug effectiveness, for example, can be determined alone or in the presence of inhibitors of selected signaling pathways. If cancer stem cells are identified, they can be separated from the tumor bulk and assessed in parallel for sensitivity to drugs. Finally, discovery projects can be implemented in the future testing conventional chemotherapy or targeted therapies together with drug, chemical, natural compound, and CRISPR/Cas9 or siRNA libraries.
5. CLINICAL PHARMACOLOGY

The CHUV Division, Pharmacometric unit and Laboratory of clinical pharmacology have been involved since many years in the pharmacological development and optimization of drug treatments in various fields of therapies. The unique translational framework established at the CHUV favors a close collaboration between experts in analytical assays, pharmacometrics and clinical pharmacology and offers strong capabilities of research in all phases of clinical drug development and in post-marketing treatment optimization.

Anticancer therapies, in particular targeted drugs, represent a major field of interest for our groups. In that respect, a high level of expertise has been developed for the characterization of dose-concentration-effect relationships and for the optimization of drug dosage within the frame of personalized medicine. Clinical Pharmacology at the CHUV offers cutting-edge technologies for data analysis and clinical interpretation, in particular for analytical developments, pharmacokinetic and pharmacodynamics analyses, and treatment individualization.

Research Platform

The core facility comprises the Laboratory, the Pharmacometrics unit and the Clinical research unit.

<table>
<thead>
<tr>
<th>Laboratory</th>
<th>Pharmacometrics</th>
<th>Clinical research unit</th>
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<tr>
<td>- drug concentrations -</td>
<td>- analysis -</td>
<td>- interpretation, trials -</td>
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<tr>
<td>o Mass spectrometry Platform (HPLC-MS/MS)</td>
<td>o Drug, biomarkers and disease modeling and simulation</td>
<td>o Large and unique expertise in drug level interpretation</td>
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<tr>
<td>o Unique versatility for customized analytical developments</td>
<td>o Clinical Phase I-IV data analysis</td>
<td>o Pharmacovigilance</td>
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<tr>
<td>o Wide range of matrices (total and plasma, whole blood, tissue samples, intracellular drug levels)</td>
<td>o Optimal sampling</td>
<td>o Development of innovative dosage adjustment tools</td>
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<td></td>
<td>o Standardized procedures using state-of-the-art tools (WinNonlin®, NONMEM®)</td>
<td>o Clinical trial unit for phase I and Ila studies, including intensive PK-PD investigations</td>
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</table>

We offer the capability to characterize many aspects related to drugs’ clinical pharmacology, from measurement in blood or
other matrices to assessment of clinical efficacy and tolerability, while integrating all components necessary to understand underlying factors susceptible to modify treatment outcomes.

The Laboratory of Clinical Pharmacology, led by Prof Laurent Décosterd, is in charge of the development, implementation and high-flux use of LC-MS/MS techniques for measuring blood, cells and tissue concentrations of many of the current targeted anticancer drugs and some of their metabolites, for routine therapeutic drug monitoring (TDM) and for fundamental and clinical studies in oncology.

The Mass Spectrometry Platform at Lausanne is equipped with state-of-the art mass spectrometry equipments (HPLC-MS/MS, for quantification) and High Resolution Orbitrap technology (Q-Exactive) for metabolites identification. The Laboratory is strongly implicated in the clinical study organization and logistics of samples and clinical data collection, sample analysis at the laboratory, maintenance of dedicated database, and data analysis for various studies in the field of oncology and infectious diseases.

The unit of Pharmacometrics led by Prof Chantal Csajka is very active in the field of modeling and simulation of pharmaceutical drugs, and has contributed to a better understanding and optimization of drug use in various fields of drug therapy, notably in oncology.

The unit performs state-of-the-art population analyses. Models include classical pharmacokinetics (PK), pharmacodynamics (PD) and PK-PD modeling and simulation, targeted mediated disposition models, tumor growth, biomarker modeling and time to event analyses. Translational models from animal to human are being developed.

The Clinical research unit of the Division of Clinical Pharmacology led by Prof Thierry Buclin has a long-standing culture and line of research in the development of TDM approaches and tools for the optimization of critical treatments. The Division of Clinical Pharmacology is responsible for an investigational phase I unit involved in the CHUV Centre for Clinical Research network. This unit regularly undertakes contract research trials with high academic added value (first-in-man, intensive PK-PD assessments, original PD biomarkers).
Through both assistance and teaching to health professionals involved in clinical research, it maintains a high degree of expertise in good clinical practice, subjects’ recruitment and inclusion, data collection and management, statistical analysis and critical interpretation of study results.

The unit currently participates in the elaboration of an innovative, drug-flexible, user-friendly, highly interconnected TDM software designed by computer engineers. During clinical trials, the unit uses computer tools for the preparation and completion of paper-based or electronic CRF and the constitution of databases (SecuTrial® or MS-Access®) as well as for the graphical presentation and statistical analysis of results (Graphpad Prizm®, STATA® and further tools).

**Group assets**

The group is part of a unique translational research platform within the CHUV and the EPGL (Geneva-Lausanne School of Pharmacy), which provides key advantages for increased collaboration, expertise, and performance in clinical research.
6. SURGICAL ONCOLOGY PROGRAMS

The SCCL features several important surgical programs from the CHUV, which offer cutting-edge expertise and are developing innovative technologies for the surgical management of oncologic patients as well as research programs.

Some underlying programs are highlighted below.

6.1. HEAD AND NECK ONCOLOGY SURGERY

The Service of Head & Neck Surgery at the CHUV is headed by Prof. Christian Simon and organizes its surgical oncology program into seven sub-units.

Transoral surgery

The unit of transoral surgery is headed by Prof. Christian Simon. In this unit, transoral techniques are used to treat predominantly early stage oropharyngeal and supraglottic cancers. The unit is making use of the minimally invasive Da Vinci robotic system which is available on the robotics platform, a collaboration between the CHUV and the Clinique de la Source. This unit has existed since August 2012 and is currently the strongest performing unit in Switzerland. It also includes transoral laser microsurgery on the platform for selected cases.
Endoscopic skull base surgery

This unit is directed by Prof. Philippe Pasche. Prof. Pasche has been developing a platform for endoscopic skull base surgery, which is mostly focused on the treatment of malignancies of the anterior skull base. The approaches are purely endoscopic in order to avoid major morbidity known to be brought about by external approaches. This also includes techniques of dural closure. There is a strong collaboration between the unit and the service of neurosurgery (Prof. Roy Daniel, Prof. Marc Levivier).

Reconstructive surgery

Reconstructive surgery, in particular the reconstruction with microvascular anastomosed free flaps, plays an increasingly important role in the field of head and neck surgical oncology. The service of oto-, rhino-, laryngology and head and neck surgery has a major expertise in this field. There are currently three consultant surgeons who are covering these complex procedures, including Prof. Philippe Pasche with a special interest and expertise in the field of facial reanimation, PD Dr. Martin Broome who is concerned with mandibular and maxillary reconstructions, and Prof. Christian Simon who focuses on free flap reconstruction in the head and neck region, mostly regarding the oral cavity or pharynx/larynx and hypopharynx. This is a highly performing unit with more than 60 free flaps every year.

Maxillofacial oncology

The unit of maxillofacial oncology is part of the division of maxillofacial and oral surgery at the CHUV. This division is directed by PD Dr. Martin Broome. His great expertise in the field of maxillofacial oncology, notably in osseous sarcomas for children and adults, led him to become head of the unit.

Upper airway surgery

The upper airway surgery unit is directed by Dr. Kishore Sandu and Prof. Philippe Monnier. It is part of the Airway Unit that was accredited by the MHS. Complex pathologies of the upper airway are treated there, particularly for children. Malignancies
of these regions are also treated on this surgical and endoscopic platform.

**Lateral skull base surgery**

The lateral skull base surgery unit is directed by Dr. Mercy George and Prof. Christian Simon and functions in very close collaboration with the service of neurosurgery (Prof. Roy Daniel, Prof. Marc Levivier). Almost all cases are performed within this collaboration. Pathologies of the lateral skull base, which comprise malignancies of the parotid gland or the skin with extension into the temporal bone, are treated here as well as pathologies of the cerebello-pontine angle and pathologies of the middle fossa. Great experience with Gamma Knife technology (Prof. Marc Levivier, Head of the Service of Neurosurgery) adds up to the unit’s high level of expertise.

**Translational head and neck oncology**

The unit of translational head and neck oncology is run by Dr. Genrich Tolstonog and Prof. Christian Simon, where Dr. Genrich Tolstonog is heading the research. This unit consists of a large laboratory platform located in Epalinges. With more than three post-docs, several technicians and multiple students, the laboratory is concerned with elucidating mechanisms involved in tumor invasion and metastasis that may contribute to the development of local recurrences after surgical treatments of oropharyngeal cancer. Multiple animal models have been developed to study these types of biological phenomena and are currently in use in a small mouse hospital that was built within the structure and is run by the members of the laboratory.

### 6.2. THORACIC ONCOLOGY SURGERY

Headed by Prof. Hans-Beat Ris, the Service of Thoracic Surgery of the CHUV provides over 700 specialized surgeries per year and has long-lasting collaborations with other specialties such as pneumology, oncology, radiation-oncology and a research/developmental pole for the adaptation of novel technologies/treatment concepts to the clinic with prior validations in pre-clinical models. Surgical approaches include
l Lung cancer surgery (minimal invasive, part of a complex multimodal management with extended resections such as the tracheo-bronchial tree, major vessels, vertebrae, chest wall), mediastinal surgery (minimal invasive, thymoma, esophageal perforations), pleural surgery for the management of thymoma and mesothelioma (extended pleural decortications and pleuropneumonectomy), chest wall deformity surgery, cervical-thoracic junction surgery (thoracic outlet surgery, cancer surgery) and a program of lung transplantation. Over the past 10 years, the Service of Thoracic Surgery has continuously developed, innovated and improved its expertise for the management of thoracic malignancies. A small summary of the current activity is described hereafter.

**Surgical innovations for managing advanced Non Small Cell Lung Carcinoma (NSCLC) using multimodal approaches**

For many years, our service has been interested in the management of locally advanced NSCLCs using multimodal approaches. Multiple SAKK protocols were developed and co-chaired by members of the service. Currently, the SAKK 16/08 protocol is directed by a joint team of oncologists and surgeons of Lausanne. The trial was designed to determine the role of immunotherapy in the neoadjuvant setting as an adjunct to neoadjuvant chemo-/radiation therapy combined to surgery for the management of locally advanced (T4N0-1M0 or T1-4N3M0) NSCLC patients.

Our service was very innovative regarding novel techniques in order to push the limits of surgery in the context of locally advanced NSCLC with local invasion. One example is the use of extra-thoracic muscle flaps to substitute airway/esophageal defects or alleviate anastomotic tension for tracheo-carinal reconstructions (Figure). We have shown low postoperative mortality and rewarding functional long-term results in a recently updated follow-up on 71 patients. Other innovations also include vena cava or other great vessel resections and reconstructions. With these surgical innovations, a complete resection is more likely to be obtained after surgery and induction therapy, which results in rewarding overall and progression free survival for T4N0-2 NSCLC disease. In the close future, we plan to complete the ongoing SAKK16/08 trial.
and contribute to improve the management of locally advanced NSCLCs with multimodal therapies.

**Minimal invasive video assisted thoracoscopic (VATS) approaches**

Over the past years, minimal invasive procedures for thoracic malignancies have gained acceptance in the scientific community. The minimal invasive VATS program was initiated in the service in 2010. The proportion of patients and complexity of the procedures have been increasing dramatically with a current 50 to 50 ratio of open versus VATS procedures. We have observed a clear reduction in the mean hospital stay and morbidity of patients with the VATS technique and have developed standardized perioperative protocols for patient management. We are also initiating an enhanced recovery after surgery (ERAS) program to further improve the perioperative management of patients undergoing VATS procedures. Finally, we have demonstrated the equivalence of the VATS procedure compared to open for mediastinal lymph node dissection. The limits of minimal invasive surgery are being pushed further every day. In Lausanne, we have built upon our experience and have developed a left-sided VATS approach for the management of anterior mediastinal lesions/malignancies (Figure). This approach allowed equivalent thymic resections while avoiding sternotomy and improving perioperative morbidity and hospital stay. We will continue to extend these minimal invasive approaches to more challenging cases and plan to begin a robotic surgery program for specific and challenging VATS cases.

**Lung Metastases**

Resection of lung metastases (LM) from colorectal cancer (CRC) is increasingly performed with a curative intent. In a systematic review and meta-analysis to determine which risk factors were associated with poorer survival after lung metastasectomy for
CRC, we could identify four parameters significantly associated with poor survival: short disease-free interval between primary tumor resection and development of lung metastases, multiple lung metastases, positive hilar and/or mediastinal lymph node involvement and elevated prethoracotomy carcinoembryonic antigen. This aggressive approach may result in prolonged survival and seems to occur only in patients with a single lung lesion. These results have been confirmed in a recent multi-institutional pooled analysis. Due to the progress of radiological imaging with thin-slice high-resolution CT-Scan, solitary lung metastasis is increasingly resected by video-assisted thoracic surgery (VATS).

**Study protocols for the management of pleural malignancies**

Our service has generated important pre-clinical and clinical results on photodynamic therapy (PDT) used as an intraoperative adjunct after surgery for the treatment of pleural mesothelioma. More recently, we have explored the use of low-dose PDT combined with systemic chemotherapy in the field of pleural malignancies. We have shown that low-dose PDT could improve the transport properties of tumor vessels, reduce interstitial fluid pressure and enhance vascular convection and subsequent chemotherapy distribution in tumors. Building upon these results and based on pre-clinical safety studies in animal models, we are in the process of initiating a phase I clinical trial in patients with malignant pleural effusions. We plan to apply intrapleural low-dose PDT by thoracoscopy to help potentiate the tumor response with subsequent systemic cisplatin-based chemotherapy application. Based on our pre-clinical findings, low-dose PDT is expected to improve tumor vascular transport for up to one month. This is predicted to improve tumor response to chemotherapy.

A separate protocol for resectable mesothelioma was also initiated by Lausanne. In this protocol, we plan to combine chemotherapy and radiation-therapy to lung-sparing surgery for the management of stage I-III epithelial mesothelioma. Because of the improvements in radiation therapy (IMRT approaches), we plan to apply a maximal cytoreduction concept combining neoadjuvant chemo-radiation therapy for best resectability, while preserving the lung parenchyma. This phase
I-II study based on a Simon’s two-stage approach will determine the feasibility of this approach as a primary endpoint as well as the patient quality of life, overall survival and progression free survival in a phase I-II trial.

6.3. VISCERAL ONCOLOGY SURGERY

The Service of Visceral Surgery at the CHUV is led by Prof. Nicolas Demartines and offers specific surgical oncology programs.

**Hepato-Pancreatico-Biliary surgery**

The service treats all liver, biliary and pancreas tumors and metastasis, and works on a multidisciplinary basis with interventional radiology, hepatology, gastro-enterology and medical oncology. Liver metastasis, cholangiocarcinomas, hepatocellular carcinomas, and pancreatic adenocarcinomas, as well as neuro-endocrine tumors are the main tumors treated. All modern surgical and innovative approaches are offered. In 2014, 24% of liver resections were performed by laparoscopy.

**Upper GI: Oesophagus Cancer, Gastric Cancer**

As gastric cancer incidence decreases, oesophagus cancer increases dramatically, and thanks to progress in anesthesiology, almost all patients may be offered surgery. The best outcomes are for patients with complete response to pre-operative chemo-radiations, without increasing the morbidity. Minimal invasive approaches are included.

**Colorectal surgery**

All colonic, rectal and anal cancers are operated generally using a minimal invasive approach (70% of operations). The service also offers robotic rectal surgery. An original data assessment study suggested that robotic total mesorectal excision quality is superior to laparoscopic specimen. However, oncological benefit has not been demonstrated yet. The service also provides expertise in transanal surgery.
Endocrine and neuro-endocrine tumors

Endocrine and neuro-endocrine tumors are treated on a multidisciplinary basis, utilizing minimally invasive and radio-guided surgery.

HIPEC and PIPAC

Hyperthermic Intraperitoneal Chemotherapy (HIPEC) and Pressurized Intraperitoneal Chemotherapy (PIPAC) are two strategies to treat peritoneal carcinosis, which is the presence of neoplastic nodules caused by the spreading of a primary or secondary tumor in the peritoneal cavity. HIPEC consists of a two-part operation: during the first part, the surgeon debulks as much of the neoplastic nodules in the peritoneal cavity as possible, and in the second stage the peritoneal cavity is washed with a hyperthermic chemotherapy solution, where a solution containing a high concentration of chemotherapy drugs is heated to above body temperature (usually 41.5°-42.5°C) which increases absorption of the drugs by the target tumor and therefore their effectiveness. PIPAC is a technology by which chemotherapeutic agents are administered to the tumor, using a pressurized aerosol applied directly into the abdomen. The CHUV has had expertise in the field for about 8 years, in particular for colorectal, gastric, ovarian or primary peritoneal carcinomas. These strategies require advanced surgery, oncology, anesthesia and intensive care competences. Outcomes are very promising for advanced disease as well.

Specific Melanoma and Sarcoma surgery

Sarcoma and melanoma surgery is highly specialized and requires a dedicated surgical and medical oncology team, combined to various other specialists like plastic and reconstructive surgery professionals. For extreme melanoma and sarcoma cases, the service is the only accredited center for Isolated Limb Perfusion (ILP) with tumor necrotizing factor. This treatment is a way of giving high doses of anti-cancer drugs, such as chemotherapy, directly into a leg or an arm to control cancer that is confined to that area. This treatment prevents amputation of limbs.
6.4. UROLOGIC ONCOLOGY SURGERY

Genito-urinary cancers, mainly prostate, bladder and renal cancers are extremely frequent diseases. Under the direction of Prof. Patrice Jichlinski, Head of the Department of Urology at the CHUV, the following research programs are ongoing.

Non-muscle-invasive bladder cancer (NMIBC) management

A fundamental and clinical research program was launched in 1993 within a UNIL, CHUV and EPFL collaboration to develop and market a photodiagnostic substance for early bladder cancer detection and Non-Muscle-Invasive Bladder Cancer (NMIBC) disease management. This detection approach has been commercialized in Europe in 2005 as Hexvix™ PDD (PhotoDynamic Diagnosis) and in the U.S. in 2010 as Cysview®. The principle is to induce a specific sensitization to light for cancer cells that are found in the bladder and make them fluorescent. Hexyl aminolévulinate is the name of the molecule instilled into the patient's bladder about an hour before the exam. This product is capable of getting cancer cells to accumulate and produce more photoactive porphyrins. These natural molecules have in fact the property of being fluorescent. The doctor may then examine the inside of the bladder using an endoscopic camera - or cystoscopy - not only equipped with a standard white light but also a special blue light that detects fluorescent spots identifying the tumor cells.

The advantage of fluorescence cystoscopy is to detect small tumors that remain invisible in conventional examinations, in particular carcinoma in situ. In addition, the surgeon can remove
tumors with much greater precision, thus promoting a significant reduction in the risk of recurrence. Resulting from a strong collaboration between different Lausanne institutions (CHUV, UNIL and EPFL), this success illustrates perfectly the immediate clinical applications that basic and translational research can generate.

Additional research is ongoing in an international collaboration between the University of Lorraine - France, the Ludwig Maximilian University-University Hospital - Germany, and the CHUV to develop a new concept of bladder endoscopic exploration called 4M-Cysto or Multispectral Macro-Magnification Mosaicing Cystoscopy.

Furthermore, under the leadership of Dr. Nardelli Haefliger and Dr. Laurent Derré, the Urological Research Unit of our Department is currently developing new immune strategies for NMIBC management. These progresses are of prime importance as NMIBC, known as a highly recurrent disease for years, deeply impacts health costs.

**Low and intermediate risk localized prostate cancers**

In our multidisciplinary prostate cancer unit, a program is raised aiming at developing minimally invasive approaches for low and intermediate risk localized prostate cancers. Protocols in progress include active surveillance, targeted prostate biopsy guided by MRI-US fusion image system and focal therapy. Regarding the latter, a program involving a new and innovative robotic High Intensity Focused Ultrasound (HIFU) device fully dedicated to focal therapy of prostate cancer will start in early 2015 in collaboration with the Department of Urology at the HUG-University Hospital in Geneva headed by Prof. Christophe Iselin.

Focal therapy in prostate cancer aims to treat only the part of the gland harboring clinically significant disease while preserving the rest of the tissue. This approach may substantially reduce treatment-related toxicity without compromising disease control outcomes. Short- to medium-term functional and oncological results in prospective interventional studies are promising, but comparative effectiveness research against standard of care is required to incorporate focal therapy among standard options.
6.5. GYNECOLOGIC ONCOLOGY SURGERY

Under the direction of Prof. Patrice Mathevet, Head of the Service of Gynecology at the CHUV, the service is developing several aspects of clinical research in the field of gynecologic oncology.

Sentinel node technique

The first domain relates to the development of the sentinel node technique for gynecologic cancers and in particular cervical and endometrial carcinomas. We have demonstrated through several prospective studies that identification of sentinel nodes (SN) enhance the management of early cervical and endometrial carcinomas.

The first advantage of the SN technique is the identification, in 15-20% of cases, of SNs that are located in abnormal position due to aberrant lymphatic drainage. These lymph nodes would be missed with a classical pelvic lymph node dissection and they can display a metastatic involvement without implication of the other pelvic lymph nodes. The second benefit of the technique is the intraoperative identification of SNs that can be submitted to frozen sections. This identification can modify the surgical strategy: in case of positive SN, the lymph node dissection is extended to the para-aortic area and the patients are referred to a radiotherapist while omitting radical hysterectomy. The third advantage of the SN technique is that it allows the performance of ultrastaging with serial sectioning and immunohistochemistry on a limited number of nodes. The detection of micrometastases is an important risk factor of recurrence in apparently node-negative early cervical cancer and the presence of this risk factor in some patients should specify them for adjuvant treatment. Last, performing a limited resection of SN and omitting full pelvic lymph node dissection provide a decreased morbidity and enhance patient recovery.

We currently develop new markers for the identification of the SN. The benefits arising from these new markers encompass enhanced detection rate, decreased risk of allergy and easier handling. We are also setting a prospective multicentre study in order to better identify the lymphatic pathways of endometrial
carcinomas dissemination so that the SN technique detection rate for this tumor is improved.

**Fertility preservation**

The second domain of clinical studies development relates to the preservation of the fertility and features two different approaches.

First, we have created a multidisciplinary network around fertility and cancers, the “Réseau Romand Fertilité et Cancers”. This network includes all hospitals and private clinics of the French-speaking part of Switzerland (Cantons of Geneva, Vaud, Valais, Neuchatel, Jura and Fribourg) and gathers multiple specialists around oncology and fertility: gynecologists, oncologists, radiotherapists, urologists, pediatrics, biologists, hematologists etc.

All patients wishing to preserve their fertility are asked to participate to the network. Upon their agreement, their medical data are transmitted to the network, examined and therapeutic options are thus proposed in order to protect and maintain their fertility. A prospective anonymous database has been set up with all different cases referred to the “Réseau Romand Fertilité et Cancers”. There have already been publications through this database. In addition, a one-day conference meeting on fertility and cancer is organized by the network every 18 months. The goal of this network is to improve the management of young cancer patients while trying to provide them with fertility preservation options without decreasing their chance of being cured.

Second, we have developed new oncologic treatments in order to preserve the fertility of patients with gynecologic cancers. For cervical cancer patients, our team offers the option of radical trachelectomy, an operation that allows patients with early cervical cancer to be efficiently treated while preserving their uterine corpus, tubes and ovaries. New development of this approach is a prospective study of chemotherapy followed by radical trachelectomy for patients with more advanced cervical cancer. Fertility preservation surgical options are also offered to patients with early endometrial and ovarian carcinomas.
7. PEDIATRIC ONCOLOGY

Under the leadership of Dr. Maja Beck Popovic, the Unit of Pediatric Hematology Oncology keeps expanding existing and developing new clinical and research activities.

Clinical care

The care of pediatric patients with cancer is centralized at the CHUV. Diagnostic procedures, choice of treatment and follow-up are discussed and reviewed within specific recurrent tumor board meetings featuring multidisciplinary teams with designated collaborators from pediatric surgery, orthopedics, radiology, neuroradiology, nuclear medicine, pathology, radiotherapy, ophthalmology. The unit has been designated by the Swiss Organism for Highly Specialized Medicine as a national reference center for retinoblastoma (in 2011), and a regional reference center for neuroblastoma and sarcoma in children (2013). This allowed establishing well-defined patient channels, to improve communication among the specialists and to establish a common tumor board with the pediatric oncology unit in Geneva.

Our expertise in treatment and care of retinoblastoma, in collaboration with Prof. Munier’s team from the Jules Gonin Eye Hospital, allowed the introduction of new conservative treatment techniques for eye preservation and avoidance of radiotherapy:
- Intraarterial chemotherapy in collaboration with interventional radiology of the Radiology Department (Dr. Stefano Binaghi),
- Intravitreous chemotherapy, performed at the Jules Gonin Eye Hospital.

In addition, our activity within the European Group of neuroblastoma (SIOPEN), as national PI for the High risk protocol, international PI for localized neuroblastoma, as reference laboratory for some immunohistochemical and molecular analyses for neuroblastoma (in collaboration with the laboratory of Prof. J. Schoumans) allowed the launch of innovative treatments such as immunotherapy with anti-GD2 + interleukin 2, as well as radio-immunotherapy using radiolabelled metaiodobenzylguanidine (MIBG) for metastatic
neuroblastoma. The latter is performed in tight collaboration with Dr. Ariane Boubaker.

Moreover, in collaboration with the Service of Medical Genetics (Dr. Sheila Unger), the unit will develop regular genetic counseling for families with children that present genetically based pediatric tumors and for patients with cancer predisposition due to their basic genetic disease.

Importantly, on the strength of the CHUV experience in neuro-oncology, with the upcoming of new radiotherapy techniques and increased knowledge in molecular biology of brain tumors, a collaborative work with Prof. Bourhis from the Service of Radiation Oncology and the adult neurooncology research laboratory is planned to explore possible benefits of novel radiotherapeutic techniques and the role of systematic enlarged molecular analysis of brain tumors for potential use of new drugs.

Concomitantly to the development of the regional and national platform for fertility preservation in young women, the unit started a collaboration with the HUG pediatric unit in Geneva for fertility preservation in prepubertal girls receiving gonado-toxic chemotherapy and/or radiotherapy. The same approach has been developed for prepubertal boys, as a prospective clinical research protocol.

**Research aspects**

After over 20 years of international scientific acknowledgements in the field of neuroblastoma research, Dr. Nicole Gross will hand over the direction of the pediatric oncology research laboratory to Dr. Raffaelle Renella, with the aim to i) keep reinforcing research in neuroblastoma in collaboration with other laboratories such as in pathology (Prof. Stamenkovic), in molecular biology and cytogenetics (Prof. Schoumans), ii) extend to other pediatric embryonal tumors, and iii) develop new research fields such as gene therapy and cellular therapy for which Dr. Renella has remarkable expertise. This will require additional collaborations with laboratories active in the field of cancer and immunology and with colleagues from adult oncology and hematology disciplines.
8. NEW INTERDISCIPLINARY COLLABORATIONS

8.1. THE CHUV BRAIN METASTASIS PROGRAM

Brain metastases are cancer cells that have spread to the brain from primary tumors in other organs in the body. Metastatic tumors are among the most common mass lesions in the brain. In recent years, newer systemic treatments have resulted in significant extension of survival for patients with various types of cancer, including melanoma, breast and lung cancer, allowing many patients to live longer with the disease than ever before. Unfortunately, because of the presence of the blood brain barrier, the brain still represents a safe harbor where metastatic cells can develop, protected from chemotherapeutic treatments, and many patients will develop brain metastasis, sometimes months or even years after their original cancer treatment.

Thanks to a good systemic control of those new therapies, clinical conditions of patients are also increasingly improved. Clinical management of brain metastasis has therefore become critical to ensure the best possible outcome for the patients, regarding both extension of survival and quality of life. For many years, whole brain radiation therapy represented the standard approach for all patients with brain tumors. With the development of new approaches, the management of brain metastasis has become more and more complex as treatment needs to be tailored to the situation of each individual treatment.

At the CHUV, a number of cutting edge approaches are available for patients with brain metastasis:

**Surgery:** Neurosurgical resection of a single (or a limited number of lesions) might be considered to achieve maximal disease control and/or to alleviate the neurological symptoms induced by the metastasis. To ensure both an optimal resection and to minimize the risks of secondary complications, the neurosurgeons at the CHUV may use intraoperative monitoring or awake surgery.
Radiation therapy: radiotherapy plays a critical role in the treatment of brain metastasis, and includes whole-brain irradiation, fractionated radiotherapy, and radiosurgery. Stereotactic radiosurgery alone or with whole brain radiation therapy has been shown to achieve excellent local tumor control. Addition of stereotactic radiosurgery to whole brain radiation can increase the control rate and functional status of patients. At the CHUV, depending on the situation, the specialists may use Gamma Knife, Cyberknife or Linnac systems to ensure the optimal delivery of RT.

Chemotherapy: In some rare situations, chemotherapy that is able to cross the blood brain barrier might be the optimal treatment for patients with brain metastasis.

To ensure the optimal management of patients with brain metastasis, the Brain Metastasis Program was set up between the Services of Radiation Therapy (Prof. Bourhis & Dr. Schiappacasse), Neurosurgery (Prof. Le vivier), Neuro-radiology (Prof. Meuli), and the Unit of Neuro-oncology (Dr. Hottinger). This multidisciplinary CHUV team works to promote a unique medical scientific platform including all the existing possibilities for ablative treatments along with other innovative systemic approaches. This new brain metastasis clinic started in June 2014.
and is being held weekly through joint tumor board meetings, with the aim of providing a personalized approach for each patient and for each brain metastasis. Optimal management of every patient with brain metastasis and referred for radiation therapy is indeed discussed and the most appropriate treatment approach is determined, depending on clinical review, neuroradiological images, overall prognosis and the extent of neurological deficits.

Since the tumor board has been established, a total of 138 cases have been reviewed. Main diagnoses, as well as the number of metastasis per patient and the treatment decisions are showed in the following graphics.

**Diagnosis (N = 138 patients)**

![Diagnosis Pie Chart]

- Lung: 61%
- Melanoma: 13%
- Colorectal: 12%
- Breast: 3%
- Esophagus: 1%
- Prostate: 1%

**Number of Metastasis per patient (N=138)**

![Number of Metastasis Chart]

- 1: 3%
- 2 - 4: 13%
- 5 - 10: 4%
- Multiple: 1%

**Treatment decisions (N = 138)**

![Treatment Decisions Pie Chart]

- Gamma Knife or CyberKnife: 42%
- Surgery: 12%
- Whole Brain Tomotherapy: 3%
- Systemic treatments: 13%
- Follow-up: 2%

8.2. **RECENT COLLABORATIVE RESEARCH INITIATIVES**

Developing interdisciplinary research collaboration programs is one of the highest priorities of SCCL. We promote initiatives by integrated teams from all SCCL institutions and our collaborators, aimed at developing new knowledge and/or technologies that will advance therapeutic, preventive or diagnostic interventions, with potential to make a significant impact on clinical practice.

Below we present two such recent initiatives.

**Translational Research in Melanoma**

This is a program supported by a Swiss National Science Foundation TransMed grant (CHF 1.9M): “Co-clinical trials multi-targeting oncogenic drivers, angiogenesis, and the tumor-promoting lymphatic microenvironment in melanoma”

**Collaborative team:** Prof. Douglas Hanahan (EPFL), Dr. Krisztian Homicsko (CHUV/EPFL), Prof. Olivier Michielin (CHUV/UNIL), Dr. Emanuela Romano (CHUV), Prof. Daniel Speiser (CHUV/UNIL) and Prof. Melody Swartz (EPFL)

**Background**

Malignant melanoma, a curable disease when discovered early, carries a poor prognosis when diagnosed late as locally advanced or disseminated disease. Melanoma genetics led informed development of therapies blocking the BRAF-MAPK pathway (vemurafenib, dabrafenib, trametinib). Patients on therapy live longer but the survival benefit is typically measured in months, and most patients relapse. Blockade of inhibitory immune-checkpoint regulators (via anti-CTLA4 and anti-PD1 antibodies) in the tumor microenvironment (TME) has also shown benefit, although lasting tumor control is only achieved in a subset (15-20%) of patients with malignant melanoma.

There is an evident need to better understand the mechanisms limiting efficacy, with the goal of extending the duration of both classes of melanoma therapy. Little is known about the roles that the tumor microenvironment (TME) might play in
resistance mechanisms to either class of current therapy. Previous studies from the Swartz and Hanahan labs at EPFL have shown that lymphangiogenesis and blood vessel angiogenesis are instrumental in shaping tumor phenotypes during progression, and explored the efficacy and adaptive/evasive resistance to targeted therapies, including the VEGF/VEGF-receptor signaling axis that governs both forms of angiogenesis. Notably, however, clinical trials of anti-angiogenic mono-therapies have not proved efficacious in metastatic melanoma, implicating adaptive resistance.

Goal

The platform’s goal is to improve melanoma therapy and propose novel combination therapies by investigating the concordant inhibition of MAPK signaling, angiogenesis and lymphatic-based tumor tolerance. This will be tested first in mechanism-guided preclinical trials in mouse models of melanoma at EPFL, and then in small proof-of-concept co-clinical trials at the CHUV. Clarifying the parameters and potential roles of the TME in resistance both in mice and humans will guide rational combination treatment strategies.

Axes of the Initiative

The platform will house the four following projects:

Project 1. Profile the effects of B-Raf/Mek inhibition on the angiogenic phenotype in mouse models of melanoma and perform preclinical trials combinatorially targeting B-Raf and angiogenesis.

Project 2. Profile the angiogenic phenotype in human melanoma prior, during, and upon failure of B-Raf/Mek inhibitors, and initiate Phase Ib combination trials guided by the pre-clinical trials.

Project 3. Analyze the lymphatic microenvironment in melanoma models for immunosuppressive signaling, and perform preclinical trials with pharmacological agents aimed to unleash tumor immunity.

Project 4. Similarly analyze the lymphatic microenvironment in patients with melanoma and launch phase I trials, guided by the pre-clinical trials.
The potential ‘return on investment’ of this platform is to translate, from studies in mouse models of an intractable human cancer, combined with cross-species comparisons of mouse and human melanoma, new knowledge of mechanisms of the disease, with a particular focus on better understanding the tumor microenvironment and the associate lymphatic microenvironment, the roles of both in adaptive resistance to therapy. The translational culmination of the closely integrated teams at EPFL and CHUV will be in proof-of-concept clinical trials, guided, incentivized, and prioritized from mechanism-based pre-clinical trials performed in mouse models of melanoma. The end result could be improved therapies for melanoma patients, who almost invariably relapse in the face of current standards.

**Antibody Discovery and Engineering: an Integrated Platform Initiative**

**Collaborative team:** Dr. Steven Dunn (CHUV), Prof. Olivier Michielin (SIB/CHUV/UNIL), A. Prof. Elena Dubikovskaya (EPFL)

**Background**

Following the pioneering invention of B cell hybridoma technology in the 1970s by Milstein and colleagues, monoclonal antibodies derived from immunized rodents have led to paradigm shifts across many areas of life science R&D, underpinning an explosive evolution in diagnostic, imaging and assay technologies, and driving the emergence of powerful ‘biologic’ therapeutic approaches as alternatives to traditional small molecules. Over the last few decades, sophisticated *in vitro* approaches have been developed to essentially exploit sequence knowledge of the immune gene loci in order to generate fully recombinant ‘libraries’ of rearranged and permuted immunoglobulin repertoires. Such repertoires can be expressed as polypeptides and screened for binders to *in principle* any antigen, independent of species and not subject to host animal immune response constraints. These so-called ‘display’ technologies exploit the principle of phenotype/genotype linkage, allowing the rapid and easy isolation of DNA sequences
corresponding to the binding antibody fragment of interest. This in turn facilitates subsequent manipulations of the molecule, including fragment reformatting for expression, additional mutagenesis and screening (affinity maturation), and optimization of quality parameters for therapeutic development. For the latter, a key attraction of *in vitro* display approaches is the ability to generate libraries directly from human donors.

**Goal**

It is apparent that a strong demand exists within the global LICR and its collaborative network for novel monoclonal antibodies (mAbs) and immunoglobulin reagents - with properties and specificities not currently available commercially - in order to support basic scientific discovery and translational therapeutic programs. The project therefore aims to build a coherent and structured platform resource capable of addressing these challenges, the L-AbCore or Ludwig Antibody Core.

**Axes of the Initiative**

This initiative will comprise four distinct yet highly complementary core activities aimed at developing optimized affinity reagents:

- **Centralized phage display discovery and screening platform for *de novo* discovery:** *de novo* mAb discovery and general antibody and T-cell receptor affinity engineering activities. This will involve the construction of phage display libraries from the peripheral blood of human donors who can be either considered healthy (‘naïve’) or diseased (‘immunized’). Following the establishment of a primary naïve library resource, additional sub-libraries derived from alternative tissues, Ig isotypes and diseased human donor cohorts can be generated on an *ad hoc* basis as sources of additional, exploratory content. In addition, the parallel construction of a large naïve murine library resource remains a further option, as does the routine construction of small project-specific libraries derived from immunized mice.

- **In vivo immunization and NextGen sequencing** capability, providing options with wild type or immunocompetent knock-out mice as well as mice engineered with human immune systems to isolate fully human antibodies.
In silico modeling and structure-guided design to integrate state of the art in silico rational design, modeling, and affinity prediction expertise. These have the potential to impact on all aspects of immunoglobulin discovery and optimization, including the early structural evaluation of target molecules in order to help guide project feasibility and prioritization decisions.

Application-tailored immunoconjugate synthesis. This activity will in fact incorporate sophisticated downstream chemistry expertise that will allow the customized functionalization of antibodies with conjugates appropriate for diagnostic, therapeutic, or other in vitro or in vivo applications.
9. CENTERS OF EXCELLENCE

A Center of Excellence provides leadership, best practices, research, supportive care, education and training for a focus area. Within the field of cancer, its aims are to optimize the treatment and care of patients diagnosed with a malignant disease.

The CHUV plans to develop centers of excellence for all main tumor areas within the next 3-4 years. Each center unites all the skills necessary to take care of patients diagnosed with a malignant disease within a patient-centered structure. This approach secures the coordination of care, from the diagnosis to post-treatment follow-up, in accordance with best practice recommendations of each specialization (EBP-Evidence Based Practice), creating as many fast-track clinical pathways and one-stop-shop opportunities to care.

The goals of a center are to:

- assure the quality of care: personalized, timely, safe, equitable, fair, efficient and effective
- guarantee interdisciplinary team work
- offer a comprehensive treatment plan to the patient
- develop innovation through clinical and translational research
- ensure the development of skills
The SCCL clinical platform with the CHUV, works on developing Centers of Excellence in oncology by stipulating that the following criteria are met:

- interdisciplinary teams, composed at the very least of: a team of surgeons, a team of medical oncologists, a team of radio-oncologists, a dedicated radiologist and a dedicated pathologist. The final composition of the teams can vary according to the relevant pathology.
- recommendations of good clinical practices (guidelines)
- clinical pathways to make guidelines operational, to coordinate and ensure the continuity and consistency of care, to minimize delays and maximize efficiencies.
- weekly tumor boards to discuss diagnostic and therapeutic strategies
- unique entry point allowing the patient to be easily guided through the various treatment stages (secretarial office and telephone number).
- clinical referring nurse to cover the bio-psycho-social needs and provide information and advice to the patient
- database allowing the systematic gathering of a clinicopathologic and experimental dataset in order to support evaluation of practices, benchmarking and research

Anne-Claude Griesser
Adjunct Medical Director, CHUV

« I supervise the creation and organization of the Interdisciplinary Centers in Oncology. This assumes that I oversee the constitution of the interdisciplinary teams in each center, the coordination of patient management, the developments based on good clinical practices, the monitoring of our quality of care evaluation policy. My priority is to make sure that the centers are being established with a main focus on patients.

What I like in working towards the establishment of these centers is not only provide assurance that first-class technologies and treatments are being set-up and used but also develop patient care under a humanistic approach with a strong management of patient care (information to patient, support to patient and family, symptom management).

The SCCL will evidently create a reservoir of distinguished scientists, bring competences together, facilitate exchanges and collaborations between them to develop the best treatments and care. It will also benefit to a critical mass of patients in Switzerland and internationally. »
The Breast Center

The CHUV Breast Center was awarded the Quality Label of the Swiss Breast Centers by the Ligue Suisse contre le Cancer and the Swiss Senology Society. By providing measurable comparison criteria and transparent audit proceedings, these organizations aim to promote the quality of treatment and care of women suffering from breast cancer. Their audit (November 2013) concluded that the one hundred criteria - relating to subjects such as information, patients’ rights, the diagnostic procedures and treatments - are met at the CHUV.

The award of this Quality Label attests the quality of the coordinated, interdisciplinary and patient-centered care. “This certificate highlights our commitment to women suffering from breast cancer. It is also a worthy acknowledgement of the work of all of our team”, underlines Professor Jean-François Delaloye, Medical Director of the Breast Center.

In 2013, 220 new cases were treated at the Breast Center. Sixty-seven patients were included in local, national or international studies.

“This certificate highlights our commitment to women suffering from breast cancer. It is also a worthy acknowledgement of the work of all of our team”

Professor Jean-François Delaloye, Medical Director of the Breast Center.
The collaboration agreements planned with Geneva and the Suisse Romande cancer network, which will largely increase the number of patients with access to innovative clinical trials, and the integration of SCCL research groups investigating breast gland development, breast cancer oncogenesis, BRCA genetics, and the tumor microenvironment, will complete the Breast Center of Excellence.

Innovative clinical studies are being prepared, including investigator-initiated radio-immunotherapy with $^{149}$Tb-bombesin targeting the gastrin-releasing peptide receptor; a phase I study testing the combination of hypofractionated stereotactic radiation with immune therapy for locally advanced breast cancer; a whole tumor lysate vaccine; and adoptive T cell therapy using TILs in Her2$^+$ and triple-negative tumors, in addition to targeted molecular therapy driven by pharma and cooperative groups.

**Future plans for center development**

The CHUV has launched the **Center for Thoracic Oncology** in 2014. Over 200 new patients suffering from thoracic tumors are treated by the CHUV annually. The recommendations for clinical practices have been finalized and have been made available in pocket-format for optimal distribution to the medical teams. The restructuring of the consultation pathways entailed the creation of a dedicated oncology consultation by the pulmonology service, the installment of two referring nurses, and a standardized form for case-presentation at the weekly interdisciplinary tumor board. The Center features several signature programs of clinical innovation, including innovative imaging-guided bronchoscopic biopsies, advanced surgical procedures, state-of-the-art medical management featuring sequencing and biomarker-guided personalized therapy, immunotherapy, and stereotactic hypofractionated radiation combined with diaphragm immobilization respiratory assistance which maximizes precision targeting. In addition, pilot studies with intrapleural photodynamic therapy are available for mesothelioma. An advanced immunotherapy program with adoptive T cell therapy for NSCLC is planned for 2016.
The preparations for the creation of the Center for Genitourinary Cancers include the establishment of a clinical fast-track pathway for the diagnostic phase, the reorganization of the urology consultations, the elaboration of a standard case-presentation form for the weekly interdisciplinary tumor board, and the creation of a database. The recruitment of an internationally acclaimed urologic endoscopic surgeon, which is ongoing, will enhance the visibility of the CHUV GU Center.

Jacqueline Jeanmonod

Project Leader at Medical Direction Office and Administrative Director of the Breast Center, CHUV

« I manage a team of 10 collaborators within the Interdisciplinary Center in Oncology, the objective of which is to bring the right competences and expertise to the development of interdisciplinary centers until the declaration of their official accreditation. To guide them towards successful building of the center, we organize meetings with the field protagonists including medical doctors, nurses, chief clinical nurses, physiotherapists, surgeons, oncologists, radiotherapists, pathologists, radiologists etc... We create guidelines to ensure good clinical practice in the center, we formalize the center interdisciplinary Tumor Board meeting.

Working together and in synchronization with numerous field professionals is very satisfying: we create spaces for dialogue to discuss interdisciplinarity, administrative improvement of health care management, with the common ultimate goal to reach clinical care excellence for the patient. In the end, the emergence of an established or accredited center is very rewarding.

The further development and consolidation of these centers under the SCCL enterprise will undeniably create functional synergies between the centers and will facilitate exchanges between them. The SCCL will also be a good communication vector for advocating the excellence of the centers. »
10. ONCOLOGY NURSING

Novel screening and diagnostics technologies, together with innovative treatments, have contributed greatly to the evolution of patients needs for care and medical attention in various therapeutic areas including chemotherapies, radiotherapies or targeted therapies.

Cancer diagnosis announcement remains a major upheaval for patients and their family. In the face of the disease, patients expect the nursing and medical staff to devote time and explain what exactly is happening to them. They want to be taken care of with respect and dignity and need to develop a trust relationship with their care team.

Our missions and values

The healthcare circuit in oncology is a complex multi-step process involving different cancer specialists. Our care team will therefore focus on an adequate healthcare coordination and interdisciplinary collaborative work.

The patient is, above all, at the heart of oncology nursing. Throughout the healthcare path, disease and treatments, oncology nurses from the CHUV combine knowledge and competences focused on the disease impacts for the patient and their family. The nurses offer physical, psychological and social support throughout patient care management. Fully considered as partners, the patient and their family are informed and educated in order to protect their autonomy, to prevent treatment side effects and to manage the symptoms.
When recovery is no longer possible, nurses implement personalized support for the disease terminal phase including respect of human dignity, reduction of physical and moral sufferings while respecting the patient’s choice.

As a result, the values that are crucial to us include:

- Offering global patient care management within a care system that implicates multiple highly specialized medical and nursing care professionals
- Ensuring a continuous relationship between the patient and their own designated nurse who assists them during visits and addresses their issues.

Our resources

The CHUV Department of Oncology is constituted of about 80 nurses and support staff. Two-thirds work in outpatient clinic and one-third is dedicated to inpatient clinic. Nurses are present in all patient care management structures including medical oncology, onco-hematology, radiotherapy, interdisciplinary centers. Our teams will keep expanding in September 2015 when the new outpatient oncology building opens.

Remarkable progress in oncology knowledge and technologies now enables to offer novel treatments and new care management options for patients. Caregivers therefore have to adjust their practices and procedures to these innovations.

Consequently, in collaboration with the CHUV Care Management (DSO) and the Institute of Training and Research in Nursing Sciences (IUFRS) at the University of Lausanne, the CHUV Department of Oncology has developed a top-level on-the-job training program allowing the nursing staff to specialize in clinical research programs and participate in knowledge production. Our care teams are composed of front-line nurses, oncology clinical specialists and practitioners-trainers. Moreover, head nurses may undergo post-graduate training in management making them successful resources for the promotion of quality, security and project management.
Our key projects

In addition to receiving treatments at the forefront of scientific knowledge, patients treated at the CHUV benefit from a network of experts who will provide support care services according to personalized evaluation of patient needs in areas such as psycho-oncology, nutrition, palliative care, aesthetic care workshops, physiotherapy, and social service.

Our nurses with advanced practice in oncology play a key role in care information and coordination for patients cared for in interdisciplinary centers where they provide specialized nurse consultations.

Clinical studies-enrolled patients receive specific care management. They are taken care of by specialized nurses with strong experience in oncology and knowledge of intensive or emergency care, which raises the level of care security. Each team member has undergone clinical investigation training to guarantee the respect of Good Clinical Practices. Furthermore, clinical research nurses can support patients and protect their interests as patient advocates, especially regarding ethical issues.
11. COLLABORATIONS & PARTNERSHIPS

11.1. PARTNERSHIP WITH HUG

In the context of the development of the regional Suisse Romande Réseau d’Oncologie (SRO), a privileged link is being established with the University Hospital of Geneva (HUG, Hôpital Universitaire de Genève) and the University of Geneva (UNIGE).

Spearheaded by the Department of Oncology at UNIL-CHUV and the Center of Oncology at the HUG, the two hospitals are entering in a collaborative agreement aiming to create an integrated program of medical oncology in the Lake Geneva area. This is paralleled by an already existing agreement in bone marrow transplant, which has established an integrated program of Hematologic Oncology between the two hospitals, and a collaborative agreement in progress between the Radiation Oncology services of the two hospitals.

This initiative will seek to maximize coordination and harmonization of clinical practices between CHUV and HUG in medical oncology; integrate clinical oncology research between HUG and CHUV; and maximize integration of HUG Oncology research groups in the SCCL.

Background

CHUV and HUG oncology share a common vision, and together employ over 50 oncologists and over 400 researchers. The two clinical programs combined see more than 2000 new patients and manage more than 50,000 consultations per year. Together they can extend the best treatments to patients within the Lake Geneva region, while maximizing opportunities for world-class clinical and translational research.

Goals

The UNIL-CHUV and HUG partnership in oncology aims to:

- Improve patient care
Harmonize practices and establish common guidelines

Improve communication between doctors and other health professionals by establishing tele-video tumor boards

Improve access to new and best ad-hoc treatments, improve access to clinical studies, and increase the number of patients included in clinical studies

Eliminate barriers to opening clinical trials in both hospitals and establish a rapid bilateral clinical study approval processes

Boost translational research opportunities and collaborations between the two hospitals and integration of HUG groups with the Swiss Cancer Center Lausanne

Improve teaching and training, research and development, and career development

Increase competitiveness and visibility of Lausanne-Geneva as an international cancer center of excellence

Proposed structures

The partnership will be developed around the formation of “programs of excellence” in various oncology domains, starting with melanoma, brain tumors, thoracic malignancies, gynecologic cancers, and oncogenetics.

Each program of excellence will be co-led by a HUG and a CHUV leader for the respective subspecialties. The two co-leaders will work together to define overall clinical strategy and clinical and translational research priorities, as well as operations on common clinical and research activities.

We established a groundbreaking initiative in 2014, focused on brain tumors and melanoma, aiming to the development of integrated clinical programs and innovative collaborative translational research projects in GBM and melanoma, aiming to:

Develop personalized therapy for GBM, including personalized vaccine as well as develop high-resolution imaging – in collaboration with the Center for Biomolecular Imaging (CIMB) - and integrated genomics in GBM patients and matched patient-derived mouse xenografts and make treatment correlations.
• Launch a drug development program between HUG and CHUV in GBM testing new drugs that target the GBM micro-environment hypoxia and cell metabolism

• Develop a project in immune engineering for glioblastoma between HUG and Ludwig Center for Cancer Research of the University of Lausanne/CHUV, including the development of CAR T cell therapy targeting the tumor stem cell and vasculature surface markers

• Assess tumor micro-environmental mechanisms of drug resistance in melanoma

• Develop novel lysate vaccines in melanoma

• Test immuno-radiotherapy combinations

To support this collaboration, the two hospitals are agreeing to harmonize the contracts and ethics approval process, to facilitate building an integrated phase I/II clinical trials program, where clinical trials can be opened simultaneously in both institutions. In addition, the two hospitals will create an information technology interface to allow communication between electronic medical records and clinical research databases.

Pierre-Yves Dietrich
Director, Center of Oncology, HUG, and Full Professor, UNIGE Faculty of Medicine, Geneva

After a complete medical training in internal medicine, hematology and oncology, his research interest focused on Immunology. In 1994, he founded the Laboratory of Tumor Immunology at the Geneva University Hospital with main focus on brain tumor immunology. His research group is providing seminal work in this field, paving the way for the ongoing clinical development of therapeutic vaccines and T cell therapy for malignant glioma. Since more than 30 years, he has been active both as a clinician and a researcher, promoting interactions between biologists and physicians to build a successful translational medicine. He is now playing a major role to design a lemanic concept of cancer care and research.

“The current advances in our understanding in cancer biology and the ongoing development of novel treatment opportunities are fascinating and highly promising. However there are still many challenges and obstacles that we need to face together. In the French part of Switzerland, we are lucky to have two outstanding University Hospitals and Faculties of Medicine, a world-class Polytechnic school (EPFL) and a high level of innovation. Working together to exploit and synergize complementary expertises is just an evidence.” says Prof. Dietrich.
11.2. COLLABORATION WITH THE SIB

The SIB Swiss Institute of Bioinformatics (SIB) is an academic, non-profit foundation recognized of public utility and established in 1998; it is organized as a federation of bioinformatics research groups from leading Swiss universities and the Swiss Federal Institutes of Technology (EPFL and EPFZ).

SIB coordinates research and education in bioinformatics throughout Switzerland and provides high quality bioinformatics services to the national and international research community.

Its 45 world-class research and service groups are currently active in the fields of: proteomics, transcriptomics, genomics, systems biology, structural bioinformatics, evolutionary bioinformatics, modeling, imaging, biophysics, population genetics and clinical bioinformatics in Basel, Bern, Fribourg, Geneva, Lausanne, Lugano and Zurich. Its expertise is widely appreciated and its services, software tools and databases are used worldwide by researchers in life sciences. Specifically, the SIB has a long-standing tradition of producing state-of-the-art software for the life science research community, as well as carefully annotated databases including UniProtKB / Swiss-Prot, the world’s most widely used source of information about proteins.

Several members of SIB are members of the SCCL, their experience and knowledge enhancing the potential of the SCCL research activities. The CHUV which is the SCCL’s clinical platform is one of the SBI’s two partners, along with BioAlps (the Lake Geneva biocluster).

The institutional members of SIB are the Swiss Federal Institute of Technology Lausanne (EPFL), the Swiss Federal Institute of Technology Zürich (ETH Zurich), the University of Basel – Biozentrum, the University of Bern, the University of Fribourg, the University of Geneva, the University of Lausanne, the University of Italian Switzerland, the University of Zurich, the Geneva School of Business Administration (HEG), the Ludwig Institute for Cancer Research (LICR), the Friedrich Miescher Institute for Biomedical Research (FMI), the Geneva Bioinformatics (GeneBio) S.A., and Hewlett Packard.
11.3. **SUISSE ROMANDE ONCOLOGY NETWORK**

Suisse Romande is the French-speaking, Western part of Switzerland, an economically and technologically advanced region with a linguistically and culturally homogeneous population of 1.9 million. Unique strengths of this region include a very high quality of health care, ensured by significant public and private investments, mandatory health insurance, a very high rate of patient compliance, a very strong medical record keeping, and a very high level of competence of physicians. For example, French Switzerland has the highest rates of tumor registry compliance (98%) among Swiss regions. Switzerland (along with Sweden) enjoys the highest cancer survival rates in Europe.

A priority of the SCCL is to establish strong partnerships with the community oncology doctors in the canton of Vaud and the broader Suisse Romande region, in order to maximize the opportunities for high-quality, highly specialized and harmonized care across the whole region, which will also allow patients from the whole region to gain increased access to clinical trials.

To this end, the CHUV is leading the launching of the Suisse Romande Réseau d’Oncologie (SRO) – a network of public and private hospitals and individual clinicians in the canton of Vaud and Suisse Romande who provide oncology care, linked to the two leading University hospitals, the CHUV and the HUG.

This structure aims at maximizing treatment opportunities of community patients, whilst minimizing their motility, by promoting the motility of tumor samples and medical information within the network, and maximizing effective communication among regional doctors and the multidisciplinary teams of the CHUV and HUG integrated program.

In this model, patients who can receive treatment locally will not need to be displaced to the CHUV or HUG, thus maintaining the patient’s comfort and supporting local practices. Patients requiring more advanced care or enrollment in a clinical trial will be referred to the CHUV or HUG, returning to the referring doctor after treatment.
CHUV and HUG together will offer consultation services including second opinions for rare tumors, difficult cases and advanced patients, recommendation on treatment options based on molecular profiling, rapid access to clinical trials, which will be accomplished via tumor boards through videoconferencing.

The CHUV and HUG are establishing Onco-sequencing facilities, which will provide next generation sequencing and other tumor molecular analyses to partners of the network.

In addition, the network will allow continuous medical education through televised high-quality seminars featuring national and international speakers.

**Research infrastructure**

The SRO will provide opportunities for increased accrual to clinical trials of patients from the community. The network collectively sees approximately 8,000 new cases annually. A clinical database infrastructure will be established across the network to enable the accurate capture of follow-up data for all patients.
12. COMMUNITY BUILDING INITIATIVES

The multi-institutional Swiss Cancer Center Lausanne has presently three major sites of operation:

- The CHUV Medical Center in central Lausanne
- The Epalinges/Biopôle Biomedical Research Campus of UNIL in north Lausanne
- The EPFL and UNIL campuses in West Lausanne.

Faculty from the Hospital of the University of Geneva (HUG) and the University of Geneva (UNIGE) are also part of the SCCL. Finally, faculty from other Swiss institutions may become members of the SCCL in the near future. This fragmentation requires top down initiatives to foster communication and collaborations across the various institutions. Below are some of these initiatives launched.

12.1. COMMUNITY-BUILDING RETREATS

- Faculty-Only Networking Retreats

For three years we have invited and gathered all faculty in the Lausanne community with interest in cancer for a one-day offsite retreat. The agendas have included introducing the faculty from different sites and disciplines/expertise to each other, discussing plans and progress toward establishing an innovative multi-institutional, multi-site cancer center, brainstorming about future initiatives and opportunities, and...
informing the attendees about the remarkable technological capabilities available in one or another of the three institutions.

- **Faculty and Staff Cancer Research Retreats**

In 2012, 2013 and 2014 we held 2-day offsite retreats involving all interested faculty and their research staff, with the goal of highlighting the diverse talent, expertise, and research agendas embedded in the various sites of the SCCL. The retreats have included a few longer talks by senior faculty, along with short talks from PhD students, postdoctoral fellows, junior group leaders, and technology platform managers. Interspersed were coffee breaks, and stand-up lunches and an evening cocktail to stimulate mingling and interactions. Both retreats were highly successful. A fourth retreat is planned for fall 2015.

These retreats have been financially supported by the ISREC Institute at EPFL, and co-organized by an ISREC/EPFL faculty member (Etienne Meylan) and a UNIL-CHUV faculty member (Olivier Michielin), with input from the directors of the SCCL (George Coukos and Douglas Hanahan).

- **ISREC/SCCL Faculty lunch seminars**

On the 3rd Friday of the month, ISREC hosts a faculty-only lunch meeting in which one faculty member gives a research presentation. The speakers and participants come from CHUV, UNIL and EPFL. All faculty from the three institutions interested in cancer are welcome to attend. This highly successful series is helping to build bridges and community across the multiple sites of the SCCL.

### 12.2. DISTINGUISHED LECTURES

**Lectures in basic, translational and clinical cancer research**

We have implemented three distinctive lecture series that bring in world-class basic, translational, and clinical cancer scientists. The goals are two fold: to inform the constituency of the SCCL about cutting edge basic and applied cancer research; and to introduce our prominent visitors to the depth and breadth of talent in the SCCL, and about our plans and progress toward developing an innovative new comprehensive cancer center. Importantly, each lecture is televised to the two other major sites.
of the SCCL, using teleconferencing technology (Polycom) that enables Q&A from the remote sites.

- **The Lola and John Grace - ISREC Distinguished Lectures in Cancer Research**
  Co-funded by the Grace family and the ISREC@EPFL Institute, these monthly lectures bring in prominent basic and translational cancer researchers from Europe and the USA. The Grace Lecturer spends day one at ISREC/EPFL, meeting faculty and students, presenting their (televised) lecture there. On day two the lecturer visits for a half day the CHUV and/or Epalinges/Biopôle campuses to meet faculty based in these locations.

- **The Ludwig Distinguished Lectures**
  Funded by the Ludwig Center of the University of Lausanne, this lecture series focuses on tumor immunology, immunotherapy, and translational cancer research, again bringing in internationally prominent researchers. The lectures are presented at CHUV or Epalinges, and transmitted to the other sites. The Ludwig Lecturer spends day one at CHUV and Epalinges/Biopôle, followed by a half day at ISREC/EPFL.

- **The CHUV Distinguished Clinician in Oncology Seminars**
  Funded by CHUV Oncology, this series brings in nationally and internationally prominent physician scientists involved in cancer care and clinical cancer research, aiming to inform the SCCL clinical (and translational research) constituency about current topics of interest and importance, and to foster interactions with the clinical community at CHUV.
12.3. PROGRAMMATIC MEETINGS

Programmatic intergroup meetings are being established to foster more focused interactions amongst faculty and staff of the SCCL. Several are illustrative;

- **The Tumor Modeling Intergroup Meeting**

  Twice a month research groups involved in genetic engineering of mouse models of human cancer meet at ISREC. There are presentations of 30-40 minutes from PhD students and postdocs, with updates on their research involving tumor models.

- **The Leukemia/Lymphoma Network**

  Faculty with research interests in hematopoietic malignancies have created a working group, chaired by Werner Held and Margot Thome, aimed to foster interactions, cross-feeding, and collaboration. There are 21 faculty members on the mailing list, spanning basic to translational to clinical research, at all three sites of the SCCL.

- **Ludwig Center Weekly Tumor Immunology Meeting**

  Every week, the “Ludwig Center Weekly Tumor Immunology Meeting”, co-organized by Pedro Romero and Daniel Speiser, features basic scientific, translational and clinical topics focused on tumor immune biology. PhD students and postdocs present progress reports on their work, followed by intense discussions for critical evaluation and input from the scientific community.

- **CIIL Seminars**

  The seasonal “CIIL Seminars” (Center of Immunology and Infections, Lausanne) are organized by Fabio Martinon and take place every week in every other year rounds. Each Principal Investigator on the Epalinges campus summarizes his/her work once a year, by covering all aspects relevant for broad information and review. Topics cover a wide spectrum of biomedical research from inflammation, infectious diseases, autoimmunity and cancer.

- **Cancer Progress Reports**

  “Cancer progress reports” is a bi-weekly meeting organized by Monika Hegi, Tatiana Petrova and Paolo Dotto. The meeting provides the opportunity for PhD students and postdocs to present and actively discuss their ongoing work in the field of cancer biology.”
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<td>Engineered Cancer Models: From Basic Science to Therapeutic and Diagnostic Discovery&lt;br&gt;Mouse Cancer Genetics Program&lt;br&gt;National Cancer Institute&lt;br&gt;Frederick, Maryland; USA&lt;br&gt;Targeting K-Ras signaling in lung and pancreatic tumors&lt;br&gt;Molecular Cancer Genetics Program&lt;br&gt;National Cancer Institute&lt;br&gt;Frederick, Maryland; USA</td>
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<td><strong>Mariano Barbacid, PhD</strong>&lt;br&gt;Molecular Oncology Program&lt;br&gt;Spanish National Cancer Research Center (CNIO)&lt;br&gt;Madrid; Spain</td>
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<td><strong>Dave Tuveson, MD PhD</strong>&lt;br&gt;Cold Spring Harbor Laboratory&lt;br&gt;Cold Spring Harbor, NY; USA</td>
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<td><strong>Tyler Jacks, PhD</strong>&lt;br&gt;David H. Koch Institute for Integrative Cancer Research at MIT&lt;br&gt;Cambridge, Massachusetts; USA</td>
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<td><strong>Luis Parada, PhD</strong>&lt;br&gt;Department of Developmental Biology&lt;br&gt;University of Texas Southwestern Medical Center at Dallas&lt;br&gt;Dallas, TX; USA</td>
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<td><strong>Thanos Halazonetis, PhD</strong>&lt;br&gt;Department of Molecular Biology, UNICE, Geneva; Switzerland</td>
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<td><strong>Wilhelm Krek, PhD</strong>&lt;br&gt;Institute of cell Biology, ETHZ, Zürich; Switzerland</td>
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<td><strong>Peter Carmeliet, MD PhD</strong>&lt;br&gt;VIB Vesalius Research Center, Leuven; Belgium</td>
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<td><strong>Stefano Piccolo, PhD</strong>&lt;br&gt;University of Padua; Italy</td>
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<td><strong>Lisa Coussens, PhD</strong>&lt;br&gt;Department of Cell &amp; Developmental Biology, Knight Cancer Institute, Oregon Health &amp; Science University, Portland, OR; USA</td>
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<td><strong>Dafna Bar-Sagi, PhD</strong>&lt;br&gt;NYU Langone Medical Center&lt;br&gt;Department of Biochemistry and Molecular Pharmacology&lt;br&gt;New York, NY; USA</td>
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<td><strong>Kornelia Polyak, MD PhD</strong>&lt;br&gt;Dana-Farber Cancer Institute&lt;br&gt;Harvard Medical School&lt;br&gt;Boston, Massachusetts; USA</td>
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<td><strong>George Coukos, MD PhD</strong>&lt;br&gt;Department of Oncology&lt;br&gt;UNIL-CHUV&lt;br&gt;Lausanne; Switzerland</td>
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<td><strong>David Baltimore, PhD</strong>&lt;br&gt;Department of Biology&lt;br&gt;California Institute of Technology&lt;br&gt;Pasadena, California; USA</td>
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<tr>
<td>Malcolm Brenner, MD PhD</td>
<td>Houston Hospital Research Institute, Houston, TX; USA</td>
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<td>Tatiana Petrova, PhD</td>
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### The Ludwig Distinguished Lectures: Guest speakers in 2013 and 2014

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<td>Hans-Georg Rammensee, PhD</td>
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<td>Guido Kroemer, MD PhD</td>
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<td>Tumor Heterogeneity: an active process</td>
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<td>David Lane, PhD</td>
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<td>Philip Greenberg, MD</td>
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<td>Paul Mischel, MD</td>
<td>Ludwig Institute for Cancer Research University of California San Diego; USA</td>
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<td>Philip Greenberg, MD</td>
<td>Fred Hutchinson Cancer Research Center Seattle; USA</td>
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### Other Lectures

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  - Ludwig Institute for Cancer Research
  - University of California
  - San Diego; USA
  - Tumor Heterogeneity: an active process

- Paul Mischel, MD
  - Ludwig Institute for Cancer Research
  - University of California
  - San Diego; USA
  - Hide and Seek: An unanticipated role for extrachromosomal DNA in targeted therapy resistance

- Malcolm Brenner, MD PhD
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  - Houston; USA
  - Will T cell therapy ever be standard of care for solid tumors?
The CHUV Distinguished Clinician in Oncology Seminars: Guest speakers in 2013 and 2014

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<td>Chaitanya Divgi, MD</td>
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<td>Vincenzo Valentini, MD</td>
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<td>Fabio Petrocca, MD</td>
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<td>John Yarnold, MD</td>
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<td>Vincent Grégoire, MD PhD</td>
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<td>Jakob Passweg, MD</td>
<td>Basel University Hospital, Basel; Switzerland</td>
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<td>Affaires de Ligue Suisse du Cancer - Swiss Cancer league</td>
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<td>Michael Baumann, MD</td>
<td>Institute of Radiation Oncology, Helmholtz-Zentrum Dresden-Rossendorf; Germany</td>
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<td>David Bowtell, PhD</td>
<td>Peter MacCallum Cancer Centre, Melbourne; Australia</td>
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<td>Jeroen Goede, MD</td>
<td>Division of Hematology, UniversitätsSpital, Zürich; Switzerland</td>
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<td>David Kirn, MD</td>
<td>Kirn Oncology Therapeutics Consulting; CA; USA</td>
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Niklaus Schaefer, MD  
Department of Oncology and  
Department of Nuclear Medicine,  
UniversitätsSpital, Zürich;  
Switzerland  
Theragnostics: Current Principles and New Frontiers

Olivier Tredan, MD PhD  
Centre Léon Bérard,  
Lyon and Rhône-Alpes;  
France  
Breast cancer treatment: contribution of molecular biology

Sergio Roman-Roman, PhD  
Translational Research  
Department, Institut Curie,  
Paris; France  
Translation challenges in uveal melanoma

Daniel Hohl, MD  
Department of Dermatology,  
CHUV, Lausanne;  
Switzerland  
Basal cell cancer, sonic hedgehog and beyond

Thomas Ruhstaller, MD  
Department of  
Oncology/Hematology,  
Kantonsspital, St Gallen;  
Switzerland  
HER2-positive Breast Cancer Multiple choices – what to use when?
13. EDUCATION

13.1. CLINICAL TRAINING

Training programs are organized in accordance with the regulations established by the Swiss Institute for post-graduate medical training (ISFM), an autonomous institute of the Swiss Medical Association.

Pre- and Post-graduate training programs are offered to medical students and to Medical Doctors, respectively, aspiring to become oncology specialists. These programs exist in the following fields: Medical Oncology, Radio-Oncology and Hemato-oncology.

The general goals of these training programs are:

- to acquire theoretical knowledge and practical skills necessary to engage in an independent activity under full responsibility in all domains of medical oncology
- to integrate knowledge and skills in a multidisciplinary approach
- to interpret correctly publications and scientific reports in own specialty domain
- to broaden one’s practical experience by the direct application of theoretical knowledge
- to develop clinical competences
- to acquire and consolidate new technical competences
- to improve communication skills with the patient and his/her family and to learn ethical and health economical aspects
Medical Oncology Post-graduate Training

This 3-year program teaches medical oncology-related disciplines including prevention, clinical diagnostic, medical treatment and measures of readaptation for all neoplastic conditions as well as follow-up control procedures. It is based upon the post-graduate training program of the Swiss Institute for post-graduate medical training (ISFM).

The training itself is divided in 3 main parts.

- The first part relates to theory and covers topics as diverse as cancer epidemiology and prevention; the basics of molecular and cellular cancer biology; of cancer genetics; the basics of hematology and immunology and their applications in diagnostic and treatment; histopathology; pharmacology; the basics of radiobiology; biostatistics applied to clinical studies, clinical aspects and genetic basis of familial predisposition, the basics of bioethics in cancer healthcare and research; and introduction to economical aspects of health.

- The second part is practical and allows the candidate to develop his/her know-how competences in areas such as the management of the relationship between the oncologist and the patient; the management of ethical issues in medical oncology; the analysis of prevention campaigns, the exploitation of biological and clinical patient information; all care and exam techniques, all activities related to the planning and execution of oncology treatments, follow-up and palliative care procedures; risk an patient safety management.

- The third part refers to pharmacotherapy with the knowledge of drugs used for diagnostic and therapeutic purposes, the learning of juridical aspects of drug prescription, and the knowledge of drug control in Switzerland.
Radio-Oncology Post-graduate Training

This 4-year program is dedicated to train doctors on how to treat malignant and benign tumors using ionizing radiation alone or in combination with radio-sensitizing and/or radio-protective substances, as well as with chemotherapies, anti-hormonal therapies or immunotherapies. It is based upon the post-graduate training program of the Swiss Institute for post-graduate medical training (ISFM).

The training program covers the following topics:

- Basic knowledge learning of radiological physics, radioprotection, radiobiology, tumor biology, radio-anatomy, radiation devices, general oncology, pharmacotherapy, medical statistics, informatics, quality-assurance for executing a radiotherapy, legal aspects of medical radiation, and patient security
- Specific learning of epidemiology, diagnostic and staging of malignant tumors, planning and execution of radio-oncology therapies and inter-disciplinary therapies, planning of disease follow-up, execution of radiotherapies for non tumor conditions
- Practical experience development under the supervision of a radio-oncology/radiotherapy expert including therapeutic application of ionizing radiation on patients and quality-control
- Medical ethics and health economics
- Patient security

Hematology Post-graduate Training

This 4-year program trains doctors to become experts in diagnostic, treatment and prevention of conditions affecting hematopoietic, hemostatic and lymphatic systems, as well as interactions between blood and vessels wall. It is based upon the post-graduate training program of the Swiss Institute for post-graduate medical training (ISFM).

The program consists of 3 years of clinical hematology including clinical and analytical activities in hematology followed by 1 year specialized in either specific hematology disciplines (transfusion medicine, hematology transplantation) or medical
oncology or pediatric onco-hematology or general hematology. It will allow the candidate to acquire clinical and scientific competences in clinical hematology and hemostasis, in onco-hematology, in medical hematological and hemostasis analysis, in transfusion medicine and in immuno-hematology.

13.2. BASIC RESEARCH TRAINING

Programs @ UNIL-CHUV

The Master of Science in Medical Biology is intended for students who take an interest in biological research in the medical field.

The first semester consists of an introduction to human biology in its broadest sense, tackling fundamental cellular functions and systems of signal transduction within and between cells, as well as normal and pathological workings of the main systems of the human organism. The second semester offers four fields of specialization, among which Immunology and Cancer. The third semester is dedicated to the completion of the personal research.

The PhD program in Cancer and Immunology is focused on molecular and cellular biology of cancer and immunology, with their applications to clinical problems. Not only does it offer doctoral courses and tutorials spanning a wide range of topics from UNIL, EPFL and SIB, it also includes Immunology Progress Reports to provide PhD students of the "Cancer and Immunology" program and postdocs from the Epalinges site and from the Ludwig (CHUV) an opportunity to give a formal presentation of their research in Immunology and to discuss their ongoing work with colleagues and faculty, and cancer- or immunology-specific summer courses as well as cancer seminars to stimulate the interactions of PhD students of "Cancer and Immunology" school and postdocs working in cancer research at the UNIL and CHUV.
PhD Program @ EPFL

The Doctoral Program in Molecular Life Sciences (EDMS) aims at providing doctoral students with the education necessary to become leaders in biological research, implementing the latest state of the art. The combination of laboratory based research with access to modern technological platforms, coursework, in-house seminars, national and international conferences, etc., forms the basis of this education. It offers a broad spectrum of doctoral research themes encompassing cell biology, developmental biology, biochemistry & biophysics, molecular genetics, cancer research, microbiology, host-pathogen interactions, immunology, systems biology, computational biology, human genetics, stem cells, metabolism.
## 14. RESEARCH GROUPS AND PROFILES

By alphabetical order

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Chahin ACHTARI

Chahin Acthari
MD
Chief Doctor, Senior Scientist (“MER”), Service of Gynecology, CHUV
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Affiliations:
CHUV
UNIL
Robotic surgery platform, CHUV- La Source

Biography

Research interests
Cancer in pregnancy: a dedicated database was set up in order to keep a track of patients with cancer during pregnancy. Whenever possible, blood and tissue samples are collected and conserved in the biobank if the patient has either chemotherapy or surgery during pregnancy. Data are sent anonymously to a European database in order to increase numbers and draw conclusions about short and long term safety of these treatments during pregnancy and long term outcome of offsprings.

Robotic assisted surgery: robotic assisted surgery is an emerging surgical technique. Preliminary studies show a potential benefit for gynecologic oncology patients. These supposed benefits still need confirmation and will be evaluated through prospective studies.
SELECTED PUBLICATIONS


Michel AGUET

Michel Aguet
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Affiliations:
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UNIL

Funding sources

- EPFL
- SNSF (Sinergia)
- Oncosuisse
- ISREC Foundation

Key research collaborations

- Prof. Konrad Basler, University of Zürich (CH)
- Prof. Gerhard Christofori, University of Basel (CH)
- Small Molecule Discovery Center, UC San Francisco (USA)

Biography

Michel Aguet, MD, held positions in academia and industry (Associate Professor at the Institute of Molecular Biology, University of Zürich; Head of Molecular Oncology, Genentech, So. San Francisco) before he was appointed Director of the ISREC (1996-2009). In the context of the integration of ISREC into the EPFL, he was appointed Full Professor at the newly established School of Life Sciences in 2005. From 2001 to 2013, he directed the NCCR in Molecular Oncology, a program launched by the Swiss National Science Foundation to encourage translational cancer research.

Research interests

The group's research focus is on validating a protein-protein interaction within the WNT pathway as a potential therapeutic target in colon and other WNT-activated cancers, and on identifying small compounds inhibitors of this interaction.
Recent scientific contributions

We recently described phenotypic changes in mouse models of colorectal cancers (CRC) suggesting that the β-catenin binding partner BCL9/L is critical for the maintenance of stem cell-traits (Deka et al.; unpublished). Inactivation of BCL9/L in mouse colon tumors led to vast gene expression changes, including a virtual loss of stem cell and EMT markers and the appearance of a differentiation phenotype. EMT has been associated with invasive and metastatic tumor behavior, and there is growing evidence suggesting a relationship between EMT, cancer stem cells (CSCs) and tumor recurrence. These gene expression changes, which were also observed upon inactivation of BCL9/L in pre-established tumors, correlate strongly with disease-free and overall survival in human CRC. These findings suggest that the BCL9/L-β-catenin interface might represent a novel therapeutic target in CRC and other WNT-activated tumors. Inhibition of the BCL9/L-β-catenin interaction in combination with standard therapies may contribute to exhausting cancer stem cells and thereby reducing the likelihood of relapse. The absence of overt anomalies upon ablation of BCL9/L in adult mice suggests that such a therapy might be well tolerated.

Gene expression changes observed in mouse CRC models upon inactivation of BCL9/L translate into marked morphologic changes (right panel), including loss of epithelial vimentin (green), and a normalized appearance of the basement membrane (laminin staining in red).

SELECTED PUBLICATIONS


Future focus and expectations

We are extending the analysis of BCL9/L-dependent gene expression changes and their correlation to outcome data in CRC patient databases. Besides, our group has established a high throughput HTRF assay and entered collaborations with the Biomolecular Screening Facility at EPFL, the Small Molecule Discovery Center at UC San Francisco and the European Screening Port in Hamburg to screen large chemical diversity libraries. Our goal, this year, is to generate validated hits as a basis for hit expansion and optimization.
Hatice ALTUG

Funding sources

- EPFL

Key research collaborations

- Dr. Immanuel Luescher, LICR UNIL CHUV
- Dr. Pedro Romero, LICR UNIL CHUV

Hatice Altug
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Affiliation:
EPFL-IBI

Biography

Hatice Altug received her Ph.D. degree in Applied Physics (2006) and M.S. degree in Electrical Engineering both from Stanford University. Dr. Altug joined EPFL in 2013 as an Associate Professor of Biomedical Engineering. From 2007 to 2013, she was an Assistant/Associate Professor at Boston University Electrical Engineering and Biomedical Engineering. Dr. Altug is the recipient of Optical Society of America Adolph Lomb Medal, 2011 Presidential Early Career Award for Scientists and Engineers (highest honor given in USA to scientists and engineers in their early career), US ONR Young Investigator Award, US NSF CAREER Award, and was named to Popular Science Magazine's "Brilliant 10" list (2011).

Research interests

The Altug group develops cutting edge on-chip optical bio-detection and spectroscopy technologies for biomedical research in cancer and neurodegenerative diseases, early disease detection, and point-of-care applications. In particular, the group introduces new label-free, quantitative, real-time and high-throughput screening technologies, low-cost and portable biosensors.
Recent scientific contributions

The Altug lab introduced breakthroughs in the field of label-free biosensing using nanophotonics which exploits novel optical phenomena with nano-scale optics and engineered meta-materials. The laboratory develops high-throughput, quantitative, label-free and real-time protein microarrays for massively multiplexed detection of biochemicals and monitoring biochemical interaction kinetics. The laboratory uniquely integrates nano- and microfluidic systems with biosensors to process biosample solutions for analyte concentration, delivery, filtration and automatization. Using on-chip optical sensor array, the lab showed multiplexed detection of live and intact viruses in biological media at medically relevant. By integrating nano-sensor arrays with nano-fluidic systems, the lab demonstrated rapid detection of bioanalytes at low concentrations with large-dynamic ranges. Most recently, by coupling nano-photonic-based wide-field label-free protein microarrays with lens-free computational on-chip imaging, the lab demonstrated handheld, lightweight and low-cost diagnostic tools suitable for point-of-care applications.

SELECTED PUBLICATIONS


Future focus and expectations

The laboratory aims to employ their novel biosensors for high-throughput and real-time profiling of rare cells such as tumoricidal CD8+ T-cell, circulating tumor cells, certain stem cells that are important in immunology and cancer research. The laboratory is also developing new protein microarrays that can quantitatively and simultaneously detect multiple kinds of soluble key mediators such as growth factors, cytokines, chemokines and metabolites that control cell-cell and cell-host interactions.
Johan AUWERX

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Funding sources
- EPFL
- SNSF
- National Institute of Health
- Swiss Confederation (CTI)
- Ligue Suisse contre le Cancer
- SystemsX.ch

Key research collaborations
- Prof. Ruedi Aebersold, ETHZ (CH)
- Prof. Bart Deplancke, EPFL (CH)
- Prof. Matthias Lutolf, EPFL (CH)
- Prof. Robert Williams, University of Tennessee, Memphis (USA)

Biography
Johan Auwerx is Professor at the École Polytechnique Fédérale in Lausanne. He was elected as EMBO member in 2003 and received a dozen of international scientific prizes. He is an editorial board member of Cell Metabolism, Molecular Systems Biology, The EMBO Journal, Cell, and Science. Many concepts discovered and validated in his laboratory found their way to the clinic. Dr. Auwerx received both his MD and PhD in Molecular Endocrinology at the Katholieke Universiteit in Leuven, Belgium. He was a post-doctoral fellow in the Departments of Medicine and Genetics of the University of Washington in Seattle.

Research interests
Dr. Auwerx has been using molecular physiology and systems genetics to understand mitochondrial function and metabolism in health, aging and disease.
Recent scientific contributions

Much of Prof. Auwerx’s work focused on understanding how diet, exercise and hormones control metabolism through changing the expression of genes by altering the activity of transcription factors and their associated cofactors that control mitochondrial function. His work was instrumental for the development of agonists of nuclear receptors - a particular class of transcription factors - into drugs, which now are used to treat high blood lipid levels, fatty liver, and type 2 diabetes. Dr. Auwerx was amongst the first to recognize that transcriptional cofactors, which fine-tune the activity of transcription factors, act as energy sensors/effectors that influence metabolic homeostasis. His research validated these cofactors as novel targets to treat metabolic diseases, and spurred the clinical use of natural compounds, such as resveratrol, as modulators of these cofactor pathways.

SELECTED PUBLICATIONS


Future focus and expectations

We will continue our research along the lines described above.
Maja Beck Popovic
MD
Chief Physician, Priv.-Doz. & Senior Scientist (“MER”)
Maja.Beck-Popovic@chuv.ch
Affiliations:
CHUV
UNIL

Biography
Dr Beck Popovic, MD, was appointed Head of the Pediatric Hematology Oncology Unit at the CHUV in 2010. She had previously completed her internship in pediatric surgery in Bern and internal medicine in St. Gallen followed by her residency in pediatrics in Lausanne. She obtained several fellowships in Pediatric Hematology-Oncology including one for the Institut Gustave-Roussy, Hôpital Saint-Louis in Paris (1991-1992) and one for Lausanne (1992-1995). She has been holding responsibility for the CHUV Pediatric Hematology Oncology Unit since 1995.

Research interests
Dr. Beck Popovic’s research interests mainly focus on neuroblastoma and retinoblastoma. She has been leading the following studies:

LNESG2 Study: European chair and national PI for the European study on localized neuroblastoma.

HR-NBL1.5: National PI for the European Study on high risk neuroblastoma.

Plasma metanephrines: establishment of normal values in healthy children.

Reference center for diagnosis and treatment of retinoblastoma in Switzerland and neighbour countries.

SPOG-RB-2011: Chair and PI for the national phase II study for the treatment of recurrent or progressive retinoblastoma.

Fertility preservation in prepubertal girls and boys.
Recent scientific contributions

**LNESG2 Study:** Closure of the European study on localized neuroblastoma in August 2013. This prospective study evaluated the impact of certain clinical (age, stage, gender), biochemical (preoperative LDH) and biological characteristics of localized neuroblastoma on outcome. The latter included mainly MYCN amplification and 1p deletion at the activation of the protocol, then expanded numerical and segmental abnormalities, through progressive implementation of genome-wide analysis. A manuscript is in preparation.

**Plasma metanephrines:** This prospective study on establishing normal values of plasma metanephrines in healthy children was closed at the beginning of 2013. The cohort includes children from birth to 18 years. Preliminary results on a limited number of neuroblastoma patients at diagnosis indicate a very clear cut-off for abnormal values in this setting. A manuscript is being reviewed by the different co-authors.

**SPOG-RB-2011:** This first national study on recurrent/progressive retinoblastoma, including Swiss and foreign patients, all treated in Lausanne, evaluates prospectively three treatment arms (intraarterial intravitreous and periocular chemotherapy) according to the site of disease progression. The protocol was closed temporarily at the end of 2013, and the preliminary results will be presented at the annual meeting of the International Society of Pediatric Oncology. The protocol will reopen on an international European level.

SELECTED PUBLICATIONS


Future focus and expectations

Dr Beck Popovic will mainly focus on:

1. Publishing the results of the closed studies. There will be no successor study for LNESG2, as localized neuroblastoma, on a European level, will be part of the new low or intermediate risk disease protocol (LINES) based on a new classification according to numerical or segmental chromosomal aberrations. However, LNESG2 analysis will extend to surgical, radiological and pathological aspects and hopefully give new insights on this disease.

2. Activation of a national prospective study on plasma metanephrines in diagnosis and follow-up of neuroblastoma patients in Switzerland. Funding has already been obtained and the protocol will go through the ethics committee and authorities in 2014.

3. International activation of the retinoblastoma protocol including acquired knowledge and experience.

4. Activation of a prospective study on Vincristine induced neuropathy in ALL patients and Vit B (Dr. Manuel Diezi as PI).
Jean BOURHIS

Funding sources

- Partnerships with ALCEN, Debiopharm, Fond’Action, Ablatech, Accuray, Nanotargeting

Key research collaborations

- Prof. Bochud, Dr Moeckli, Dr Baylat, Dr Germond, IRA, Institute of Radiophysics Lausanne
- Dr Favaudon, Institut Curie, Paris (FR)
- Prof. Romeo, Commissariat à l’Energie Atomique, Fontenay, France (FR)

Jean Bourhis
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Biography

Prof. Bourhis has been Chairman of Radiation Oncology at the Gustave Roussy Institute (Villejuif, France) and recently moved to the CHUV as Head of Radiation Oncology. His clinical activity is focused on Head and Neck Oncology. Chairman of the GORTEC group, he is dedicated to conducting clinical randomized trials in head and neck oncology. Prof. Bourhis has also been Director of a laboratory dedicated to Translational Research in Radiation Oncology for 15 years. He authored more than 220 scientific papers with an H factor of 50. Prof Bourhis is Past President of the European Society for Radiotherapy and Oncology (ESTRO) and President of the ESTRO Cancer Foundation.

Research interests

The Radiation Oncology group is interested in head and neck carcinoma clinical research from early phase I to large phase III clinical trials.

Furthermore, a second key point of interest is translational research in radiotherapy embracing several aspects such as innovation in radiotherapy delivery and imaging, predictive markers for tumor response, and combining new molecular targeted drugs with radiotherapy.

In addition, the group is dedicated to evaluating the differential effect associated with new types of ultra-high dose rate radiotherapy.
Recent scientific contributions

Clinical research in head and neck carcinoma:

Prof. Bourhis has been Principal Investigator on several clinical trials for head and neck carcinoma (ongoing analysis) and updated the MACH-NC database (meta-analyses of randomized trials in head and neck cancers, JCO 2013). He also initiated several new projects on innovative radiotherapy approaches and combinatory strategies.

Translational research in radiotherapy: Together with Dr Vozenin, Prof. Bourhis initiated a programme at the CHUV that evaluates a new type of ultra-high dose rate radiotherapy, markedly reducing the side effects of radiotherapy and being more effective on tumor control. A translational research program is ongoing to transfer this innovative radiotherapy to patients.

Illustration of the anti-tumor effect (orthotopic lung cancer in mice) of Flash radiotherapy

SELECTED PUBLICATIONS


Future focus and expectations

Prof. Bourhis and his team will stimulate new research programs in the field of Radiation Oncology. They will especially establish the CHUV Radiation Oncology site as an Accuray International Flagship Reference Site and international training center, combine radiotherapy with new molecular targeted drugs and with immunotherapy (together with Dr. Vozenin, Dr. Herrera - Immunotherapy program under the leadership of Prof Coukos), create a research program & training center for developing advanced 4D radiotherapy (Dr. Péguret & Prof. Ozsahin), develop Flash Radiotherapy and define the optimal setting for clinical transfer (with Dr. Vozenin, Prof. Bochud, Dr. Moeckli and Dr. Germond), initiate new clinical trials testing the value of high precision radiotherapy (Dr Schiappacasse).
Cathrin BRISKEN

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Funding sources
- Swiss National Fund
- Oncosuisse
- IMI PREDECT

Key research collaborations
- William Dougall, AMGEN
- Gilbert Smith, NIH (USA)
- Seppo Vainio, Biocenter, Oulu, (FI)
- Maryse Fiche, Wassim Raffoul, Jean-Francois Delaloye, CHUV
- Kathryn Hess, Horst Pick, Horst Vogel, EPFL

Biography
Cathrin Brisken received an MD and a Doctorate in Biophysics from the University of Göttingen in 1993. She worked as a postdoc and research scientist at the Whitehead Institute, MIT, Cambridge, USA. She was Assistant Professor at the MGH Cancer Center, Harvard University before joining the NCCR Molecular Oncology at ISREC in 2002. In 2013 she was appointed Associate Professor and Dean of EPFL doctoral School. Cathrin Brisken is a member of various scientific advisory boards including the International Breast Cancer Study Group (IBCSG) and of the “Hinterzartener Kreis”, the cancer think tank of the German Science Foundation (DFG).

Research interests
The Brisken laboratory explores how hormones control normal breast development and how they contribute to breast carcinogenesis.
Recent scientific contributions

Our understanding of how hormones act on the human breast has been hampered by the lack of model systems to study this question. When human breast cells are put into culture for laboratory studies, they loose the hormone receptors. Hence they become insensitive to hormones.

Through a longstanding collaboration with clinical colleagues, Prof. Wassim Raffoul (Plastic Surgery, CHUV), Dr. Maryse Fiche (Pathology, CHUV) and Dr. Delaloye (Gynecology, CHUV), we regularly obtain normal human breast tissue from women who undergo reduction mammoplasty. We have developed procedures that allow us to obtain through careful dissociation of the freshly isolated human breast tissue little fragments, breast tissue microstructures. In these, the milk duct cells preserve all the contacts with their neighboring cells. They retain hormone receptors and most importantly, remain sensitive to hormones. Using these tissue structures, we have shown that estrogen stimulates cell proliferation only in a subset of women. Progesterone, on the other hand, is a strong proliferative stimulus in most breast samples. Excitingly, two major factors we had shown to be essential for progesterone action in the mouse mammary gland are also made by human milk duct cells in response to progesterone: Wnt-4 and RANKL. RANKL is a secreted by cells that have the progesterone receptor when progesterone levels in the blood are high. It talks to the neighboring cells and makes them proliferate. The protein is required as a mediator of the proliferative response to progesterone.

These findings have important implications because an inhibitor for RANKL, a drug called Denosumab (AMGEN), is already available and currently used to treat various bone diseases.

Hormones impinge on breast carcinogenesis

SELECTED PUBLICATIONS


Future focus and expectations

We are developing an improved preclinical model for estrogen receptor-positive breast cancer by placing human tumor cell lines into the milk duct system of immunocompromised mice. This model will allow us to test the importance of cell intrinsic versus paracrine estrogen signaling in estrogen receptor-positive breast cancers with important implications for novel therapeutic approaches and to study the role of hormones in promoting the critical transition from in situ to invasive carcinoma.
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Funding sources

- EPFL  
- SIB  
- Swiss National Science Foundation  
- SystemsX.ch

Key research collaborations

- Bernard Moret, EPFL  
- S. Antonaralis Dermitzakis, UNIGE  
- Alexandre Reymond and Sven Bergman, UNIL

Biography

Philipp Bucher was first trained as a molecular biologist at the University of Zürich, and subsequently received his PhD in computational biology at the Weizmann Institute of Science in Israel. He then worked as a postdoctoral fellow with Sam Karlin at Stanford University before he moved to ISREC in 1991 to continue his research in comparative molecular sequence analysis. In 1995, he was promoted senior scientist.

Research interests

The Bucher group is interested in gene regulation in higher organism. The general objective is to reverse-engineer gene regulatory networks from genomics data, in particular networks relevant to human health. To this end, the group develops novel bioinformatics algorithms to extract knowledge from new data types. In addition they develop and maintain public bioinformatics web servers.
Recent scientific contributions

The Bucher lab continues to develop algorithms for the interpretation of ChIP-Seq and other types of chromatin profiling data. The focus is on integrative methods that can exploit heterogeneous data from multiple sources. Highlights from 2013 were: (i) the introduction of probabilistic partitioning, a versatile algorithm to characterize chromatin signatures associated with gene control regions, (ii) a proof-of-concept study to evaluate the diagnostic value of ChIP-Seq on tumor tissue. Moreover, the group has started to develop a computational pipeline for systematic discovery of SNPs that disrupt transcription factor-DNA interactions and have consequences on chromatin state and target gene expression. In parallel, the group maintained and extended its web-based bioinformatics resources: the Eukaryotic Promoter Database (EPD), the ChIP-Seq sever providing analysis tools for chromatin profiling data, and the Signal Search Analysis (SSA) offering DNA motif analysis. More than 5000 public samples were added to the server-resident database of the ChIP-Seq server. Moreover, large collections of transcription factor binding site matrices from protein-binding microarray (PBM) and high-throughput SELEX (HT-SELEX) assays were made accessible through the SSA server.

Future focus and expectations

The focus is on developing algorithms for joint analysis of chromatin data and genetic profiles in order to gain insights into the gene regulatory code and mechanisms of gene regulation. Depending on the outcome of pending grant applications, the methods developed to this end will be applied to data from clinical cancer studies. Regarding the bioinformatics resources, a major objective is to make data from large-scale initiatives (ENCODE, Roadmap Epigenomics, etc.) exploitable and analyzable to non-bioinformaticians.

SELECTED PUBLICATIONS

Thierry BUCLIN

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Funding sources

- Swiss National Science Foundation
- Nano-Tera (SNF initiative)

Key research collaborations

- Prof. Carlotta Guidicci, Laboratory of Life Sciences Electronics, EPFL
- Prof. Yann Thoma, REDS Institute, HEIG-VD, Yverdon-les-Bains (CH)

Biography
Thierry Buclin graduated in 1984 and trained in Internal Medicine and Clinical Pharmacology in Lausanne. He also enjoyed a sabbatical leave in clinical epidemiology of therapeutic monitoring in Oxford. Since 2011, he has been heading the Division of Clinical Pharmacology at CHUV, delivering teaching and clinical services (consultation, pharmacovigilance, teratovigilance, therapeutic drug monitoring). His research focuses on clinical development of new drugs (phase I trials, PKPD modeling) and optimization of established treatments through concentration monitoring. He is interested in methodological aspects of clinical research and in its translation into efficient, rational, adapted, safe and measured use of drugs. He is aware of societal implications of drug utilization.

Research interests
Prof. Buclin’s research focuses specifically on the following studies: population pharmacokinetics of targeted anticancer agents, pharmacokinetic-pharmacodynamic relationships relevant to optimize therapeutic efficacy and tolerability, quantification and identification of sources of variability in drug response, development of therapeutic concentration monitoring approaches to individualize the administration of critical treatments.
Recent scientific contributions

Methodological developments progressed towards rational individualization of therapeutic dosage of imatinib in chronic myelogenous leukemia patients: our Bayesian approach to predict through concentrations from random sampling measurements and our formula to estimate free concentrations were validated in real-world patients; population pharmacokinetic analyses of imatinib and relationships between concentration exposure and treatment outcomes were both systematically reviewed in the literature and analyzed in a large dataset, to produce reference pharmacokinetic parameters for therapeutic monitoring. But most importantly, we completed the first prospective randomized controlled clinical trial evaluating the usefulness of imatinib concentration monitoring, which indicates a significant advantage for systematic monitoring, provided that dosages are consequently adjusted in patients. The development of analytical methods and the elaboration of reference parameters for other targeted anticancer agents are underway.

SELECTED PUBLICATIONS


Future focus and expectations

Prof. Buclin’s team wishes to extend the approach followed for imatinib to other targeted anticancer small molecules, including:

- Initiation of observational studies on drugs’ pharmacokinetic profile, variability and concentration-eficacy-tolerability relationships in the target population
- Systematic review of drugs’ reference pharmacokinetic-pharmacodynamic parameters,
- Fine-tuning of computer tools for interpretation of drug concentration results and dosage adjustment,
- Validation of the feasibility, predictive accuracy and clinical usefulness of TDM through clinical trials
Stéphane CHERIX

Key research collaborations

- Dr. HA Rüdiger, CHUV and Schulthess Klinik, Zürich (CH)

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Biography

Dr. Stéphane Cherix is in charge of orthopaedic oncology at the
Lausanne University Hospital. As an orthopaedic surgeon, he is also
active in the management of traumatized patients and in orthopaedic
septic surgery. In parallel, he is member of the multidisciplinary
sarcoma board and is active in the development of the future
Lausanne Sarcoma Centre and SwissSARCOS, a Swiss national
cohort study group. He did his orthopaedic training at Lausanne
University Hospital and affiliated peripheral hospitals and passed the
national board exam in 2010. He did the CNBS Travelling
Fellowship in Canada in 2013 and a clinical fellowship in Spring
2014 in Florence, at Careggi Hospital, in the Department of
Orthopaedic Oncology of Prof. Rodolfo Capanna. He has been
Associated Doctor in the Orthopaedic and Traumatology Unit of the
Department of Musculoskeletal Disorders of Lausanne University
Hospital since November 1st 2013.

Research interests

Dr. Stéphane Cherix is mainly active in clinical research,
mostly in oncologic fields, but also in general orthopaedic
surgery and traumatology.

Efficiency of new treatment modalities, like percutaneous
cryoablation therapy, that can be associated to surgery, on
musculoskeletal tumours metastases, has been one of his
major domains of interest in the last years.
Recent scientific contributions

Dr. Stéphane Cherix has been mainly active in the development of the future Lausanne Sarcoma Centre, including the production of guidelines for the treatment of musculoskeletal sarcomas. As an early member of SwissSARCOS, a Swiss national cohort study group on sarcomas, which was created in Spring 2014 under the leadership of Prof. Bruno Fuchs, of Zurich University Hospital, Dr. Cherix has also been involved in the creation of clinical guidelines.

In his domain, Dr. Cherix has published on new treatment modalities, mainly percutaneous cryoablation therapy, i.e. an interventional radiologic modality, that can be associated to orthopaedic surgery in the management of musculoskeletal primary tumours or metastases.

On November 6th, he organized a scientific symposium entitled: “Sarcoma symposium: from basic research to clinical practice” (cf infra)

SELECTED PUBLICATIONS


Future focus and expectations

The upcoming year should be greatly dedicated to the opening of the Lausanne Sarcoma Centre, in which Dr Stéphane Cherix will be the reference orthopaedic surgeon for adult sarcomas.

His research will focus on clinical topics, mainly new treatment modalities, and some functional analyses in soft tissue sarcoma management. He will keep on searching in general orthopaedic surgery and traumatology as well.
Daniel CONSTAM

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Funding sources
- Swiss Cancer League
- Swiss National Science Foundation
- ISREC Foundation
- Gebert-Rüf Stiftung
- Stiftung für Wissenschaftliche Forschung Zürich

Key research collaborations
- Nabil Seidah, IRCM Montreal (CA)
- Dorien J. Peters, Leiden Univ. Medical Center (NL)
- Olivier Bonny, UNIL

Biography
Daniel Constam obtained his diploma (1990) and doctoral degree (1993) in natural sciences at ETH Zürich. He worked at the University Hospital of Zürich as a graduate student (1990-93) and as a postdoctoral fellow in the Department of Molecular and Cell Biology at Harvard University (1994-1999). He has been a group leader at ISREC since 2000, and Associate Professor at EPFL since 2007.

Research interests
The Constam group uses biochemical and genetic approaches to study the regulation and function of TGFβ signals during embryogenesis and at the interface of cancer cells and their microenvironment. The goal is to harness such activities for stem cell therapies and to block oncogenic functions.
Recent scientific contributions

The TGFβ-related Nodal precursor and its proprotein convertases (PC), Furin and Pace4, control the fate of pluripotent progenitors and are thought to promote cancer invasiveness and metastasis. We found that the potential of Nodal to direct embryonic stem cell differentiation ex vivo is limited by its stability, but that a heterodimer of Nodal and Gdf1 containing cleaved propeptides is much more active and can be purified as a recombinant protein. Our results predict that Nodal homodimers have no oncogenic activity. Indeed, unlike other TGFβ family members, overexpression of Nodal in mouse or human melanoma cells did not promote primary growth or metastasis in mice. To study the function of convertases, we developed the fluorescent biosensor CLIP which detects secreted PC activities at the cell surface. We now improved the sensitivity of CLIP and derived intracellular variants to quantify when and where a given PC is active in cells and in tissues. Finally, we studied the regulation of mRNA silencing by the RNA-binding protein Bicc1. Deletion of Bicc1 disrupts the regulation of Nodal signaling in embryos and provokes polycystic kidney disease. We found that the mRNA silencing activity of Bicc1 depends on its phosphorylation.

SELECTED PUBLICATIONS


Future focus and expectations

In vivo imaging and targeted deletion of PCs will test the role of these enzymes in grafted melanoma in mice during tumor progression and in mediating the cleavage of TGFβ and other cancer-relevant substrates. We also continue to dissect the novel mechanism of gene silencing by Bicc1 and its role in polycystic kidney disease.
George COUKOS

Ge}\n
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Biography
George Coukos obtained his MD in 1986 at the University of Modena
and his PhD in 1991 at the University of Patras. He completed
training in obstetrics and gynecology at the University of Modena in
1991. He did a post-doc at the University of Pennsylvania in
Philadelphia in cell biology (1991-1994), and he completed residency
training in obstetrics and gynecology (1994-1997) and fellowship
training in gynecologic oncology (1997-2000) at the University of
Pennsylvania. In 2000 he became assistant professor at the University
of Pennsylvania. He became associate professor in 2006 and full
professor in 2010. At Penn, George Coukos founded (2007) and
directed the Ovarian Cancer Research Center, and served as Associate
Director of the Division of Gynecologic Oncology. George Coukos
relocated to Switzerland in 2012, to become Director of the new
department of oncology at the CHUV/UNIL in 2013.

Research interests
We investigate fundamental mechanisms in the tumor
microenvironment (TEM) that determine the fate of antitumor
immunity, focusing on two important aspects: First, we investigate
the deregulation of tumor-infiltrating lymphocytes (TILs) to
understand their functional specificity and avidity, and the external
influences and signaling reprogramming underlying their
dysfunction in tumors. This line of investigation is expected to yield
novel pharmacologic approaches to restore antitumor immunity as
well as novel methodologies to select and expand TILs for adoptive
therapy. Second, we investigate the tumor vasculature as a barrier
effective T cell infiltration in many tumors, but also as a potential
target for therapy. The lab is pursuing T cell engineering
approaches as a means to address the deregulation of T cells in the
TME, and for redirecting them against relevant tumor targets,
including the vasculature. Mouse models with human bone
marrow are used to test these therapeutics. Clinical translation is a
high priority. A GMP facility will support the development of
clinical trials using adoptive T cell therapy approaches.
Recent scientific contributions

We identified an important barrier function of the tumor endothelium that explains the paucity of T cells from tumors, mediated by FasL. Tumor endothelium expresses FasL under the influence of paracrine tumor factors (VEGF-A, IL-10 and PGE₂) and kills incoming activated T effector cells but not T regulatory cells, resulting in paucity of Teff cells and relative enrichment in Treg cells.

We have developed a whole tumor antigen vaccine based on oxidized lysate pulsed on dendritic cells, which is being tested in ovarian cancer in combination with therapy blocking VEGF and PGE₂ in a clinical trial at Penn.

We have developed a high affinity antibody recognizing human and mouse TEM1/endosialin, a vascular-specific surface target, with low nanomolar affinity, which is suitable for targeting tumor vasculature in vivo.

Future focus and expectations

The Coukos group in Lausanne has been fully established. We will focus on characterizing mechanisms leading to failure of T cell infiltration and function in tumors. We are now using “organotypic” tumor microenvironment cultures and are taking systems biology approaches to decipher T cell suppressive mechanisms in the tumor microenvironment, and understand how to reprogram T cell signaling to circumvent tumor-induced suppression. In parallel, we pursue approaches to T cell engineering that restore proper T cell function in tumors, and are developing novel receptors redirecting T cells against the tumor vasculature, in order to abate the endothelial barrier and reprogram the tumor microenvironment.

SELECTED PUBLICATIONS

Chantal CSAJKA

Funding sources

- Swiss National Science Foundation
- Industrial contacts
- pharmaSuisse

Key research collaborations

- Prof. T. Buclin and Prof. L. Decosterd, Division and Laboratory of clinical pharmacology, CHUV
- Dr. K. Zaman, Dr. A. Wagner, Prof O. Michielin, Dr K. Homicsko, Department of Oncology, CHUV
- Prof C.B. Eap, Pharmacogenetics and Psychopharmacology Unit, CHUV

Biography

Chantal Csajka graduated as a pharmacist from the University of Lausanne. She performed her PhD in clinical pharmacology at the University Hospital of Lausanne, and completed her training with a postdoctoral fellowship at the University of California San Francisco (UCSF). She was appointed Associate Professor in clinical pharmacy at the UNIGE and UNIL School of Pharmaceutical Sciences in 2012.

Research interests

Prof. Csajka’s research focuses on population pharmacokinetic, pharmacodynamic and pharmacogenetic modeling of pharmaceutical agents. The objectives are to better characterize the dose-concentration-response and toxicity relationships, either for marketed drugs or during their clinical development. This approach allows the development of Bayesian feedback strategies for dosage regimen individualization.
Recent scientific contributions

The group continues to investigate the variability in drug concentrations, with a special focus on protein kinases inhibitors, with the objectives to identify genetic and non-genetic sources of variability. We studied the concentration-efficacy/toxicity of imatinib in a large collaborative study (EUTOS http://www.eutos.org) and confirmed therapeutic targets for imatinib associated with optimal response while minimizing toxicity. Additionally, a first randomized clinical trial evaluating the benefit of therapeutic drug monitoring interventions for optimization of imatinib dosage regimen has been finalized. Further, we studied the population pharmacokinetic analysis of tamoxifen and of four of its active metabolites, and evaluated the impact of a doubling of the dose on drug and metabolites levels. This study also compared the performance of genetic testing, phenotyping or direct metabolite measurement to predict patients at increased risk of treatment failure and suggests that treatment or dosage individualization based on drug concentration monitoring should be considered for treatment optimization.

Integration of pharmacokinetics, pharmacodynamics and genetics for treatment optimization of targeted anticancer therapies

SELECTED PUBLICATIONS


Future focus and expectations

A comprehensive research program for the optimization of targeted anticancer therapy of solid tumors will be initiated in 2014. The objectives of this project are to provide better-defined target concentrations of current and new protein kinase inhibitors, integrating host-, drug- and tumor-related characteristics. It is expected that research protocols focusing on regorafenib/sorafenib and vemurafenib/dabrafenib-trametinib will be initiated, which will allow the start of a prospective collection of pharmacokinetic data with all relevant clinical and genetic information.
Laurent DECOSTERD

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Funding sources
- Swiss National Science Foundation
- Swiss HIV Cohort Study
- Unrestricted Research Grants from various phamras (Novartis Oncology, Janssen, Gilead, Forest Labs, etc…)

Key research collaborations
- Various Departments at CHUV
- EPFL
- Swiss HIV Cohort Study
- Swiss Tropical Center
- UNIGE
- EUTOS

Biography
Laurent Decosterd, pharmacist, obtained his PhD in 1990 with an emphasis on chromatography and analytical chemistry of bioactive products. He completed his postdoctoral studies at the US National Cancer Institute (NIH) at Frederick (MD) in the field of anticancer and anti-HIV drugs discovery, research and development. He is currently Associate Professor at the Faculty of Biology and Medicine of the University of Lausanne, and the Head of the Laboratory of Clinical Pharmacology at CHUV, which provides analytical service for the Therapeutic Drug Monitoring (TDM) of anti-infective and targeted anticancer agents. His current research and development work aims at getting a better and more secure use of drugs in patients, notably in the field of the targeted therapy of cancer.

Research interests
Prof. Decosterd’s core research interests embrace the four following activities: analytical development and validation; instrumental analysis; ultra and high performance liquid chromatography coupled to triple quadripole tandem mass spectrometry (HPLC-MS/MS; UPLC-MS/MS) to respond efficiently to analytical demands from large-scale clinical research programs in the field of pharmacogenetics and pharmacokinetics of current and new targeted anticancer therapy; high-throughput multiplex assays for the Therapeutic Drug Monitoring (TDM) of current and new classes of targeted anticancer agents, antiretrovirals, antifungals, antibiotics and new antimalarial combinations regimens.
Recent scientific contributions

The laboratory developed and validated LC-MS/MS assays for:
- First generation anti-HCV protease inhibitors telaprevir and boceprevir (Antimicrob Agents Chemother 2013)
- Newer anti-HIV drugs rilpivirine and elvitegravir (J Mass Spectrom 2013)
- Multiplex Quantification in Human Plasma of 12 antibiotics: Broad- and Extended-Spectrum Beta-Lactams, Carbapenems, Daptomycin and Rifampicin.
- Optimized Quantification of the Anti-Gram-Negatives Antibiotic Colistin A/B and its Pro-Drug Colistimethate.
- Efavirenz metabolites profiles studies.

The laboratory also participated in the analytical development of various research programs:
- Tamoxifen and metabolites in a mouse model of Duchenne muscular dystrophy. (Am J Pathol 2013)
- Lipoplatin / photodynamic therapy targeted treatment (with Pr HB Ris, Dept Thoracic Surgery)
- New drug candidates against tuberculosis (with EPFL) (EMBO Mol Med 2014)
- PK/PD/PGX analysis of the anti-HIV drugs darunavir (J Antimicrob Therapy 2014) and etravirine (Pharmacogen Genom 2013)

Future focus and expectations

The laboratory aims to:
1. Develop analytical methods by liquid chromatography coupled to mass spectrometry and elaborate reference parameters for the new targeted anticancer agents regorafenib, dabrafenib, trametinib and pazopanib.
2. Initiate a clinical program for the TDM of new and next-generation targeted anticancer agents.
Jean-François DELALOYE

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Biography
Jean-François Delaloye obtained his MD from the Medical School University of Lausanne in 1978. He trained in surgery, gynecology and obstetrics in Lausanne. He completed his training with a fellowship at the National Cancer Institute in Milan (Professor Ul. Veronesi). He is specialized in gynecologic oncology. In 2002 he was awarded the first price for Innovative Surgery in Berlin. President of the Swiss Society of Senology in 2005-2006, he was appointed Associate Professor in 2008. He is Medical Director of the Breast Center, CHUV.

Research interests
Prof. Delaloye’s clinical interests are focused on breast and uterine cancers. First he explored the mechanisms and pathways of lymphatic dissemination in endometrial cancer. He now collaborates with researchers trying to elucidate 1) the pathways and the microenvironmental signals governing the pro-angiogenic activities of monocytes expressing the Tie-2/Tek receptor tyrosine kinase in early breast cancer, 2) interactions between cancer stem cells and metastases, 3) hormonal control on breast carcinogenesis. He is concerned by supportive care in breast cancer.

Funding sources
- SNSF
- Oncosuisse

Key research collaborations
- Dr. Marie-Agnès Doucey, Dr. Sandro Carrara, Dr. Ioannis Xenarios, CHUV, EPFL, SIB
- Prof. Cathrin Brisken, Dr. Maryse Fiche EPFL, CHUV
- Prof. Nicolas Mermod, Dr. Khalil Zaman, EPFL, CHUV
- Prof. Joerg Huelsken, EPFL
- Prof. Curzio Ruegg, UNIFR
- Prof. Nicolas Favez, UNIGE
- SAKK, IBCSG
SELECTED PUBLICATIONS


Laurence de LEVAL

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Funding sources
- Plan Cancer, Belgium
- Swiss Cancer League
- Medic Foundation
- Fonds Pathologie 2000

Key research collaborations
- Philippe Gaulard, Hôpital Henri Mondor, Créteil (FR)
- The LYSA (Lymphoma Study Association)
- Randy Gascoigne, British Columbia Cancer Agency, Vancouver (CA)
- Reiner Siebert, University of Kiel (DE)
- Mauro Delorenzi, SIB
- Keith Harshmann, UNIL

Biography
Laurence de Leval is Professor of Pathology and Head of Clinical Pathology at the Institute of Pathology at the CHUV. Her diagnostic activities are focused on hematopathology and molecular pathology. She graduated as an M.D. at the University of Liège (Belgium) in 1994, and obtained a PhD degree in experimental pathology in 1998. She completed a 2-year postdoctoral fellowship in hematopathology at Harvard Medical School (Boston MA, USA). From 2000 to 2009, she was senior staff pathologist at the University Hospital, Liège, where she became Professor of Clinics in 2007. She received the Benjamin Castleman award presented by the USCAP in 2008 and was awarded the Inbev-Baillet Latour Fund Prize for Clinical Research in 2009. She has authored more than 170 scientific publications. She is a member of the executive board and of the pathology group of the LYSA, and was elected member of the International Lymphoma Study Group in 2011.

Research interests
Prof. de Leval’s team is committed to implementing and optimizing tools for the molecular diagnosis of hematological malignancies and other cancers, to characterizing lymphomas and other hematopoietic neoplasms clinically, to understanding the molecular mechanisms underlying NK/T-cell malignancies, and to studying thymic malignancies.
Recent scientific contributions

In 2013, we have focused our research on the study of peripheral T-cell lymphomas. Our works are based on tissues and cells derived from patient biopsies, collected through a research consortium (TENOMIC) linked to the LYSA. We have pursued our investigations on the molecular mechanisms underlying oncogenesis in angioimmunoblastic T-cell lymphomas and other related neoplasms derived from follicular helper T cells (T_{FH}). We are currently analyzing next generation sequencing data obtained in a series of well-characterized such tumors. We are also exploring the genetic alterations associated with the B-cell component of the microenvironment in T_{FH}-derived lymphomas. We are conducting a clinicopathological analysis of type 2 enteropathy associated T-cell lymphomas. We were the first to demonstrate recurrent TET2 aberrations in angioimmunoblastic T-cell lymphomas. Inquiring the potential role of ROQUIN in human angioimmunoblastic T-cell lymphomas, we did not find mutations of this gene in human tumors. We also focused on one study with a subset of peripheral T-cell lymphomas not otherwise specified, characterized by CD30 expression, and demonstrated shared molecular and phenotypic features with anaplastic large-cell lymphomas (see figures).

SELECTED PUBLICATIONS


Future focus and expectations

Our mission will be to decipher the mutational landscape of angioimmunoblastic T-cell lymphoma with functional analysis of recurrent mutations, and to characterize molecularly enteropathy-associated T-cell lymphomas.
Mauro DELORENZI

Funding sources

- Swiss National Science Foundation
- SystemsX.ch
- Oncosuisse
- MEDIC Foundation
- Leenaards Foundation
- EU-FP7 program
- SIB

Key research collaborations

- Dr. Arnaud Roth, HUG
- Prof. Nouria Hernandez, UNIL
- Dr. Sabine Tejpar, University Hospital Gasthuisberg, Leuven (BE)

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SIB

Biography

Mauro Delorenzi, born 1960 in Lugano, Switzerland, holds a diploma / master in Biology (1985) and one in Mathematics / Statistics (2000) as well as a Ph.D. (1990) from University Zürich. He worked as mathematics teacher in Zürich; then as postdoctoral scientist at The Walter and Eliza Hall Institute for Medical Research (WEHI) in Melbourne Australia (1999-2002). Since 2003 he has been leading a Bioinformatics and Biostatistics Core Facility (BCF) in Lausanne (Switzerland), set up with support from the Swiss Institute of Bioinformatics.

Research interests

The team contributes as bioinformatics experts to biomedical projects, analyzing last generation data for discovery in the fields of gene expression profiling and regulation, cancer subtypes, as well as developing mathematical models of prognosis and studying biomarker discovery and validation methodology.
Recent scientific contributions

The Delorenzi team continues to be involved on multiple fronts. Investigating gene expression patterns in surgical specimen of primary stage II / III colon cancer, we have proposed that the disease can be subclassified in five main gene expression subtypes (A-E) which seem to correspond to sufficiently distinct forms of the disease to suggest that their clinical behavior and their sensitivity to different treatments can be expected to be different and should be monitored. Using the same genomics data, we have revised and refined the value of BRAF and KRAS mutations in prognostic models of patient survival. The survival differences associated with these mutations depend on the patient subgroup, therefore prognostic models should include specific strata. In the more technical bioinformatics field, we reviewed and comparatively evaluated leading methods for the differential expression analysis of RNA-seq studies and have developed a method to use external spiked-in signal to improve the quality-control and the standardization of chIP-seq data.

SELECTED PUBLICATIONS


Future focus and expectations

We plan to keep studying prognostic models for colon cancer, in particular by testing a series of proposed gene expression-based risk scores to understand their relative merits and if possible develop a refined model. We also intend to run an analysis of RNA-seq gene expression data of matched primary colon tumors and their metastasis to understand tumor evolution. We also wish to initiate collaborations with cancer immunologists and apply systems biology approaches to identify and interpret the role of key genes that can regulate immune activity and might participate in tumor defense against cytotoxic immune cells.
Nicolas DEMARTINES

Funding sources

- Swiss National Research Funds
- Novartis
- Nestlé, MSD, Covidien, Ethicon

Key research collaborations

- IRCA EITS, University of Strasbourg (FR)
- Prof. Mariette, University Hospital of Lille (FR)
- John Wayne Cancer Institute, Houston (USA)

Nicolas Demartines
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Biography

Nicolas Demartines obtained his MD degree at the University of Geneva in 1985, and achieved his board of Surgery in 1990 at the University of Basel Medical School, Switzerland. He has been Professor of Surgery, and Chairman of the Department for Visceral Surgery at the University Hospital CHUV in Lausanne, Switzerland, since 2006. His clinical and surgical activities are focused on oncologic surgery, mainly hepato-pancreatico-biliary and colorectal surgery as well as Upper GI.

Research interests

Prof. Demartines’s research interests include the entire perioperative management and minimal invasive approaches especially in oncologic patients. In this field, nutrition and Enhanced Recovery After Surgery programs (ERAS) are very important. Furthermore, the influence of postoperative complications on oncological outcome, multimodal treatment of non-operable liver metastasis, HIPEC and PIPAC are in the research field of his Department.
Recent scientific contributions

The major scientific contribution of the Department of visceral surgery is the development of a very efficient perioperative program, with significant decrease of postoperative complication, especially in oncologic patients. As it has been demonstrated that complication is an independent factor of oncological outcome, these studies have an impact in surgical oncology.

Furthermore, the Department uses HIPEC and develops PIPAC which is an innovative approach of minimal invasive intraperitoneal chemotherapy by aerosol for peritoneal carcinosis.

The Department’s laboratory works on anti-angiogenesis drugs in collaboration with the Service of Medical Oncology from the Department of Oncology.

SELECTED PUBLICATIONS


Future focus and expectations

We will further develop the Enhanced Recovery Program in all major cancer surgeries, HPG, upper GI and large abdominal sarcomas.

Moreover, we will further assess the importance of postoperative complications in ontological outcome.

We will also proceed with the reverse treatment of colorectal liver metastasis with liver first approach. In addition, we aim to develop innovative liver resection after radiologic preparation of the liver to ensure good immediate postoperative liver function and long-term good oncological outcome.
Alban DENYS

Funding sources

- CNRS
- CIT
- Fonds Innova
- Private investors

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Biography

Prof. Alban Denys received his medical degree from the Medical School University of Paris V in 1987. He was radiology board certified in 1987, defended his thesis with magna cum laude. In 1987, he also received a Master of Science in Biomedical Engineering from the University of Paris XI (Orsay). He was awarded the silver medal of the Paris residency program in 1988. After a research fellowship at the University of Montreal and a clinical fellowship at the Gustave Roussy Institute and the Beaujon University Hospital in Paris, he moved to Lausanne in 1999 and received a Privatdozent title in 2000, was appointed Associate Professor in 2001 and Full Professor in 2010. He is editor of the CVIR journal and member of the program committee of ECIO and GEST, main societies in interventional oncology.

Research interests

Prof. Denys is interested specifically in developing new medical strategies in locoregional treatment both for tumor ablation or intra-arterial options.
Recent scientific contributions

We achieved 2 main goals.

We demonstrated the benefit of association of DNA repair inhibitor to ablation to increase peripheral apoptosis in a mouse and rabbit models.

We also demonstrated the synergistic effect of embolization and local delivery of anti-angiogenic factors to block the vascular rebound induced by ischemia.

Our methods of loading anti-angiogenic agents to beads are patented and patent licensing is in advanced negotiation.

SELECTED PUBLICATIONS


Future focus and expectations

We are focusing on testing new anti-angiogenic agents for local delivery in combination with ischemia, as well as extending the delivery time of the drug carrier over 3 weeks. Finally, we are developing phase 1 studies with industrial support.
Michele DE PALMA

Funding sources

- European Research Council
- Swiss National Science Foundation
- Swiss National Science Foundation
- Leenaards Foundation
- Swiss Cancer League
- Anna Fuller Fund
- Swiss National Center of Competence in Research
- Swiss Bridge Foundation
- MedImmune
- Roche

Key research collaborations

- Local: George Coukos, (CHUV/UNIL), Tanya Petrova (UNIL), Etienne Meylan (EPFL), Melody Swartz (EPFL)
- Abroad: Claire Lewis (UK), Max Mazzone (BE), Raghu Kalluri (USA), Livio Trusolino (IT)

Biography

Michele De Palma (Turin, Italy, 1973) obtained his Ph.D. in 2004 from the University of Turin Medical School, Italy, where he studied the contribution of macrophages to tumor angiogenesis. He performed post-doctoral training at the San Raffaele Institute (HSR) in Milan, Italy, to develop new strategies to target biotherapeutics to tumors using engineered monocytes. He became group leader at HSR in 2008 and was appointed Assistant Professor at ISREC/EPFL in 2012. He has received several awards from the American and European Societies of Gene and Cell Therapy, and a European Research Council grant in 2009. He is editorial board member of several international journals.

Research interests

We investigate the mechanisms whereby macrophages promote tumor angiogenesis, immunosuppression and progression, thus limiting the efficacy of antiangiogenic, chemo- and immuno-therapies. This is being studied in genetically engineered mouse models (GEMM) of cancer, in which macrophages are pharmacologically targeted or genetically modified to be visualized, depleted, or to modulate their gene expression in the context of anticancer treatments.
Recent scientific contributions

We have elucidated the role played by angiopoietin-2 (ANG2), a proangiogenic factor and TIE2 ligand, in tumor angiogenesis and resistance to anti-VEGF therapy in GEMMs of mammary adenocarcinoma and pancreatic neuroendocrine tumor (PNET). Our results indicate that evasive tumor resistance to anti-VEGF therapy may involve the adaptive enforcement of ANG2-TIE2 signaling, which can be reversed by concomitant ANG2 neutralization.

We have further analyzed the effects of ANG2 and VEGF blockade on the recruitment and functions of tumor-associated macrophages (TAMs) and T-cells in mouse models of cancer. We found that effective antiangiogenic therapy by ANG2/VEGF blockade is associated with substantial changes in the tumor immune microenvironment, including increased TAM and decreased T-cell numbers. TAM elimination by CSF1R blockade unleashed T-cell infiltration in the tumors, enabling better antitumor responses by immune-checkpoint blockade (anti-PD1).

Finally, we have identified macrophage-derived exosomes and their microRNA cargo as putative modulators of tumor angiogenesis.

SELECTED PUBLICATIONS


Future focus and expectations

We will continue to investigate the complex interactions that occur among the vascular and immune components of tumors. In particular, we will employ GEMMs of cancer (primarily breast and lung cancer) to develop anticancer treatments that combine (i) optimal antiangiogenic regimes; (ii) macrophage targeting; (iii) and activation of T-cells by immune checkpoint blockade or agonistic antibodies. The results of these studies may motivate new clinical trials, as the concerned therapeutic tools have already been tested as monotherapies.
Funding sources

- SNSF
- EMBO
- SystemsX.ch
- Marie Curie – IEF
- Human Frontier Science Program
- Carigest Foundation

Key research collaborations

- Prof. Martha Bulyk, Harvard Medical School (USA)
- Prof. Sebastian Kadener, Alexander Silberman Inst. of Life Sciences (Israel)
- Prof. Martin Klingenspor, Technical University of Munich, (Germany)
- Prof. François Leulier, Lyon Institute of Functional Genomics (FR)

Biography

Prof. Deplancke received his M.Sc. in biochemical engineering from Ghent University (Belgium), and his Ph.D. from the University of Illinois (Urbana-Champaign, USA) where he studied the role of environmental factors in the etiology of intestinal disease. After a postdoc at Harvard Medical School and then at the University of Massachusetts Medical School where he developed and applied a novel method to map the gene regulatory interactions underlying specific biological processes in multicellular organisms, he moved to the EPFL at the end of 2007 where he founded the Laboratory of Systems Biology and Genetics (LSBG) and where he is now Associate Professor. Furthermore, he has recently joined the SIB, is guest professor at Ghent University (Belgium), and co-founded the software company Genohm SA for which he currently serves as a board member.

Research interests

The LSBG is developing and using high-throughput sequencing, microfluidics, large-scale yeast screening, and computational approaches to characterize the regulatory code in Drosophila and mammals and to examine how variations in this code affect molecular and organismal diversity.
Recent scientific contributions

1) We finalized our work on developing a cross-platform approach involving large-scale yeast one-hybrid and microfluidic assays to experimentally identify and characterize interactions between mouse transcription factors and regulatory elements at unprecedented resolution and throughput (Gubelmann et al., Mol Syst Biol, 2013).

2) We published an article in collaboration with the Dermitzakis, Hernandez, and Reymond laboratories, studying the effect of sequence variation on chromatin structure and transcription (Kilpinen et al., Science, 2013). Our results uncovered transcription factors as key mediators of sequence-specific regulation of gene expression programs, with histone modifications frequently reflecting the primary regulatory event.

3) As part of the latter study, our lab also developed a new computational tool to deal with low-complexity sites when identifying allele-specific molecular events in ChIP-seq data (Waszak et al., Bioinformatics, 2013).

Future focus and expectations

In collaboration with the Dermitzakis, Hernandez, and Reymond labs, we are engaging in the largest integrative chromatin profiling initiative in a human population to date, aiming to make significant conceptual advances towards understanding the mechanisms behind variation in transcription factor DNA binding and histone modification patterns in humans. In addition, we are continuing our quest to dissect the regulatory mechanisms underlying adipogenesis, one cell and transcription factor at a time.
Laurent DERRE

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Funding sources

▪ Swiss National Science Foundation
▪ Swiss Cancer League
▪ Faculty of Biology and Medicine of UNIL
▪ Fondation pour la lutte contre le cancer

Key research collaborations

▪ Prof. Olivier Michielin and Dr. V. Zoete, SIB
▪ Prof. D. Speiser and Prof. P. Romero, LICR@UNIL
▪ Prof. D. Olive, Paoli Calmettes Institute, Marseille (FR)

Biography

Laurent Derré, born in France, received a Master degree in cellular biology and a PhD. in Immunology from the University of Sciences of Nantes (France). He moved to Lausanne for a first postdoc from 2004 to 2010 at the Ludwig Institute for Cancer Research in the laboratory of Prof. Daniel Speiser. He integrated the Urology Research Unit headed by Dr. PD D. Nardelli-Haefliger in 2010, as a postdoctoral fellow and then as a group leader. This unit is part of the Urology Dept. headed by Prof. MD. P. Jichlinski at the CHUV.

Research interests

Research projects developed in the Derré group aim primarily to understand the regulation of immune responses during the development of cancer in order to design new immunotherapies against urological cancers.
Recent scientific contributions

The Derré Lab continues to investigate intrinsic and extrinsic immune regulation mechanisms involved in the development of urological malignancies. We are particularly interested in bladder cancer which is the 9th most common malignancy and the 13th most common cause of cancer death in the world. Besides, it is the most expensive cancer to treat on a per-patient basis, due to high risk of recurrence. Bacillus Calmette-Guerin (BCG) was pioneered in the 1970s as immunotherapy for bladder cancer and is today commonly used as standard therapy for bladder cancer treatment. However, some patients show intolerance and resistance to this treatment, thus limiting the use of BCG therapy. Therefore, in one hand, we are investigating key immune regulatory mechanisms linked to the BCG failure by analyzing samples from patients (blood, tissue and urine) before and during the BCG therapy. Data are showing that a particular immune cell subset infiltrating the urine may correlate to BCG failure. On the other hand, in urological cancer patients, we specifically analyzed circulating and tumoral dendritic cell subsets expressing inhibitory receptors to correlate with cancer progression. We are also monitoring vaccine-specific T cells in blood and in urine of bladder cancer patients undergoing combinatorial therapy (MAGE-A3 vaccine from GlaxoSmithKline + intravesical BCG). Finally, in a collaborative project with the group of Prof. O. Michielin (SIB) and Prof. D. Speiser (LICR@UNIL), we are developing small molecule inhibitors of the regulatory receptor BTLA (B and T Lymphocyte Attenuator).

Optimization of bladder cancer vaccination using intravesical immunostimulants

SELECTED PUBLICATIONS


Future focus and expectations

We aim to extend DC subsets monitoring to kidney and prostate cancer patients, to focus on the MAGE-A3/BCG clinical trial outcomes (collaboration GSK and Ludwig center at UNIL), to screen large protein-protein interaction inhibitor libraries and to develop a comprehensive analysis of immune cells infiltrating urine upon BCG therapy.
Olivier DORMOND

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Funding sources
- Swiss National Science Foundation
- Oncosuisse
- Novartis
- Fondation Pierre Mercier

Biography
Olivier Dormond, born in Basel, Switzerland, received his medical diploma from the University of Lausanne in 1997. He did his MD-PhD at the CePO in Lausanne from 1998 to 2001. Between 2001 and 2004, he specialized in internal medicine at the CHUV. He did a post-doctoral fellowship at the Children’s Hospital in Boston from 2004 to 2007. Since 2008, he has been appointed group leader of the research laboratory of the Department of Visceral Surgery at the CHUV.

Research interests
The laboratory is interested in efficiently targeting signaling pathways responsible for tumor growth. In particular, we are focusing on the mTOR signaling pathway and characterizing its role in tumor cells as well as in the tumor microenvironment.
Recent scientific contributions

The Dormond lab has investigated the resistance mechanisms used by cancer cells to counteract the anti-cancer activity of mTOR inhibitors. At the cellular levels, we have investigated the role of the PAK family proteins in this process. In addition, we have also characterized the role of proteins present in the tumor microenvironment such as chemokines and cytokines that influence the response of cancer cells to mTOR inhibitors. We have also determined the consequences of mTOR inhibition through ATP-competitive inhibitors as well as rapalogs on the various components of the tumor microenvironment such as the immune infiltration. Various mouse models have been used including xenografts and genetically engineered mice.

SELECTED PUBLICATIONS


Future focus and expectations

We plan to further analyze the contribution of mTOR in various tumor compartments. To this end, mouse models in which mTOR signaling can be ablated in a cell-specific manner will be used.
Gian-Paulo DOTTO

Gian-Paulo Dotto
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UNIL - Department of Biochemistry

Biography
Dr. Dotto received his MD from the University of Turin, Italy, in 1979, and his PhD in Genetics from the Rockefeller University, New York, in 1983. After postdoctoral training with Robert A. Weinberg at the Whitehead Institute/MIT in Cambridge, Mass., in 1987, Dr. Dotto joined Yale University, New Haven, Connecticut, as Assistant Professor of Pathology. In 1992 he was promoted to the rank of Associate Professor and soon after moved to Harvard Medical School, as Associate Professor of Dermatology in the newly established Cutaneous Biology Research Center. In 2000 he was promoted to the rank of Professor at Harvard Medical School and Biologist at Massachusetts General Hospital. In 2002 he accepted a position of Professor in the Department of Biochemistry at the University of Lausanne, while retaining his position of Biologist at Massachusetts General Hospital. He has been elected to the European Molecular Biology Organization (2011), the Academia Europaea (2012) and the Leopoldina German National Academy of Sciences (2014). He is the recipient of a number of awards, including the American Skin Association Achievement Award (2012) and an Advanced ERC investigator grant award (2013).

Research interests
Our main research efforts are focused on control of epithelial tissue homeostasis and carcinogenesis, using skin as model system. We are focusing on two key questions: 1) the intracellular regulatory mechanisms that control the balance between keratinocyte stem cell renewal and differentiation; 2) the role of mesenchymal stromal cells in control of skin aging, inflammation and keratinocyte tumor development.

Funding sources
- Swiss National Science Foundation
- European Research Council
Recent scientific contributions

Notch activation in mammalian cells is commonly thought to enhance stem cell potential and promote tumorigenesis. We showed instead that in keratinocytes Notch signaling is an important determinant of differentiation and tumor suppression, with p21 WAF1/Cip1 and p63 as critical targets. Little is known on control of Notch1 gene expression. Our laboratory established this gene as a direct p53 target in antagonism to EGFR signaling, validating these findings for cancer development in the clinical setting. We also linked calcineurin signaling, usually studied in the context of the immune system, to the pro-differentiation and tumor suppressing functions of Notch1 and p53 in keratinocytes. This is of major clinical significance for the many patients under treatment with calcineurin inhibitors as immunosuppressants, who develop squamous cell carcinoma as a very frequent and often deadly complication. Epithelial-mesenchymal interactions play a key role in epithelial organ morphogenesis and homeostasis. In this context, we discovered an entirely novel and unexpected role of the Notch pathway in the mesenchymal compartment of the skin, in control of hair follicle cell fate as well as field cancerization and keratinocyte tumor development.

SELECTED PUBLICATIONS


Future focus and expectations

We will keep focusing on our ongoing studies, with the addition of a novel focus on the role of estrogen signaling in control of squamous cell differentiation and cancer.
Elena DUBIKOVSKAYA

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Biography
Elena Dubikovskaya received a PhD in "Organic Chemistry and Drug Delivery" from Stanford University (USA) in 2008. After completing her postdoctoral training at the University of California - Berkeley (USA) in the field of "Molecular Imaging", she started her own research group at EPFL in 2011.

Research interests
Prof. Dubikovskaya’s team is interested in developing novel molecular imaging probes for image-guided surgery and diagnostic of cancer, establishing novel methods for targeted drug delivery and generating new imaging reagents for visualization of tumor microenvironment and metabolic fluxes.

Funding sources
- Swiss National Science Foundation
- Leenaards Foundation
- NCCR Chemical Biology
- Commission for Technology and Innovation (CTI)
- Industrial grant (Intrace Medical, SA)

Key research collaborations
- Douglas Hanahan, EPFL
- Monika Hegi, CHUV
- Anita Wolfer, CHUV
- Krisztian Homicsko, CHUV/EPFL
Recent scientific contributions

The laboratory continues to develop novel imaging reagents for visualization of various biological processes associated with cancer progression and cancer microenvironment. This year, we made significant progress towards development of several novel imaging compounds. They include optical probes for imaging of fatty acid and glucose fluxes, activity of nitroreductase, and imaging of mitochondria membrane potential. The lab has also continued to work on the development of novel targeted chemotherapeutics for treatment of cancer based on cancer-targeting peptides.

SELECTED PUBLICATIONS


Future focus and expectations

We will continue preclinical validation of novel imaging reagents and cancer-targeted therapeutics.
Michel DUCHOSAL

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Funding sources
- European Community – FP7
- Dubois-Ferrière – Dinu-Lipatti Foundation
- CHUV-UNIL Research Commision

Biography
Michel Duchosal, born in Geneva, received his MD at the University of Geneva. After working in pathology and internal medicine at the university hospital of Geneva (1982–1986), he worked at the Scripps Research Institute in San Diego (1986–1994) where he was a faculty member in the Department of Immunology. He has been subsequently working at the service and central laboratory of hematology at CHUV, and leading this service since 2009.

Key research collaborations

Research interests
The group investigates molecular profiles of post-transplant lymphoproliferative disease and develops new biochemical targets to treat lymphomas and leukemias. In particular, a new cytotoxic antibody to human leukemia has been preclinically tested as well as NAD synthesis inhibitors developed in the context of an international collaboration including the EPFL and the Ludwig Institute for Cancer Research.
Recent scientific contributions

The group characterized leukemia/lymphoma death mechanisms and potential synergistic therapies of NAD synthesis inhibitors, revealing beclin-independent autophagy as one of the main mechanisms.

In addition, the team demonstrated a potent tumoral B cell activity of a novel defucosylated monoclonal antibody (in collaboration with Glenmark pharma).

SELECTED PUBLICATIONS


Future focus and expectations

New potent anti NAD synthesis inhibitors synthesized at the EPFL and modeled at the LICR will be tested on human lymphomas and leukemias, both in vitro and in vivo in xenochimeric laboratory models.
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Funding sources

- Swiss National Science Foundation
- Swiss Cancer League

Key research collaborations

- Grahame Hardie, University of Dundee (UK)
- Mariano Barbacid, CNIO, (ES)
- Pedro Romero, Ludwig Center Cancer Research, Lausanne

Biography

Prof. Lluis Fajas Coll was born in Barcelona, Spain. He got his Master’s degree in Biology at the University of Barcelona. He did his PhD studies at the Ernst Boehringer Institute in Vienna, Austria. After two post-doctoral trainings in France in the laboratory of Prof. Auwerx at Pasteur Institute in Lille and at the IGMM in Montpellier, he was recruited as Inserm as a scientist at the IGBMC in Strasbourg. He then got an Inserm Avenir young investigator grant. He is now Professor and director of the Department of Physiology at UNIL.

Research interests

Key research projects include:

a. Participation of cell cycle regulators in the control of metabolism in normal and cancer cells.
b. Analysis of new target of CDK4 and E2F1 involved in metabolic control
c. Lipid synthesis inhibition in cancer cells
Recent scientific contributions

We show that both E2F1 and CDK4 regulate glycolysis and modulate oxidative metabolism in normal and in cancer cells. We prove that these cell cycle regulators are major determinants of the Warburg effect. We prove that CDK4 is a key effector of the insulin / IGF signaling in normal and in cancer cells, through phosphorylation of IRS1 and IRS2 proteins. Finally we prove that CDK4 antagonizes AMPK in the control of energy homeostasis through direct phosphorylation.

We have also designed a combination therapy in order to force cancer cells to use a particular metabolic pathway that ultimately results in the accumulation of toxic products. This innovative approach consists of blocking lipid synthesis using fatty acid synthase (FASN) inhibitors, at the same time that we force the cell, through inhibition of AMPK. We showed that this leads to cancer cell death. Manipulation of metabolic pathways will certainly set up the basis of new upcoming studies defining a new paradigm of cancer treatment.

SELECTED PUBLICATIONS


Future focus and expectations

We are generating and will analyze the phenotype of tissue-specific (liver and WAT) E2F1-/-, cdk4-/-, cdk7-/-, and cdk10-/- mice. We will focus our work on the participation of these cell cycle regulators in the metabolic switch observed during carcinogenesis.
Periklis FOUKAS

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UNIL – Ludwig Center for Cancer Research  

Funding sources  
- Tositza foundation  

Key research collaborations  
- Department of Histology and Embryology (Prof. V. G. Gorgoulis), University of Athens  
- Ovarian Cancer Research Center, University of Pennsylvania School of Medicine  

Biography  
Periklis Foukas, born in Athens, Greece, graduated with a medical degree from the School of Medicine, University of Ioannina and received his Ph.D. from the University of Athens. He joined the faculty of the University of Athens at 2007 is an Assistant Professor of Pathology. Since September 2013, he has been a Visiting Assistant Professor at the Department of Oncology & Ludwig Center for Cancer Research, University of Lausanne and the head of the Biomarker Discovery Lab within the Center of Experimental Therapeutics at CHUV.

Research interests  
Prof. Foukas investigates the contribution of the two major barriers, i.e. DNA damage response and immunity, in tumor development and progression. Furthermore, his research aims to analyze the immunologic features of tumors and identify molecular biomarkers for clinical benefit.
Recent scientific contributions

Prof. Foukas’ research is focused on the evaluation of DNA damage response activation and immune status in myelodysplastic syndromes and treatment effects, the evaluation of DNA damage response activation in colorectal cancer and correlation with clinical parameters, microsatellite vs chromosomal instability and the immune status, the evaluation of anti-tumor immunity in early vs advanced gastric cancer, the evaluation of major signaling pathways in DLBCL tumorigenesis and treatment effects and the evaluation of tumor microenvironment in the context of the participation in “Inflammation and Cancer (INFLA-CARE)” European Seventh Framework research Programme (FP7).

SELECTED PUBLICATIONS


Future focus and expectations

Focus will be given to the identification of molecular biomarkers for clinical benefit using multi-analyte bright-field or fluorescence immuno-histochemistry in clinical tumor samples. We will also keep tracking anti-tumor T cell specificities in mouse and human neoplastic diseases. Finally, we will develop organotypic cultures as an ex vivo model of anti-tumor therapies.
Olivier GAIDE

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Funding sources
- Leenaards Foundation
- ONO pharma
- EDIMER pharma

Key research collaborations
- Prof. T. S. Kupper, Brigham and Women’s Institute, Boston (USA)
- Prof. M. Thome-Miazza, University of Lausanne

Biography
Olivier Gaide was born in Lausanne, Switzerland. He obtained his medical diploma from the University of Lausanne (1998) and his doctoral thesis from the University of Zurich (1999). He obtained a PhD in molecular biology in the research group of Prof. Tschopp (University of Lausanne, 2003) before training in dermatology-venereology with Prof. Saurat at the University Hospital in Geneva (board certif. in 2008). In 2010, he moved to Boston at the Harvard Institutes for Medicine as a visiting scientist. In 2012, he was recruited to head the Oncology and Interventional Unit of the Department of Dermatology at the CHUV.

Research interests
The Gaide group focuses his interest on the determinants of cutaneous T cell function and homeostasis, in mouse models of human diseases. This field has strong relevance in the mechanisms controlling the tolerance or rejection of skin cancer, as well as the development of cutaneous T cell lymphoma, our core clinical competence.
Recent scientific contributions

In 2013, we have carried out research along two axes aiming at providing a better description of the function of cutaneous T cells. The first study assessed the role of innate immunity signals arising in the skin and their impact on the development of T helper cells subtypes. We could show that a similar antigen can give rise to different T cell responses, depending on the innate immune context. Danger signaling through the inflammasome and its impact on various interleukins (IL1b and TSLP) modulate Th1 and Th2 responses from a default pathway of Treg-mediated tolerance (Schuepbach-Mallepell et al, JACI). This suggests that most tumors develop in a context of immune tolerance that is later very hard to circumvent. The second subject of focus is the discovery of a new sub-population of memory T cells that reside in the skin, and the mechanisms that govern their migration and activity in the skin (Gaide et al, submitted). We believe that these cells are highly relevant to CTCL and represent an interesting target for anti-cancer responses.

SELECTED PUBLICATIONS


Future focus and expectations

In 2013, we have set up a skin cancer clinic allowing the generation and building up of a melanoma and carcinoma library. In early 2014, we have started clinical trials aiming at facilitating the early diagnosis of skin cancer. In late 2014, our aim it to focus on the research side of our activity, supported by the publication of our two most recent articles.
Martin A. M. GIJS

Funding sources

- National Competence Center for Biomedical Imaging (NCCBI)
- European Research Council

Key research collaborations

- Prof. Laurence de Leval, Dr. Maryse Fiche, Dr. Bettina Bisig, Institute of Pathology, CHUV (CH)
- Prof. Jean-François, Delaloye, Centre du Sein, CHUV (CH)

Biography


Research interests

Use of micro-engineering and microfabrication approaches to realize microfluidic devices that enable extreme control of staining protocols, so that immunohistochemistry and in situ hybridization analysis on tissue sections can be faster and more accurately performed.
Recent scientific contributions

We reported a microfluidic tissue processor that permitted accurate quantification of the expression of biomarkers on tissue sections, enabled by the ultra-rapid and uniform fluidic exchange of the device. An important clinical biomarker for invasive breast cancer is the human epidermal growth factor receptor 2 (HER2 also known as neu), a trans-membrane tyrosine kinase that connotes adverse prognostic information for the concerned patients. Using our device, we performed tests on 76 invasive breast carcinoma cases expressing various levels of HER2. We eliminated more than 90% of the ambiguous results (n=27), correctly assigning cases to the amplification status as assessed by in situ hybridization controls, while the concordance for HER2-negative (n=31) and -positive (n=18) cases was 100%.

Future focus and expectations

The lab aims to develop an automated microfluidic platform for analysis of tissue slides and the margins of thin resections of formalin-fixed and cryo-fixated surgical specimens of tumors, also called frozen sections, to distinguish cancer cells from healthy cells via immunohistochemistry staining, and this, in a way that the diagnosis can be done in a timeframe that is compatible with the surgical intervention.

SELECTED PUBLICATIONS

Michel GILLIET

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Funding sources

- Swiss National Science Foundation
- Oncosuisse
- National Institute of Health, Bethesda, MD, USA

Key research collaborations

- Prof. Daniel Speiser, Ludwig Center for Cancer Research, UNIL
- Prof. Olivier Michielin, Dept of Oncology, CHUV
- Prof. Patrick Hwu, Dept. of Melanoma Oncology, MDACC Houston (USA)

Biography

Michel Gilliet was born in Boston Massachusetts in 1969. He did his Medical studies and his training in Dermatology at the University of Zurich (board certified in 2004). From 1999 to 2001, he did a postdoctoral fellowship in immunology at the DNAX Research Institute in Palo Alto CA. In 2004, he was recruited as Assistant Professor to the MD Anderson Cancer Center (MDACC) at the University of Texas in Houston and received his tenure as Associate Professor in 2008. At MDACC, he had a triple appointment in Dermatology (clinical), Melanoma Medical Oncology (translational research) and Immunology (Basic research). In 2010, Michel Gilliet was appointed Full Professor and Chairman of the Department of Dermatology at the CHUV in Lausanne.

Research interests

The Gilliet lab is interested in understanding the molecular mechanisms that govern immunosuppression in the tumor microenvironment, with particular focus on dendritic cells. The lab is also interested in modulating the function of these dendritic cells by providing innate activation stimuli such as activators of intracellular nucleic acid sensors to revert tumor immunosuppression and induce anti-tumor immunity.
Recent scientific contributions

The Gilliet lab has identified a unique role of resting plasmacytoid Dendritic Cells (pDC) in cancer immunosuppression via the stimulation of FoxP3+ T regulatory cell through ICOS/ICOS-L. This activity can be inhibited by TLR7 and TLR9 activation of pDC to produce IFN-alpha. Indeed, intratumoral pDC can be activated by CpGs or imiquimod to induce potent antitumor immunity. The Gilliet lab has also identified a role of cationic antimicrobial peptides in promoting activation of TLR7 and TLR9 by increasing internalization of nucleic acid sequences. By using mouse models of melanoma, the Gilliet lab has been able to demonstrate a strong capacity of the antimicrobial peptide LL37 to enhance the antitumor activity of CpG. Furthermore, they have shown that intratumoral injection of LL37 alone can induce pDC activation and antitumor immunity by promoting the ability of self-DNA released by dying tumor cells to activate TLR9 in pDCs. These data have provided the basis for the design of clinical trials in which LL37 is injected intratumorally either alone or in combination with CpG to induce antimelanoma immunity.

SELECTED PUBLICATIONS


Future focus and expectations

Efforts are now focus on the translation of the LL37 finding into a clinical trial for advanced melanoma (done both at MDACC and in Lausanne). The Gilliet lab has also gained new evidence that spontaneous immune responses against melanoma are driven by a STING-dependent activation of cytosolic DNA sensor. This is of great interest as intratumoral injection of the newly identified cGAMP can now be used to induce therapeutic activation of these sensors and elicit very potent systemic antitumor immunity. The next challenge will now be the development of suitable STING ligands for clinical use.
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Funding sources

- Swiss National Science Foundation
- European Research Council

Key research collaborations

- Michel Steinmetz, PSI, Villingen (CH)
- Ioannis Vakonanis, Oxford (UK)

Biography

Pierre Gönčzy obtained his PhD from The Rockefeller University (New York, USA) in 1995, after which he conducted postdoctoral work with Tony Hyman at the EMBL (Heidelberg, Germany). Pierre Gönčzy started his laboratory in Lausanne at ISREC in the year 2000 and joined the EPFL School of Life Sciences in 2005.

Research interests

We are interested in understanding fundamental cell division processes, in the context of a developing organism. We focus in particular on two processes that are crucial for genome integrity, centrosome duplication and asymmetric cell division. To address these fundamental biological questions, we use a combination of genetic, functional genomic, biochemical, proteomic and cell biological approaches, primarily in the nematode C. elegans and in human cells in culture.
Recent scientific contributions

Centrosome duplication. We completed a genome-wide siRNA-based screen in human cells to identify genes required for proper centriole formation. Using a custom-developed algorithm for automatic counting of centrosomes, we identified and validated candidate genes whose inactivation prevents or instead enhances centriole formation (Balestra et al., 2013). Moreover, we utilized cryo-electron tomography to reveal the architecture of the exceptionally long centriole of the flagellate Trichonympha at a resolution of 40 Å. Our findings provide a unique architectural map for understanding the mechanisms of centriole assembly (Guichard et al., 2013).

Asymmetric cell division. We uncovered that phosphorylation of NuMA on a specific site by the master mitotic regulator CDK1 during metaphase negatively regulates, and thereby limits, the presence of NuMA at the cell cortex. Furthermore, we established that upon CDK1 inactivation during anaphase, levels of dephosphorylated NuMA at the cell cortex rise, which is essential for robust cortical dynein enrichment and, thus, spindle elongation. Overall, our findings reveal a mechanism whereby the status of NuMA phosphorylation coordinates mitotic progression with proper spindle function (Kotak et al., 2013).

SELECTED PUBLICATIONS


Future focus and expectations

We will continue our investigations of the mechanisms governing centrosome duplication and spindle positioning using an array of complementary experimental approaches.
Key research collaborations

- Dr. Pascal Gervaz, Visceral Surgery Department, HUG (CH)
- Dr. Samer Salah, Medical Oncology Department, King Hussein Cancer Center, Amman (Jordan)
- Prof. Tatiana Petrova, ISREC (CH)

Biography

Dr. Michel Gonzalez completed his medical studies at the University of Geneva in 2002. He then started his General Surgery training in HUG, la Chaux-de-Fonds and Yverdon, and obtained his General Surgery Board in 2008. Since 2009, he has joined the division of Thoracic Surgery at the CHUV and obtained his Swiss Thoracic Surgery Board and the European Board of Thoracic Surgery in 2013. Since 2014, he has been a Staff Surgeon in the Division of Thoracic Surgery and has contributed to the development of minimal invasive surgery. He is a surgeon involved in the Lung Transplantation program. He obtained the Swiss Price of the Swiss Society of Surgery in 2011 for his work on colorectal lung metastases management.

Research interests

Dr. Gonzalez’s research focuses on minimal invasive thoracic surgery and pulmonary metastasectomy. In the field of pulmonary metastasectomy, he is having many contributions on the management of colorectal pulmonary metastases. He is also interested in all aspects of pre-, peri- and post-operative management in order to reduce morbidity, length of hospitalization and accelerated recovery.
Recent scientific contributions

Resection of lung metastases (LM) from colorectal cancer (CRC) is increasingly performed with a curative intent. It is currently not possible to identify those CRC patients who may benefit the most from this surgical strategy. We performed in collaboration with the Geneva University a systematic review and meta-analysis to determine which risk factors were associated with poorer survival after lung metastasectomy for CRC. We could identify four parameters which were significantly associated with poor survival: short disease-free interval between primary tumor resection and development of lung metastases, multiple lung metastases, positive hilar and/or mediastinal lymph node involvement and elevated prethoracotomy carcinoembryonic antigen. By comparison, a previous history of resected liver metastases was not associated with poorer outcome.

SELECTED PUBLICATIONS


Future focus and expectations

Palpation of the lung is recommended to detect additional metastases in patients undergoing surgical metastasectomy in curative intent. However, due to the progress of radiological imaging with thin-slice high-resolution CT-Scan, solitary lung metastasis is increasingly resected by video-assisted thoracic surgery (VATS). We planned to determine the results after thoracoscopic metastasectomy for isolated lung metastasis the local recurrence in term of local and distant recurrence rate and outcome.
Nicole GROSS

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Biography
Dr. Nicole Gross obtained her PhD in Biochemistry in 1979 from the University of Lausanne. After completing her two postdoctoral fellowships at the Ludwig Institute for Cancer Research (1979-1981) and in Paediatric Hemato-Oncology at the CHUV (1982-1992), she became Group Head of the Paediatric Oncology Research laboratory at the CHUV in 1995. In 2004, she was nominated Senior Scientist (MER) and obtained the Privat Docent title.

Research interests
Dr. Gross is interested in the biology and genetics of Neuroblastoma (NB) and paediatric solid tumors. Key research areas are:
a. Neuroblastoma tumor initiation
b. Role of ALK-wt and ALK activating mutations in neuroblastoma oncogenesis, differentiation and progression.
c. Involvement of the chemokine receptors CXCR4/CXCR7 in the control of neuroblastoma progression and selective metastasis
d. Molecular mechanisms of apoptosis resistance
e. Participation as National Responsible in SIOPEN studies (LNESG2, HR-NBL, LINES)

Funding sources
- Swiss National Science Foundation
- Schweizer Forschungskontakt Schweizerische Krebsstiftung
- FORC Foundation
- Emma Muschamp foundation
- Enfance et Cancer, Hubert Gouin Foundation

Key research collaborations
- Dr. J.-M. Joseph, Paediatric Surgery, DMCP, CHUV
- Drs I. Janoueix-Lerosey and O. Delattre, Institut Curie, Paris (FR)
- Dr N. Riggi, Massachusetts General Hospital, Boston (USA)
- Pr I. Stamenkovic, IAP, CHUV, Lausanne
- Dr A. Arcaro, Pädiatrische Hämatologie/Onkologie University of Bern (CH)
- Pr M. Thelen, Istituto di Ricerca in Biomedicina, Bellinzona (CH)
- Pr L. Sommer, Anatomisches Institut, Universität Zürich (CH)
- Pr M. Hegi, Laboratoire de biologie et génétique des tumeurs, CHUV, Lausanne
- Dr H. Sartelet, Institut Gustave-Roussey, Villejuif (FR)
Recent scientific contributions

Key genes involved in neuroblastoma initiation were identified and further validated (ALDH1, LRG5, PTN, MDRI, CD133) (Coulon et al., 2011).

In addition, the laboratory made a breakthrough discovery of the role of ALK-wt gene and its two major activating mutations, in neural crest progenitor cells fate, and in neuroblastomagenesis, and progression (Montavon et al., 2014).

Moreover, the respective involvement and interactions of the two CXCL-12 chemokine receptors (CXCR4, CXCR7) in selective homing were determined, using a newly developed model of intravenous tumor cell implantation in immunocompromised animal (NOD scid gamma mice) (manuscript in preparation).

In addition, the respective contribution of different caspase-10 isoforms in the control of apoptosis in NB cells was identified (Mühlethaler et al., 2011).

Finally, data analysis of the second European study on localized neuroblastoma (LNESG2) was performed to evaluate the impact on outcome of numerical and segmental chromosomal abnormalities and biological characteristics (manuscript in preparation).

SELECTED PUBLICATIONS


Future focus and expectations

Focus will be given to NB genetics and epigenetics with a comprehensive epigenomic characterization of NB progenitor cells (collaboration with Drs N. Riggi and JM Joseph). Recent advances in cancer research revealed the involvement of epigenetic changes in the establishment and maintenance of intratumoral cellular heterogeneity and hierarchy, and in the regulatory networks driving tumor initiation by single oncogenic events. Identification of epigenetic determinants that distinguish NB tumor initiating cells, differentiated progeny, and non-malignant counterparts will therefore be of great significance.

We plan to analyze the impact of ALK activation on oncogenesis and progression, and to identify regulatory interactions between ALK and other key genes (c-myc, MYCN, TWIST).

2014 is also a year that should be marked by the increase of activities in the SIOPEN network (Society of Paediatric Oncology European neuroblastoma Research) due to the new participation of Swiss centers.
Douglas HANAHAN

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Funding sources
- Swiss National Science Foundation
- European Research Council
- Oncosuisse
- Merck-Serono
- Leenaards Foundation
- Sante

Key research collaborations
- Olivier Michielin, CHUV
- Johan Auwerx, EPFL
- Giovanni Cirriello, MSKCC, NYC (USA)

Biography
Douglas Hanahan has a S.B in Physics from the Massachusetts Institute of Technology (MIT), and a Ph.D. in Biophysics from Harvard University, where he was elected to the Harvard Society of Fellows. He worked at Cold Spring Harbor Laboratory first as a graduate student and then as a group leader. Then he worked as a Professor at the University of California San Francisco before moving to EPFL. Hanahan’s accomplishments have been recognized by election to the American Academy of Arts & Sciences, the Institute of Medicine of the US National Academies, the US National Academy of Science, and the European Molecular Biology Organization.

Research interests
The laboratory’s research focuses on the following topics:
- a. Pathways of multistep tumorigenesis,
- b. Mechanisms of tumor progression, in particular angiogenesis, invasion, and metastasis
- c. Genetically-engineered mouse models of human cancer, including pancreas, brain, melanoma, HPV-induced oral/cervical
- d. Pre/co-clinical trials guiding mechanism-based clinical trials targeting hallmarks of cancer
- e. Functions of the tumor microenvironment
Recent scientific contributions

The team reported (Li & Hanahan, Cell, 2013) that a neuronal signaling pathway, involving autocrine activation of glutamate stimulated NMDA receptor, is hijacked in various cancer types, in particular pancreatic neuroendocrine; that glutamate secretion and receptor activation are regulated by a polymorphic modulator (GKAP) and physical cues in the tumor microenvironment.

We described a classification system for human colorectal cancer that associates developmental and cellular phenotypes, and response to therapy, with five molecular subtypes (Sadanandam et al, Nature Med. 2013).

We also reported that bioavailable copper is limiting in certain solid tumors, consequently influencing tumor growth (Ishida et al, PNAS, 2013).

SELECTED PUBLICATIONS


Future focus and expectations

We are determined to pursue investigations of cancer mechanisms and evaluating therapeutic efficacy of innovative combinatorial strategies in mouse models of human cancer – melanoma, glioma, pancreas, HPV16-induced squamous – in concert with translational studies in cognate human cancers.
Oliver HANTSCHEL

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Funding sources
- ISREC Foundation
- Swiss national Science Foundation
- Swiss Cancer League
- Anna Fuller Foundation

Biography
Oliver Hantschel, born in Offenbach/Main, Germany, studied biochemistry at the University of Regensburg and at Rockefeller University in New York City. He received his PhD in 2004 from the European Molecular Biology Laboratory in Heidelberg and did postdoctoral work at the Research Center for Molecular Medicine of the Austrian Academy of Sciences in Vienna. In 2011, he became Tenure Track Assistant Professor at the EPFL School of Life Sciences and was awarded the ‘ISREC Foundation Chair in Translational Oncology’.

Key research collaborations
- Shohei Koide, University of Chicago (USA)

Research interests
Research in the Hantschel laboratory focuses on oncogenic kinase signaling pathways that play a key role in the pathophysiology of leukemias and lymphomas. Interdisciplinary approaches at the interface of biochemistry, proteomics, chemical biology and protein engineering are being used with the aim to identify innovative and novel ways for therapeutic intervention.
Recent scientific contributions

The Hantschel lab has established a novel way to target intracellular protein-protein interactions and post-translational modifications with engineered high-affinity protein antagonists, termed monobodies. The lab developed effective and highly specific monobodies that inhibit SH2 domain-phosphotyrosine interactions of the tyrosine phosphatase SHP-2, phospholipase C isoforms and BCR-ABL in vitro and when expressed in cells. These results delineated the molecular pathways that regulate the enzymatic activity of these enzymes and validated monobodies as valuable antagonists of protein-protein interactions in cancer cells. The analysis of the oncogenic signaling network of the NUP214-ABL fusion, which is expressed in a subset of T-cell acute lymphoblastic leukemias, identified targetable interactors/effectors that are critical for cell proliferation and survival of tumor cells. In addition, the mechanism-of-action and specificity of two JAK2 tyrosine kinase inhibiting drugs that are in clinical use was studied and revealed several unexpected off-targets of these drugs, and highlighted potential mechanisms of resistance.

SELECTED PUBLICATIONS


Future focus and expectations

The Hantschel lab plans to develop cellular delivery systems for monobody proteins using cell-permeable peptides and other approaches that will enable the evaluation of the therapeutic potential of monobodies in haematological and solid tumors in vivo.
Keith HARSHMAN

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Biography
Keith Harshman received his Ph.D. in biochemistry from the California Institute of Technology in 1990. Following post doctoral fellowships at the University of Zurich and the Sloan-Kettering Cancer Center NYC, he joined Myriad Genetics Inc. in 1993, where he worked first as a Senior Scientist and later as the Director of Central Nervous System Disease Research. In 1997 he moved to the Department of Immunology & Oncology of the Spanish National Biotechnology Center as the Head of the Functional Genomics Unit. He has been the Coordinator of the Genomic Technologies Facility of the Center for Integrative Genomics at the University of Lausanne since November 2002.

Research interests
The Facility performs high throughput nucleic acid analysis methods and applications.
Facility activities

The mission of the Genomic Technologies Facility (GTF) is to provide its user community with access to and support in the use of state-of-the-art genomic technologies designed to detect and measure quantitative and qualitative variations in nucleic acids.

The primary technology platforms supported by the GTF are:

- **Ultra high throughput DNA sequencing technologies including the Illumina HiSeq and MiSeq instruments as well as the Pacific Biosciences RS II for the analysis of RNA and DNA**

- **Affymetrix GeneChip** oligonucleotide arrays for mRNA expression analysis

- **Agilent Technologies** oligonucleotide arrays for the analysis of miRNA gene expression

- **Nanostring nCounter** Analysis System for RNA analysis and DNA Copy Number Variation (CNV) analysis

- **Applied Biosystems 7900HT Sequence Detection System** for quantitative real-time PCR analysis of mRNA, miRNA and DNA

- **Fluidigm C Single-Cell Auto Prep System** for capture and nucleic processing of single cells

- Bioinformatics support and consultation services at the stages of experimental design, data collection and storage, image analysis as well as higher level data analysis
Monika HEGI

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Funding sources

- Swiss National Science Foundation
- Swiss Bridge
- Swiss Cancer League
- Brain Tumors Funders Cooperative, USA
- NovoCure

Key research collaborations

- Roger Stupp, University Hospital Zurich
- Mauro Delorenzi, Swiss Institute for Bioinformatics
- Cristina Cudalbu, CIBM-EPFL
- Thierry Gorlia & The Brain Tumor Group, EORTC
- Wim van Criekinge, Gent University, Belgium

Biography

Monika Hegi obtained a Master’s degree (1986) and a PhD (1989) in Natural Sciences from the Swiss Federal Institute of Technology in Zurich. She pursued post-doctoral training at the National Institute of Environmental Health Sciences (NIH), NIH, RTP, NC, USA (1989-93), and moved as research associate to the Institute of Neuropathology, University Hospital Zurich in 1993. In 1989 she was nominated director of the Lab for Brain Tumor Biology and Genetics, Neurosurgery, CHUV. Since 2009 she is Associate Professor for Translational and Experimental Neuro-Oncology. She has been coordinator for translational research of the brain tumor group of the European Organisation for Research Treatment of Cancer (EORTC) since 2003.

Research interests

We work at the interphase of clinical and basic cancer research, analyzing multidimensional molecular profiles of gliomas from patients treated in clinical trials. We aim at identifying predictive factors for response to therapy and new druggable targets, with a particular focus on epigenetics. Candidate genes/pathways are followed up with a systems medicine approach, combined with experimental studies in vivo and in vitro to evaluate clinical utility.
Recent scientific contributions

(1) Biological consequences of loss of WIF1 expression, a soluble inhibitor of WNTs that we identified as tumor suppressor in glioblastoma, comprise increased migration and invasion and shorter survival as determined in an orthotopic glioma derived sphere line mouse model. Mechanistically, these effects are mediated both through the canonical and non-canonical WNT-pathway, involving increased expression of the long non-coding RNA MALAT1. The diffuse invasion is an important biological characteristic of glioblastoma, prohibiting complete resection, with almost invariable recurrence of the tumors within 2-3 cm. Based on our data, there is a rational to target both the canonical and non-canonical WNT pathway.

(2) Using a systems biology approach we investigated the mechanism for aberrant expression of a HOX-dominated self-renewal signature that is associated with resistance to therapy in glioblastoma. This developmental HOX-signature is not involved in the development of the brain. Our systems biology approach suggests that enhanced gene dosage mediated by recurrent trisomy of chromosome 7, on which the HOXA gene cluster resides, attenuated by aberrant DNA methylation, initiates the aberrant HOX expression signature. Similar to development, the HOX expression program expands to the other HOX clusters, B, C & D, located on other chromosomes, and interestingly also includes PROM1 that encodes the stem cell marker CD133.

SELECTED PUBLICATIONS


Future focus and expectations

We have completed the methylome from over 500 glioma of patients treated in 3 clinical trials for low grade and high grade glioma. The data will be interrogated for distinct molecular subgroups, inherent data structures, and respective reflected biological properties and associations with benefit from therapy. We expect to identify epigenetically affected pathways revealing druggable targets.
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Biography
Werner Held obtained a Ph.D. in Immunology (University of Bern, 1990) and did postdoctoral training at the Ludwig Institute in Lausanne (1990-93) and the University of California (Berkeley) (1993-96). He received a START fellowship (Swiss National Science Foundation) and became an Assistant Member of the Ludwig Institute (1996). He was promoted to Associate Member (2002) and to Associate Professor at the University of Lausanne (2006). Since 2011 he has been a Full Professor at the Ludwig Center for Cancer Research, University of Lausanne.

Research interests
Cytotoxic CD8 T cells and Natural Killer (NK) cells play important protective roles against infected, stressed and transformed cells. We are studying signaling pathways that impact the ability of cytotoxic lymphocytes to respond to diseased cells.
Recent scientific contributions

1.) We have previously found that the canonical Wnt signaling pathway plays an essential role for the development of functional memory CD8 T cells, which behave in a stem cell-like fashion. We are currently investigating at what stage of the immune response CD8 T cells receive canonical Wnt signals and whether signaling is associated with specific cell fates (renewal vs differentiation).

2.) We have a long term interest in understanding the modulation of immune responses by inhibitory receptors. We have made progress in defining how “inhibitory” receptors can exert positive effects, i.e. improve the fitness of NK cells (Bessoles et al 2013).

Future focus and expectations

1.) We are addressing whether the Wnt pathway impacts the differentiation of NK cells in ways that are similar or distinct to those seen in CD8 T cells.

2.) We are investigating whether the maintenance/self-renewal of transformed lymphocytes i.e. acute lymphoblastic leukemia (ALL) depends on the Wnt signaling pathway.

SELECTED PUBLICATIONS

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Funding sources

- Swiss National Science Foundation

Key research collaborations

- Vincent Zoete, SIB
- Nicolas Guex, SIB
- Daniel Constam, EPFL
- Ji-Joon Song, KAIST South Korea
- Nouria Hernandez, UNIL

Biography

Winship Herr received his PhD from Harvard University in 1982 for studies on recombinant retroviruses in leukemogenic mice with Walter Gilbert. After postdoctoral studies with Frederick Sanger in Cambridge England and Joe Sambrook at Cold Spring Harbor Laboratory, he joined the Cold Spring Harbor Laboratory faculty in 1984. There he served as assistant director of the Laboratory from 1994-2002 and from 1998-2004 was the founding dean of the Watson School of Biological Sciences, a doctoral degree-granting school. He arrived at the CIG, UNIL in September 2004. Winship Herr is EMBO member since 2008 and also director of the "Ecole de biologie" of Faculty of Biology and Medicine since August 1st, 2009.

Research interests

Two complete sets of instructions contained within the genomes we inherit from our parents are responsible for directing a single cell - the zygote - to become an adult human being. This process results from controlled patterns of gene expression that are maintained as well as changed during many rounds of cell division, differentiation, and death. The laboratory is interested in the control of gene transcription, fundamental to these processes, with genetic and epigenetic defects in transcriptional regulation often leading to human disease including cancer, and study a key regulator of human-cell proliferation that is also implicated in embryonic stem cell maintenance and cancer.
Recent scientific contributions

We study a key regulator of human-cell proliferation that is also implicated in embryonic stem cell maintenance and cancer. This protein, called HCF-1 for herpes simplex virus host-cell factor-1, binds to many promoters by recognizing site-specific DNA-binding proteins and recruits histone-modifying activities for activation and repression of transcription. HCF-1 function is conserved in animals. We are taking advantage of this property to perform genetic, genomic, biochemical, bioinformatics, and molecular studies in diverse organisms including *C. elegans* worm, *Drosophila* fruit fly, mouse, and human.

In 2013, we contributed the following published work to pursue our understanding of the regulation of cell proliferation and differentiation:

- “HCFC1 is a common component of active human CpG-island promoters and coincides with ZNF143, THAP11, YY1, and GABP transcription factor occupancy”

- “HCF-1 is cleaved in the active site of O-GlcNAc transferase”

SELECTED PUBLICATIONS


Future focus and expectations

We focus on a regulator of human-cell proliferation — HCF-1 — implicated in embryonic stem cell maintenance and cancer. HCF-1 binds to many promoters with transcription factors (e.g., E2Fs) and recruits histone-modifiers for activation and repression of transcription. After synthesis, it is proteolytically cleaved by O-GlcNAc transferase to create associated subunits that, in cell culture models, regulate different cell-cycle phases. We now focus on using partial mouse liver hepatectomy to uncover roles of HCF-1 in hepatocyte cell proliferation.
Fernanda HERRERA

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Key research collaborations

- EORTC Radiation Oncology Group and Gynecology Cancer Group, Brussels (BE)  
- Prof. George Coukos and Prof. Jean Bourhis laboratories, CHUV and LICR@UNIL  
- Multidisciplinary Prostate Clinic, and Multidisciplinary Gynecology Clinic, CHUV

Biography

After receiving her MD degree from medical school at the National University of Cordoba, Dr. Herrera, born in Argentina, worked as a physician at the University of Buenos Aires, Radiotherapy Clinic, and the Hospital Rivadavia, Gynecology and Radiotherapy Services on gynecological cancers. From 2005 to 2007, she was a clinical research fellow in gynecological and genito-urinary cancers at the Princess Margaret Hospital in Toronto, Canada. In 2010, she got her radiation oncology certification in Switzerland (FMH) and joined the Radiotherapy Service at the Swiss Cancer Center in Lausanne where she leads the gynecological tumor site. She is now performing a PhD in the laboratories of Prof. George Coukos and Prof. Jean Bourhis aiming to understand the role of radiotherapy as an immune modulator in tumors and their microenvironment.

Research interests

Her clinical interests are focused on gynecological and genitourinary cancers. Her research interests include clinical studies of immune-therapy to improve the effectiveness of radiotherapy and chemotherapy; studies of the effects of the immune suppressive tumor microenvironment on the clinical behavior of gynecological cancers and response to treatment; new radiotherapy technologies for the treatment of cervical and prostate cancers; incorporation of metabolic imaging in the radiotherapy treatment of cervical cancers; translational studies in prostate cancer to determine the host immune response to radiotherapy.
Recent scientific contributions

Dr Herrera contributed to various projects that were published including:

• Long-term Outcome and Late Side Effects in Endometrial Cancer Patients Treated with Surgery and Postoperative Radiation Therapy.

• Prostate cancer center: a multidisciplinary approach to accurately manage patients with prostate cancer.

• Immunotherapy: a therapeutic revolution against prostate cancer

• The role of PET/CT in cervical cancer.

• Retrospective feasibility study of simultaneous integrated boost in cervical cancer using Tomotherapy: the impact of organ motion and tumor regression.

SELECTED PUBLICATIONS


Future focus and expectations

The European Organization for Research and Treatment of Cancer (EORTC) is the leader group in Europe to provide the needed network and infrastructure to advance science and new treatments. As a chairman of the Gynecology Working Party- Radiation Oncology Group at the EORTC, I lead a group of innovative and outstanding clinical investigators who join forces to fulfill the lack of evidence in gynecological cancers. We have a strong collaboration with the multidisciplinary EORTC-Gynecology Cancer Group. Both groups are now on track to meet the research expectations in 2014 by starting together a new trial in cervical cancer, combining the power of immunization with concomitant chemo-radiotherapy. This international project is headed by Prof. Coukos and his team from the Swiss Cancer Center. We also expect to broaden the success of this trial to other aggressive gynecological cancers.

Standard anti-cancer therapeutic modalities like chemotherapy and radiotherapy evoke host reactions that include involvement of the immune system. Radiotherapy is a particularly interesting partner for immunotherapy as it can be harnessed to specifically modify the immunogenicity of the primary tumor and its microenvironment, in the attempt to generate an in situ vaccination against a patient's own cancer. The complexity of the interaction between the tumor and its immunosuppressive microenvironment needs to be better understood. For this reason, I expect to start a PhD in cancer and immunology at the Ludwig Center for Cancer Research, UNIL.
Daniel HOHL

Funding sources

- SNSF
- Novartis Foundation
- Gottfried und Julia bangerter-Rhyner Foundation
- FBM-UNIL
- Dind Cottier Skin Foundation
- Oncosuisse

Key research collaborations

- Prof. Sabine Werner, Institute for Molecular Health Sciences, ETHZ Zürich (CH)
- Dr. Asma Smahi, Imagine Institute, INSERM 1163, Paris (FR)
- Prof. Peter Koch, Department of Cell and Developmental Biology, University of Colorado School of Medicine, Aurora (USA)

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Biography

Dr. Hohl trained at the University of Zurich and its Dermatology Clinics from 1985-1990 when he also spent a three years sabbatical at NCI, NIH in Bethesda, Maryland and the Baylor College, Houston. He was invited professor at ETHZ from 2000 to 2005 and went for a sabbatical to Paris at the Hôpitaux Necker and St. Louis in Paris in 2013. Dr. Hohl has served in diverse international societies, and is currently President of both the MD-PhD Commission UNIL and EPFL and the European Society of Pediatric Dermatology. Recipient of diverse awards, Dr. Hohl is also Honorary Member of the French and Serbian Societies of Dermatology.

Research interests

Prof. Hohl focuses on the following topics:

- Dermatooncology
- Dermatopathology
- Dermatogenetics
- Pediatric Dermatology
Recent scientific contributions

Prof. Hohl’s group has worked on the identification of the molecular cause of the Basex Dupré Christol tumor syndrome and further characterization of cylindromatosis Spiegler-Brooke. The group’s research further includes several animal models on cutaneous carcinogenesis (Nrf-2, Prdx6, Activin, NQO1, CD1d and Pparβ/δ).

Future focus and expectations

Research will be centered on basal and spinous cell cancer of the skin, notably characterization of the molecular cause of the Basex Dupré Christol tumor syndrome, on the function of the tumor suppressor HOPX and the mitotic checkpoint protein TRAIP.
Krisztian HOMICSKO

Krisztian Homicsko  
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Funding sources

- Leenaards Foundation  
- Oncosuisse  
- UNIL  
- Swiss TransMed  
- Roche  
- Nuovo-Soldati

Key research collaborations

- Prof. Douglas Hanahan, EPFL-ISREC  
- Prof. Olivier Michielin, SIB- UNIL-CHUV

Biography

Dr Homicsko received his MD degree from Semmelweis Medical University in Budapest, Hungary in 2001. After obtaining his PhD from the University of Lausanne in 2006, he moved to Scotland for a postdoctoral fellowship at the University of St Andrews. From 2007 to 2009, he was junior physician, first at the Curie Institute hospital in Paris, then at the Pluridisciplinary Center of Oncology, CHUV. In 2012, he became Head of Clinic in the new Department of Oncology, CHUV, as well as a research scientist in the Hanahan laboratory at EPFL-ISREC.

Research interests

Dr Homicsko’s primary research is focused on the role that the tumor microenvironment plays in adaptation to diverse therapies including tyrosine kinase inhibitors but also chemotherapies or immunotherapies. His secondary research interest lies in the investigation of biomarkers or predictors of responses to therapies including cancer genetics (NGS), subtype profiling, circulating cell-free DNA, or circulating tumor cells. Dr Homicsko’s clinical interest focuses on early phase I clinical trials combined with multidimensional tumor profiling.
Future focus and expectations

Dr Homicsko hopes to complete a marker-independent characterization of the tumor microenvironment at the level of expression profiling and is expecting the development of a novel drug combination that could further increase the efficacy of MAPK pathway inhibitors in the treatment of metastatic melanoma.

In the Phase I unit of the Center for Experimental Therapeutics, his plans are to further increase the number of patients included.

SELECTED PUBLICATIONS

2. Fusion of the BCL9 HD2 domain to E1A increases the cytopathic effect of an oncolytic adenovirus that targets colon cancer cells. BMC Cancer. 2006 Oct 4; 6:236.
Andreas HOTTINGER

Funding sources

- Swiss Bridge Foundation
- MSD research grant

Key research collaborations

- EORTC
- CIBM
- UniversitätsSpital Zürich (CH)
- UNIGE (CH)

Andreas Hottinger
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Biography

Andreas Hottinger, born in 1970 in Zürich, received his Federal Medical Degree in 1995 and completed his PhD in the field of neurodegenerative disorders at the University of Lausanne in 2001. Thereafter, he specialized in Neurology at the Insel University Hospital in Bern and specialized in Oncology at the Geneva University Hospital. He completed a fellowship in Neuro-oncology at Memorial Sloan Kettering Cancer Center, NY. He joined the CHUV in 2012 where he is leading the Neuro-oncology unit.

Research interests

Our team is responsible for the clinical management of patients that suffer from brain tumors or neurological metastasis. Our goal is to develop novel and innovative clinical approaches to improve the outcome for these patients. Our group is also heavily involved in several international clinical trials that target key tumoral pathways. Within the institution we also work in a close interdisciplinary network to ensure collection of clinical data and tissue.
Recent scientific contributions

In 2013, we contributed to demonstrate in a phase III trial that the integrin inhibitor cilengitide combined with radiotherapy and temozolomide was ineffective to extend survival in newly diagnosed glioblastoma (GBM). Our unit continues to investigate promising therapeutic targets for the treatment of brain tumors. Angiogenesis plays a key role in the development of high grade brain tumors. We are evaluating in randomized trials the role of bevacizumab, in addition to radiotherapy in elderly patients with newly diagnosed GBM (ARTE trial) as well as in patients with recurring anaplastic gliomas (TAVAREC), or in combination with the alkylating agent lomustine in recurrent GBM (EORTC 26101). We are also interested in the modulation of key pathways, including mTOR with temsirolimus in newly diagnosed GBM (EORTC 26082), the sonic hedgehog pathway in recurrent medulloblastoma (MEVITEM) and EGFR using a vaccine against the EGFRv3 mutant in newly diagnosed GBM (ACT IV trial). We are evaluating the potential of intermediate frequency alternating electric fields in patients with newly diagnosed GBM (Novocure).

Future focus and expectations

In 2014, we are planning to open 2 key clinical trials to evaluate the role of the immunomodulation through inhibition of PD1 in recurrent GBM (phase II). The other phase I/II trial will evaluate the role of the addition of a Met/AXL/FGRFR inhibitor to bevacizumab in patients with recurrent GBM. We will also lead an international trial to evaluate alternating electrical fields in PCNSL. On the clinical level, a large focus will be given to neurological complications of cancer and especially chemobrain. On the translational level, our group will be working on the radiologic, metabolic and molecular validation of GBM models based on patient-derived orthotopic xenografts (see above figure).
Martin HÜBNER

Funding sources
- Surgical Research Committee, Mayo Clinic, Rochester MN (USA)
- Research grants: Nestlé, Novartis, Fresenius
- Research funds: Department of Visceral Surgery, CHUV

Key research collaborations
- Olle Ljungquist, Karolinska Institute (Sweden)
- Dawid W. Larson, Mayo Clinic, Rochester MN (USA)

Biography
Martin Hübner obtained his German medical diploma and Doctoral thesis at the University of Freiburg in 2002. Following residency training in Zürich (USZ), Ilanz and Lausanne (CHUV) between 2003 and 2008, he became Junior Staff in general and visceral surgery at the CHUV in 2008-2010. He then did a fellowship in 2011 in colon and rectal surgery at the Mayo Clinic, Rochester MN, USA. Dr. Hübner has been appointed Attending Surgeon since 2012 at the CHUV. He is a FMH specialist both in General Surgery (2008) and Visceral Surgery (2013).

Research interests
Dr Hübner’s research interests encompass:
- Enhanced recovery after surgery – optimizing perioperative care
- Perioperative nutrition
- Prevention of surgical site infections
- Minimal-invasive surgery
- Treatment of peritoneal carcinomatosis
Recent scientific contributions

Dr Hübner’s recent scientific contributions are described in the following publications:

Hübner M Ann Surg 2014
Randomized clinical trial on Epidural versus Patient-controlled Analgesia for laparoscopic colorectal surgery within an enhanced recovery.

Mantziari S World J Surg 2014
Impact of preoperative risk factors on morbidity after esophagectomy: Is there room for improvement?

Valerio M Can Urol Assoc J 2014
Comorbidity and nutritional indices as predictors of morbidity after transurethral procedures: a prospective cohort study.

Huebner M J Am Coll Surg 2014
Timing of complications and length of stay after rectal cancer surgery.

Venara A Langenbeck’s 2014
Surgery for incarcerated hernia: short-term outcome with or without mesh.

Roulin D World J Surg 2014
Enhanced recovery pathway for urgent colectomy.

SELECTED PUBLICATIONS


Future focus and expectations

We are working towards the future development, implementation and extension of enhanced recovery in abdominal surgery.

In addition, we are setting up a competence center for peritoneal carcinomatosis: CRS+HIPEC and PIPAC (see Figure above).

Furthermore, we will be evaluating surgical stress response and early prediction of outcomes.
Joerg HUELSKEN

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Funding sources
- Swiss National Science Foundation
- Swiss Cancer League
- EMBO

Key research collaborations
- Werner Held, LICR@UNIL
- Sebastian Maerkl, EPFL
- Christian Heinis, EPFL
- Hinrich Abken, University of Cologne (GE)

Biography
Joerg Huelsken, born in Oberhausen, Germany, received a master’s degree in Biology from Ruhr University Bochum (1993), and a Ph.D. in Molecular Biology from Humboldt University Berlin (1998). He worked at the Max-Delbrück-Center for Molecular Medicine in Berlin from 1993-2002 initially as graduate student and then as postdoctoral scientist. From 2002-2005, he was Principal Investigator at the Swiss Institute for Experimental Cancer Research (ISREC) in Epalinges, Switzerland and since 2005 he is Professor at the EPFL, Lausanne and holds the Debiopharm chair in “Signal Transduction in Oncogenesis”.

Research interests
The Huelsken group investigates mechanisms of tumor progression and metastasis using mouse models of cancer, with strategic goals to develop new therapeutic strategies for translation to clinical trials. A focus of the group lies on immunotherapy approaches using genetically modified T cells and antibody drug conjugates.
Recent scientific contributions

The Huelsken lab continues to investigate mechanistic and therapeutic implications of the Cancer Stem Cell concept, seeking to identify targetable mechanisms of cancer progression. New approaches of immunotherapy are currently developed which aim to eradicate established tumors by elimination of Cancer Stem Cells and immune check point blockade. Furthermore, in the last couple of years a focus has been the development of new therapeutics based on drug screens and therapeutic antibodies and antibody drug conjugates isolated and produced in the lab. The laboratory is currently studying mouse models of breast, lung, pancreas and colon cancer with an emphasis on metastatic disease. Topics of investigation include mechanisms of niche induction, stromal reprogramming, and immune evasion. Additional research topics include the development of microfluidic platforms for the isolation and analysis of Cancer Stem Cells.

Future focus and expectations


Lana KANDALAFT

Key research collaborations

- Daniel Powell, Upenn (USA)
- Mark Morgan, Upenn (USA)
- Robert Burger, Upenn (USA)
- Janos Tanyi, Upenn (USA)

Lana Kandalaft
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Biography
Dr. Kandalaft holds a doctorate degree of Pharmacy and a Ph.D. in Cell Biology and Therapeutics from the Welsh School of Pharmacy, Cardiff, Wales. She then joined the Cell and Cancer Biology Branch at The National Cancer Institute where she completed her postdoctoral training and research fellowship in cell cancer biology focusing on screening novel therapeutics in preclinical animal models. She also holds a masters degree in Translational Research from The University of Pennsylvania.

She took a Director of Clinical Development appointment at the Ovarian Cancer Research Center in 2008 and was also appointed Assistant Professor of Gynecologic Oncology. She joined the CHUV and Ludwig Branch in 2013 to head the Center for Experimental Therapeutics and to pursue her research career in personalized vaccine development. She is also currently an Adjunct Assistant Professor at the University of Pennsylvania, School of Medicine.

Research interests
For the past 5 years, Dr. Kandalaft has been working on bringing personalized autologous whole tumor lysate vaccines to the clinic and recently, she has started working on vaccine optimizations strategies. She is also leading the clinical development of a new generation of cancer vaccines which will be generated by identifying only the immunogenic tumor antigens specific to each patient’s tumor by new methodologies which integrate deep proteomic and genomic analyses as well as bioinformatics assimilations with sophisticated immune analyses. This project is a group effort in her discipline.
Recent scientific contributions

We published our first pilot trial using a vaccine made out of supernatants of autologous tumor cells freeze-thaw lysate pulsed onto autologous Dendritic Cells (DC). Six subjects with recurrent advanced ovarian cancer, heavily pre-treated and progressing on chemotherapy, completed treatment. There were no grade ≥2 adverse events. Four of six patients (66%) achieved clinical benefit with the combination of chemotherapy (Bev/mCy) and vaccine. Interestingly, we detected a significant increase of tumor-reactive T-cells after vaccination (but not after chemotherapy alone) in all four subjects who exhibited clinical benefit (p< 0.05), but found no immune response in the two subjects who experienced disease progression.

We further optimized the DC-vaccine platform in the laboratory and opened another clinical trial using an enhanced vaccine of autologous DCs loaded with HOCl-oxidized autologous tumor lysate administered intranodally. We also assessed the additive effects of Bev (bevacizumab) and Cy (cyclophosphamide) with the three-cohort sequential protocol design of vaccine alone (Cohort 1), in combination with bev alone (Cohort 2) or in combination with Bev and CY (Cohort 3). Preliminary results indicate a clinical benefit rate of 40% in cohort 1, 60% in cohort 2 and 80% in cohort 3 with significant improvement in progression free survival (PFS) compared to a matched control group of patients who have undergone secondary debulking and have had Cy and Bev as standard of care therapy.

Future focus and expectations

- Developing Novel Vaccination Strategies: this will be studied by testing different powerful immunomodulation strategies to maximize the effects of vaccine in established tumor cancer preclinical models, with the aim of translating the best combination to the clinic.

- Enhancing the DC platform and Tumor Lysate Preparation for Personalized Cancer Vaccines through Genetic Engineering. In an attempt to design more effective vaccines for clinical application, Dr Kandalaft will use genetic modification approaches of DC populations and tumor lysates preparation to induce improved tumor-antigen presentation for the development of specific cellular and humoral immunity.


Thorsten KRUEGER

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Biography
Thorsten Krueger performed his medical studies at the Medical University of Lübeck, Germany. He was then a research fellow in the Thoracic Surgery Division of the University Hospital of Lausanne (CHUV) between 1999 and 2001. He achieved residency in General Surgery at the CHUV and Morges Hospital, Switzerland from 2001 to 2006, and in Thoracic Surgery within the Division of Thoracic Surgery from 2006 to 2012. He became a FMH Specialist in General and Thoracic Surgery in 2011. In 2013, Dr. Krueger was a Clinical Fellow in the Division of Thoracic Surgery, Toronto General Hospital in Canada.

Research interests
Intravital microscopy, photodynamic therapy: After the assessment of photodynamic therapy as an adjuvant treatment after surgery for malignant pleural mesothelioma and introduction of intravital microscopy, research has been focusing on investigating how photodynamic therapy can selectively enhance the uptake of circulating macromolecular drugs into tumor tissue through its effects on the vascular system.

Cytostatic isolated lung perfusion, normothermic ex-vivo lung perfusion: Dr. Krueger has investigated different methods of lung selective chemotherapy delivery to intra-operatively treat lung micro-metastatic spread were under investigation and since 2011, the research activity is here focused on normothermic ex-vivo lung perfusion (EVLP) in the context of lung transplantation.

Minimal invasive lung cancer surgery: Since the introduction of the VATS (video assisted thoracic surgery) approach for minimal invasive anatomic lung resection more than 200 VATS lobectomies for lung cancer have been performed. Today, almost all early stage lung cancer patients can benefit from this approach.

Funding sources
- Fondation Loterie Romande
- Fondation Lausannoise de la Transplantation d’Organes

Key research collaborations
- EPFL, Lausanne (CH)
- Huazhong University of Science & Technology, Wuhan (China)
Recent scientific contributions

Dr Krueger’s recent scientific contributions are described in the following publications:


SELECTED PUBLICATIONS


Future focus and expectations

The aim of our current research project is to establish a versatile ex-vivo lung perfusion platform allowing the development of this promising technology in the field of lung transplantation and oncology. EVLP keeps the lung in a physiologically protective normothermic condition outside the body. This technology allows for an accurate ex-vivo assessment of the organ and will permit selective delivery of therapeutics to lung tissue in the future. As a very unique and innovative element we prepare to start a novel research project developing intravital microscopy on lung tissue.
Funding sources

- Swiss National Science Foundation
- European Research Council
- European Commission FP7 ITN
- Swiss Cancer League
- EPFL

Key research collaborations

- Daniela Rhodes, LMB in Cambridge and NTU in Singapore
- Marc Moniatte, EPFL proteomics core facility

Biography

From 1989 to 1992, Joachim Lingner did his PhD at the Biocenter, University of Basel under the supervision of Prof. Walter Keller. He then moved to the group of Prof. Thomas Cech at the Howard Hughes Medical Institute, University of Colorado for a postdoctoral fellowship between 1993 and 1997. From 1997 to 2001, he was junior group leader at EPFL-ISREC, Associate Professor at EPFL in 2005 and appointed Full Professor at EPFL in 2009. Among honors and grants, Prof. Lingner received a START-fellowship from the Swiss National Science Foundation in 1997, the Friedrich Miescher Prize from the Swiss Society of Biochemistry in 2002; was elected EMBO member in 2005 and got an ERC advanced investigator grant in 2008.

Research interests

Prof. Lingner’s team is interested in telomeric chromatin in health and disease. Telomeres protect chromosome ends from degradation and rearrangements that are typically seen in cancer. Telomeres also serve as cellular clocks, shortening in the absence of telomerase. In most tumors, however, telomerase is upregulated. Our laboratory combines telomeric chromatin analysis by mass spectrometry and molecular genetics to study telomere function in human cells under normal and pathological situations.
Recent scientific contributions

In 2013, our laboratory has made the following major contributions. For the first time, we reported, in collaboration with the laboratory of Daniela Rhodes (LMB, Cambridge), a low resolution structure of human telomerase obtained by EM analysis (Sauerwald et al. 2013). Telomerase forms dimeric complexes which have two active centers for elongating chromosome ends. We identified the molecular defects at telomeres that are observed in Coats Plus/Dyskeratosis congenita patients carrying mutations in the CTC1 gene (Chen et al. 2013). Notably, CTC1 mutations lead to accumulation of internal gaps in telomeric DNA indicating defects in telomere replication. Third, we published an article on the development of a quantitative telomeric chromatin isolation protocol (Q-TIP), which involves purification of telomeric chromatin and its analysis by mass spectrometry (Grolimund et al. 2013). By including SILAC labeling, we are now able to compare different telomeric states to identify the molecular changes at telomeres during normal development, in cancer and in telomere syndromes. Finally, we improved our understanding of the biogenesis of the telomeric long noncoding RNA TERRA and its abilities to inhibit telomerase (Pfeiffer et al. 2013; Redon et al. 2013).

SELECTED PUBLICATIONS


Future focus and expectations

Currently, our laboratory is applying the Q-TIP method (Grolimund et al. 2013) to various cellular models in order to elucidate telomeric chromatin composition in a comprehensive manner and define its molecular changes during different stages of cancer development. In addition to improving the understanding of telomere function in normal development and disease, this work may identify new molecular markers and targets in cancer therapy. We are also pursuing our efforts to elucidate the functions of the telomeric long noncoding RNA TERRA.
Immanuel LUESCHER

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Funding sources
- Swiss National Fund
- Swiss Cancer League

Key research collaborations
- Olivier Michielin, SIB
- Curzio Rüegg, University of Fribourg (CH)
- Monilola Olayioye, University of Stuttgart (DE)

Biography
Immanuel Luescher, born in Pasadena, California, USA, received a master’s degree in organic chemistry from the University of Zürich and a Ph.D. from the University of Bern in 1981. Then, he was a postdoctoral fellow at the Weizmann Institute in Israel, working on photo-reactive compounds and their use to photo-label molecules involved in cell signaling. In 1985 he went to the Department of Pathology of Washington University, St. Louis, USA for a second postdoc, where he researched molecular aspects of antigen recognition by CD4+ T cells. Since 1989, he has been group leader at the Ludwig Institute for Cancer Research (LICR) pursuing research on various aspects of molecular immunology. Since 2011, has been group leader at the Ludwig Center for Cancer Research at UNIL, and since 2012, President of TCMetrix, the Swiss Tetramer Company (www.tcmatrix.ch).

Research interests
The Luescher group explores new modalities to reprogram the tumor environment by adoptive transfer of genetically modified tumor-specific CD4+ and CD8+ T cells, to allow the generation of endogenous tumor specific immunity capable of eradicating established tumors. The group is also interested in mechanistic studies for translation studies.
Recent scientific contributions

Growth of tumors relies on tumor-mediated suppression of immune attacks. Transduction of CD8α+ T (CTL) cells with CD8β and acute viral infection allowed the generation of super CTL, capable of eradicating completely and permanently established B16 melanoma tumors. Upon tumor entry, these cells released high levels of inflammatory cytokines and chemokines and thus reprogrammed the tumor environment from an immune suppressive one to one supporting the induction of endogenous, tumor-specific immunity.

SELECTED PUBLICATIONS


Future focus and expectations

1) Tumor specific CD4+ Th1 T cells will be engineered with chimeric antigen receptors (CAR) to promote strong Th1 responses in the tumor environment.

2) The PI3K/Akt-dependent activation of CD8+ cytotoxic T cells will be mechanistically elucidated and be translated using CAR technology.
Matthias LUTOLF

Funding sources

▪ SNSF
▪ EMBO
▪ SystemsX.ch
▪ Marie Curie
▪ EU-FP7
▪ ERC
▪ Bertarelli Foundation
▪ KTI
▪ JDRF

Key research collaborations

▪ Prof. Johan Auwerx, EPFL (CH)
▪ Prof. James Briscoe, NIMR, London (GB)
▪ Prof. Austin Smith, Cambridge (GB)
▪ Prof. Elly Tanaka, CRTD, Dresden (Germany)

Biography

Prof. Matthias Lutolf is Director of the Institute of Bioengineering at EPFL. He was trained as a Materials Engineer at ETH Zurich where he also carried out his Ph.D. studies (awarded with the ETH medal in 2004). Lutolf carried out postdoctoral studies at the Baxter Laboratory in Stem Cell Biology at the Stanford University. He started up his independent research group at EPFL in 2007 with a European Young Investigator (EURYI) award. Prof. Lutolf serves as an editorial board member of four international journals and he co-founded the biotech company QGel SA.

Research interests

By interfacing advanced biomaterials engineering, microtechnology and stem cell biology, the overarching goal in the Lutolf Laboratory is to uncover mechanisms of stem cell fate regulation; knowledge that will contribute to better ways to grow stem cells in culture and use them for various applications. A major recent goal in his lab is on inducing organogenesis in 3D stem cell culture.
Recent scientific contributions

The behavior of cells in tissues is governed by the 3D microenvironment, which involves a dynamic interplay between biochemical and mechanical signals. The complexity of microenvironments and the context-dependent cell responses that arise from these interactions have posed a major challenge to understanding the underlying regulatory mechanisms.

To systematically dissect the role of the various factors that can determine cell fate in 3D, we have developed novel experimental paradigms to simultaneously generate thousands of unique microenvironments and probe their effects on (single) cell fate in vitro (e.g. Ranga et al., Nature Communications, 2014). We have applied this unique approach to discover minimal artificial niches for hematopoietic stem cells (Roch et al., in revision), as well as chemically defined 3D microenvironments that promote neuroepithelial differentiation of pluripotent stem cells and their self-organization into neural tubes (Meinhardt et al., Stem Cell Reports (2014)).

SELECTED PUBLICATIONS


Future focus and expectations

A major focus in the lab is to uncover how the delicate balance between stem cell self-renewal and differentiation is regulated. In this context, we are studying how cellular metabolism regulates hematopoietic stem cell function. Furthermore, we will expand our studies on inducing organogenesis in 3D pluripotent stem cell culture.
Sebastian MAERKL

Funding sources

- Swiss National Science foundation
- EPFL

Biography

Sebastian Maerkl received two bachelor degrees (biology and chemistry) from Fairleigh Dickinson University, New Jersey, USA, in 2001. He then received a PhD from the California Institute of Technology in 2008, for which he was awarded the Demetriades-Tsafka-Kokkalis prize for the best Caltech PhD thesis in the field of biotechnology. Since 2008, he has been an Assistant Professor at the Institute of Bioengineering at the Ecole Polytechnique Federale de Lausanne (EPFL).

Research interests

Our lab is interested in a broad spectrum of fields. We develop and apply state-of-the-art microfluidic technology to pertinent biological problems. Our interests span Systems Biology, Synthetic Biology, and Diagnostics.
Recent scientific contributions

The Maerkl lab has recently conducted the first global analysis of protein dynamics in yeast. The lab developed a novel microfluidic microchemostat array, which allows the parallel analysis of 1052 yeast strains at the single cell level and with high spatio-temporal resolution (PNAS 2013). We also were able to show that quantitative transcription factor binding energy landscapes determined in vitro allow the prediction of transcriptional levels in vivo. The same study also revealed that small modifications of transcription factor binding site strength allows fine-tuning of promoter output (Nature Genetics 2013). In the field of synthetic biology, we built and characterized the first in vitro genetic oscillator (PNAS 2013). We also develop a suite of microfluidic devices, capable of quantitating protein biomarkers in thousands of cell or human serum samples (Integrative Biology 2013, Lab on a Chip 2013).

SELECTED PUBLICATIONS

Fabio MARTINON

Funding sources

- European Research Council
- Human Frontier Science Program
- Swiss National Science Foundation
- ISREC
- UNIL

Key research collaborations

- Laurie H. Glimcher, Weill Cornell Medical College, NY (USA)
- Claudio Hetz, University of Chile and Harvard School of Public Health, Boston, MA (USA)

Biography

Fabio Martinon received his PhD in 2003 from the University of Lausanne for his work on the characterization of the Inflammasome in the laboratory of Jürg Tschopp. After a short post-doctoral fellowship in Jürg Tschopp’s laboratory, he moved in 2006 to the laboratory of Laurie Glimcher at the Harvard School of Public Health, where he investigated the link between inflammatory programs and the endoplasmic reticulum stress response. In August 2010 he joined the Department of Biochemistry as Assistant Professor.

Research interests

Our goals are to elucidate the signal transduction of stress pathways that regulate innate immune responses, and to address the physiological role of specific stress response pathways in inflammation and cancer.
Recent scientific contributions

In an effort to identify non-toxic inducers of ER-stress signaling branches, we identified the HIV-protease inhibitors as robust inducers of the integrated stress response (ISR), a translational and transcriptional program that orchestrate adaptation to stress. The HIV-PIs were developed 20 years ago and their incorporation into highly active antiretroviral therapy (HAART) led to remarkable suppression of HIV replication in patients. Beyond their broad use as anti-HIV drugs, the HIV-PIs have been found to have HIV-unrelated functions including anti-tumoral properties. However the mechanisms of action are unknown. We discovered that most HIV-PIs selectively activate the IRE1 branch of the ER-stress response and regulate translation rates and the integrated stress response by modulating a phosphatase complex. We also identified the AIM2 inflammasome as a target of the HIV-PI.

In another project we initiated a study aimed at defining the role of the IRE1/XBP1 pathway in diffuse large B-cell lymphomas (DLBCL) and identified a subgroup of DLBCL with deficiencies in this stress-response pathway.

Model: stress load and stress responses determine cell outcome.
Many tumors undergo basal stress as a result of harsh conditions of tumor microenvironment. This leads to the activation of the stress response pathways that are aimed at restoring homeostasis and promoting survival. If the stress cannot be resolved, tumor cell death will occur. Drugs such as the HIV-PIs aimed at increasing stress and decreasing the adaptation response may therefore contribute to the elimination of stressed tumors.

SELECTED PUBLICATIONS


Future focus and expectations

In 2014 we would like to identify the pathways that are responsible for the HIV-PIs antitumoral effect in vitro and in vivo. We will first focus on the possible role of the inflammasome and the integrated stress response pathways. In addition, we use genetics (Crispr/Cas9 genome-wide screen) to identify additional pathways involved in the HIV-PIs biological effects and to discover the direct cellular target of these drugs.

We will interrogate the significance of the IRE1/XBP1 pathway deficiency in DLBCL.
Patrice MATHEVET

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Funding sources
- French National Cancer Institute
- French Institute for Research in Medical Sciences
- Novartis

Key research collaborations
- GINECO Group
- EORTC
- French Society of Gynecologic Oncology
- French group of cancer Centers

Biography
Patrice Mathevet, born in France, received an MD degree in Gynecology-Obstetrics and a PhD in Genetics and Immunology from Lyon university in 1990 and 2002, respectively. He worked in Lyon in the Department of Gynecologic Oncology, E. Herriot Hospital, under the direction of Pr D. Dargent. From 2005 to 2012, he was on the faculty of the Department of Gynecologic Oncology, E. Herriot Hospital, in charge of the Breast Clinic. In 2013 he has been appointed Head of the Department of Gynecology of the CHUV. He spent several months in 1993 and 1998 at the MD Anderson Cancer Center (Houston, Tx, USA) as visiting Assistant Professor.

Research interests
Prof. Mathevet’s research is being directed towards the following topics:
a. Surgical treatment of cervical carcinoma: vaginal radical trachelectomy, sentinel node technique
b. Biology of cervical carcinoma: lymphatic dissemination, lymphangiogenesis, therapeutic vaccine
Recent scientific contributions

Patrice Mathevet is the principal investigator of a randomized multicentre study comparing sentinel-node biopsy vs sentinel-node biopsy + pelvic lymph-node dissection in early cervical cancer patients (named Senticol 2). This study sponsored by the French National Cancer Institute (budget of 620 000 €) was closed after full recruitment in 2013 and the data are currently under investigation.

Patrice Mathevet is also the principal investigator of a translational study sponsored by Novartis (850 000 €), aiming at evaluating the clinical and biological impact of biphosphonates as part of neo-adjuvant treatment of advanced breast cancers (named NEOZOL). This study was also closed in 2013 and the data are under investigation.

In addition, mechanisms of lymphatic dissemination in early cervical cancer have been evaluated and results are under publication. Survival in relation with the sentinel-node status and the factors of lymphatic dissemination are going to be published.

SELECTED PUBLICATIONS


Future focus and expectations

Full analysis of Senticol 2 and NEOZOL studies are expected to be presented and published. Our department is participating in the development of a new therapeutic vaccine for adjuvant treatment of cervical cancer. Development of the sentinel-node technique in endometrial carcinoma would be evaluated through clinical studies. Also, evaluation of new lymphatic markers is under investigation.
Etienne MEYLAN

Funding sources

- Swiss National Science Foundation
- Swiss Cancer League

Key research collaborations

- Solange Peters, CHUV
- Darius Moradpour, CHUV
- Mauro Delorenzi, SIB
- Jean Bourhis, CHUV

Biography

Etienne Meylan received a PhD in Life Sciences from the University of Lausanne in 2006, for his work on innate immunity performed in the laboratory of Jürg Tschopp. From 2007 to 2010, he worked as a postdoctoral fellow in the laboratory of Tyler Jacks, at the Koch Institute for Integrative Cancer Research, MIT, Cambridge USA. In 2011, he established his research laboratory at ISREC, as a Swiss National Science Foundation Professor and Tenure-track Assistant Professor. His laboratory focuses on the molecular mechanisms that contribute to the development of non-small cell lung cancer.

Research interests

Our laboratory studies how the signaling pathways that are known to regulate innate immunity or glucose metabolism contribute to the development of non-small cell lung cancer (NSCLC). To study these crucial components of tumors, we use a combination of genetically-engineered mouse models of the disease, human lung cancer cell lines and tumor tissue specimens.
Recent scientific contributions

Using cell culture systems, mouse models of cancer and bioinformatics analyses, we have begun to characterize the ties between metabolic or inflammatory pathways, and lung tumor development. Specifically, we have focused on:

- The expression and function of specific glucose transporters in lung cancer progression,
- The implication of a kinase in a novel, inhibitory control of STAT3 signaling and tumor development,
- The role of the antiviral-like response in the antitumor response.

Hopefully, through our analyses, we will be able to better understand the links between glucose metabolism, inflammatory pathways and tumor development, with the goal to identify novel ways to combat this devastating disease.

Molecular Mechanisms of Lung Cancer Development Laboratory

I. Glucose metabolism
II. Pathways of inflammation and innate immunity

SELECTED PUBLICATIONS


Future focus and expectations

In 2014, we will continue to explore the molecular mechanisms that contribute to lung tumor development, elaborating on our two main research directions (see Figure):

1) The alterations of glucose homeostasis of tumor cells
2) The connections between pathways of innate immunity or inflammation and tumor progression.
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UNIL – Center for Integrative Genomics

Biography
Liliane Michalik received her PhD from the University Louis Pasteur of Strasbourg in 1994. She then joined the group of Walter Wahli at UNIL for her post-doctoral training, during which she initiated a research project aimed at elucidating the roles of the nuclear hormone receptors PPARs in skin homeostasis and repair. Between 1996 and 2002, she pursued her research in the same field as “Maître Assistant” (Junior scientist), then “Maître d’Enseignement et de Recherche” (Senior Scientist) at UNIL. She arrived at the Center for Integrative Genomics in 2003 as “Maître d’Enseignement et de Recherche (MER)”, and has been “MER”-privatdozent since 2008.

Research interests
We are interested in the transcriptional control of skin wound healing and UV-induced carcinogenesis by the nuclear hormone receptor PPARs. Using genetically modified mice, various organ and cell culture models, as well as genomic approaches, we study PPAR functions in inflammation, epithelial homeostasis, and epithelium-mesenchyme interactions.
Recent scientific contributions

We previously showed that PPARβ/δ activity promotes murine skin wound repair, by activating keratinocytes differentiation, resistance to apoptosis and directed migration. PPARβ/δ also regulates the interactions between the epidermal and dermal compartments in healing wounds, through moderating the activity of the IL-1 pathway.

While PPARβ/δ activity favors skin healing, it also favors squamous cell carcinoma progression in murine skin. We unveiled a cascade of events involving PPARβ/δ and the oncogene Src, which promotes the development of ultraviolet (UV)-induced skin cancer in mice. UV-induced PPARβ/δ activity increases Src kinase activity, enhances the EGFR/Erk1/2 signaling pathway, resulting in increased epithelial-to-mesenchymal transition (EMT) marker expression. Consistent with these observations, PPARβ/δ null mice developed fewer and smaller skin tumors. Furthermore, the expression of PPARβ/δ positively correlates with the expression of SRC and EMT markers in human skin squamous cell carcinoma, and linear models applied to several human epithelial cancers revealed an interaction between PPARβ/δ and SRC levels. Taken together, these observations motivate the future evaluation of PPARβ/δ as a modulator of the development of several epithelial cancers.

SELECTED PUBLICATIONS


Future focus and expectations

The group will mainly focus on the study of i) the PPARβ isoform and miRNA in non-melanoma skin cancer and skin repair, and ii) the role of the PPARγ isoform in the progression of melanoma.

Our data will benefit to basic research by deepening our understanding of the transcriptional regulation of these processes by PPARs. Furthermore, our project is also relevant to the search for innovative therapies, since the nuclear hormone receptors PPARs are targets of choice for therapeutic intervention.
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Funding sources
- Swiss National Science Foundation
- Swiss Institute of Bioinformatics
- UNIL
- OncoSuisse
- Solidar Immune
- EU FP7
- Swiss-Polish Research Grant
- CTI
- Merck Serono

Key research collaborations
- G. Coukos, CHUV
- D. Hanahan, EPFL
- B. van den Eynde – Louvain University (BE)
- M. Karplus – Harvard & Strasbourg Universities (USA, FR)

Biography
Prof. Olivier Michielin obtained a diploma of Physics in 1991 at the EPFL and an MD from the University of Lausanne in 1997. He pursued his PhD training under the supervision of Jean-Charles Cerottini (LICR) and Martin Karplus (Harvard and Strasbourg Universities). He was appointed Group Leader of the Swiss Institute of Bioinformatics in 2002 and became an Assistant Professor and Privat Docent at the Medical Faculty of Lausanne in 2004 and 2005, respectively, and an Associate Professor in 2010. In parallel, he has trained as a medical oncologist and obtained his board certification in 2007 at the Multidisciplinary Oncology Center (CePO) of Lausanne where he is currently heading the melanoma clinic.

Research interests
Our group is involved in the rational development of new therapies for melanoma, mainly in the field of cancer immunotherapy. We use structure-based approaches to design small molecule inhibitors of important targets like IDO, as well as to optimize protein structures like tumor specific TCR. We validate these compounds in vitro and in vivo with the aim to push them into phase I clinical trials.
Recent scientific contributions

In 2013, the Molecular Modeling Group achieved the scientific development of two new strategies for computer-aided drug design. The SwissBioisostere database collects over 4.5 million molecular substructural replacements extracted from the literature, along with information on their frequency of use, and the observed impact on the compounds’ activity. This knowledge is of particular interest for researchers in drug discovery, who can get a better understanding about possible molecular modifications of their current lead compound. SwissSidechain is a database that gathers information on hundreds of commercially available non-natural side chains for peptide design, which can be used to study, in silico, their insertion into peptides or proteins. In 2013, the group also developed a new drug design tool, the SwissTargetPrediction approach, which aims at predicting the targets of bioactive small molecules in human. This is useful to understand the molecular mechanisms underlying a given bioactivity, to rationalize side-effects, or to predict off-targets of known molecules.

An experimental screening of small molecules against IDO1 followed, which identified new potential lead series for IDO1 inhibition. The group started the development of a mouse model to test in silico optimized TCRs for immunotherapy of melanoma. Finally, full exome and RNA sequencing technology was used to decipher resistance to BRAF inhibition in melanoma.

Future focus and expectations

The SwissTargetPrediction drug design approach will be released as a new web service freely available for the scientific community. The project will evolve into a fully integrated suite of algorithms called SwissDrugDesign that will allow to perform all the required step of a drug design project. The group will continue the design of new IDO1 inhibitors based on the screening hits. The development of melanoma mouse models will be pursued, allowing our computer-optimized TCRs to be thoroughly validated in vivo, paving the way to clinical trials.

A large program has been launched to systematically type the adaptive resistance of melanoma to MAPK inhibitors.

SELECTED PUBLICATIONS

4. Gfeller D, Michielin O, Zoete V. SwissSidechain: a molecular and structural database of non-natural sidechains for peptide design, which can be used to study, in silico, their insertion into peptides or proteins. In 2013, the group also developed a new drug design tool, the SwissTargetPrediction approach, which aims at predicting the targets of bioactive small molecules in human. This is useful to understand the molecular mechanisms underlying a given bioactivity, to rationalize side-effects, or to predict off-targets of known molecules.

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A large program has been launched to systematically type the adaptive resistance of melanoma to MAPK inhibitors.
Edoardo MISSIAGLIA

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Funding sources

▪ MEDIC Foundation
▪ FORCE Foundation

Key research collaborations

▪ Mauro Delorenzi, SIB
▪ Janet Shipley, ICR (UK)
▪ Annie Tremblay, Harvard (USA)
▪ Aldo Scarpa, University of Verona (IT)
▪ Henning Wackerhage, University of Aberdeen (UK)

Biography

Edoardo Missiaglia, born in Vicenza, Italy, obtained his bachelor’s degree in biology (1994) from the University of Padova, master’s degree in genetics (1998) from the University of Bologna and PhD in pathological oncology (2003) from the University of Verona. He worked at the ICRF (Cancer Research UK) (2001-2003) as research assistant and at University of Verona (2003-05) and ICR (2005-2010) as Post-Doc and bioinformatician. He has been working as Project Manager at the SIB (2010-2014). He became the scientific director of the molecular pathology laboratory of the Institute of Pathology at CHUV in August 2014.

Research interests

The research interest of the group is molecular and clinical cancer research (either solid or haematological tumors). Our goal is to implement molecular predictive and prognostic biomarkers in the clinical practice with the aim of tailoring treatment, based on genetic and molecular profile of the tumor. Our group is also interested in translational research in sarcomas and hematologic malignancies.
Recent scientific contributions

As project manager of the Bioinformatics Core Facility of the SIB, I have been working on several cancer research projects. Specifically, I am involved in the validation of colorectal cancer molecular subtyping within an international consortium which is part of the Sage bionetworks. Besides, we established the molecular, pathological and clinical differences between proximal and distal colon cancer and their effect on prognosis and response to targeted therapy. In addition, in collaboration with a group at Harvard University, we showed that YAP1 protein plays a pivotal role in the development of embryonal rhabdomyosarcoma, and that its activation is associated with tumor aggressiveness. Regarding rhabdomyosarcoma, we are also integrating gene expression profiling, copy number variations as well as miRNA expression profiling data generated by Next Generation Sequencing (NGS). Our group is involved in a collaborative project with the TENOMIC consortium to explore the molecular aspects of peripheral T-lymphoma tumors. Finally, I have been collaborating with the University of Verona on a project involving NGS analysis of rare pancreatic tumors as part of the International Cancer Genome Consortium (ICGC).

SELECTED PUBLICATIONS


Future focus and expectations

Staring August 2014, I have started working at the Institute of Pathology, CHUV, to become the scientific director of the molecular pathology laboratory, where we will implement NGS techniques in molecular cancer diagnostic. Through the collaboration with other centers, we are planning to introduce specific panels of genes to detect genetic and genomic alterations with predictive and/or prognostic potential.
Vincent MOOSER

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Funding sources

- CHUV/UNIL

Biography

Vincent Mooser MD is board certified in internal medicine. His research training encompasses clinical pharmacology (CHUV), experimental pharmacology (University of Melbourne, Australia), genetics and lipidology (UT Southwestern, Dallas TX). After a 6-year assistant professorship at CHUV, Vincent Mooser joined GSK in 2002 in Philadelphia, where he took roles of increasing responsibilities in R&D and in the Rare Diseases Unit. He came back to CHUV in 2011, as Head of Laboratories Department and Head of Service de Biomedicine. Since 2012, he has been Vice-Dean in charge of clinical research at the UNIL Biology and Medical School.

Research interests

Prof. Mooser’s research interests cover the following specific topics including: Laboratory medicine, Pharmacological sciences (drug discovery and development), Clinical pharmacology, Biomarkers, Pharmacogenetics, Environmental and genetic determinants of diseases.
Scientific contributions in 2013

The Lausanne Institutional Biobank is a new initiative in CHUV/UNIL which was launched on January 7th, 2013. The major goal of this project is to collect biomedical data and samples from a large number of properly consented CHUV patients which can be used in genomic medicine research and other applications. Over the first 18 months, more than 10,000 patients have consented to participate in this project. This is a bioresource which shall facilitate the development of preventive oncology programs, among other applications.

Steps for the construction of genomic medicine. Black box defines position of the Platform

SELECTED PUBLICATIONS


Focus and expectations for 2014

Decision was made by General management of CHUV and UNIL to build a dedicated, integrated Platform to support clinical research at CHUV. This Platform integrates the Biobank, the Clinical Research Center and an IT group. Oncology shall greatly benefit from this investment. Plans are underway to identify pilot projects.
Alexandre MOULIN

Funding sources
- Openeyes Foundation
- Fond’Action contre le cancer

Key research collaborations
- Carlo Rivolta, Department of Medical Genetics, UNIL
- D Rimoldi, LICR@UNIL

Biography
Alexandre Moulin graduated from Lausanne University Medical School in 1998. From 1999 until 2009, he completed two residencies both in Pathology and Ophthalmology as well as a fellowship in Eye Pathology at Massaschussetts Eye and Ear Infirmary in Boston. His thesis focused on epigenetics in uveal melanoma. Since 2009, he has been the Head of the Eye Pathology Laboratory in Jules Gonin. In 2013, he was appointed scientific secretary for the pathology and oncology section of the European association for vision and eye research (EVER).

Research interests
At Jules Gonin Eye Hospital, national and international reference center for eye oncology, we focus on adult and pediatric ocular tumors (uveal and conjunctival melanoma, retinoblastoma). We aim to understand the mechanisms of development and metastasis of uveal melanoma. In conjunctival melanoma, we are trying to understand the migration mechanisms as well as the underlying signaling pathways.
Recent scientific contributions

In 2013, we started a whole genome sequencing project in uveal melanoma (primary and metastatic tumors) in collaboration with Dr Carlo Rivolta’s group in the Department of Medical Genetics and D. Rimoldi from the Ludwig Center for Cancer Research. In collaboration with D. Rimoldi and M. Nicolas at Jules Gonin Eye Hospital, we established a new conjunctival melanoma cell line. The identification of BRAF and NRAS mutations in 47% conjunctival melanoma led to investigate, ex vivo, the activation status of the MAP kinase pathway and pi3K/mTOR in benign and malignant conjunctival melanocytic proliferations. We are assessing in vitro the response of conjunctival melanoma cell lines to BRAF inhibitors, MEK inhibitors and pi3K inhibitors. We are also continuing our efforts to understand the role of miR-211 in conjunctival melanoma migration and invasion.

SELECTED PUBLICATIONS


Future focus and expectations

The focus will be to keep our efforts on the Whole Genome Sequencing of Uveal melanoma and to deepen our understanding of the role of Mir-211 in conjunctival melanoma migration and invasion, together with identifying an in vitro targeted therapy.
Francis MUNIER

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Funding sources
- Swiss Cancer League
- Elitha Foundation

Key research collaborations
- Maja Beck-Popovic, Pediatric Hematology-Oncology Unit, CHUV
- Stefano Binaghi, Department of Radiology, Neuroradiology Unit, CHUV
- Daniel Schorderet, Institut de recherche en Ophtalmologie, Sion, (CH)
- Botond Roska Friedrich Mischer Institute, Basel, (CH)
- Meritxell Bach Cuadra, CIBM, EPFL
- Damien Weber, Paul Scherrer Institute, Villigen, (CH)

Biography
Prof. Francis Munier obtained his medical degree at the University of Lausanne Medical School, Switzerland, in 1983. On top of clinical training at Jules Gonin Eye Hospital and Division of Medical Genetics in Lausanne, he received additional training in Pediatric Ophthalmology and Ocular Oncology at Childrens Hospital Los Angeles, University of Southern California, USA from 1991 to 1993. Professor Munier is board certified in both Ophthalmology and Medical Genetics. He is presently Head of the Retinoblastoma Unit and the Oculogenetic Unit at Jules Gonin Eye Hospital. In addition Prof. Munier is an Associate Researcher at the Institut de Recherche en Ophtalmologie (IRO) in Sion, Switzerland.

Research interests
Prof. Munier’s research interests include: i) Drug delivery (chemotherapy in situ, such as intra-arterial and intra-vitreal injections for retinoblastoma), ii) Evaluation of the retinal toxicity of chemotherapy in situ, iii) Identification of pathways involved in the intra-ocular seeding of retinoblastoma (metabolic remodeling, resistance to anoikis …etc), iv) Infra-clinical imaging of early steps of retinal oncogenesis in retinoblastoma patients, v) Induction of apoptosis or blockage of cell division in an in vivo model using newly identified molecules, vi) Proton-therapy for retinoblastoma: computer assisted treatment planning using advanced image processing in a multi-modal framework.
Recent scientific contributions

The Lausanne Retinoblastoma Clinics serves not only as the only HSM-certified national referral center, but also as a tertiary referral center recruiting patients all over Europe and abroad.

At the clinical level, the main focus was the study of efficacy of intra-vitreal chemotherapy combined or not with intra-arterial injection of melphalan in advanced and/or recurrent retinoblastoma.

Fundamentally, we found and published that The Bcl-2/Bcl-XL inhibitor ABT-737 promotes death of retinoblastoma cancer cells.

SELECTED PUBLICATIONS


Future focus and expectations

We are planning to launch an International multicentric phase II study for recurrent or progressive intraocular retinoblastoma (RB-2014) and to study the development of retinoblastoma in a human retina derived from human iPS.
Denise NARDELLI HAEFLIGER

Funding sources

- Swiss National Science Foundation
- Swiss Cancer League
- UNIL-FBM
- Glaxo SmithKline

Key research collaborations

- John Schiller, NCI, NIH, Bethesda (USA)
- Pedro Romero and Daniel Speiser, LICR@UNIL
- Glaxo-Smith Kline, Vaccines and Biological, Rixensart (BE)
- Olivier Michelin and Vincent Zoete, SIB
- Daniel Olive, INSERM, Marseille (FR)
- Doug Hanahan, ISREC EPFL
- Enrico Giraudo, IRCC, Turin (IT)
- Christian Simon, ORL Dpt, CHUV

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Biography

Denise Nardelli Haefliger received a PhD in molecular biology from UNIL (1988) and pursued as a post-doc at Harvard in developmental biology. Since 1992, she has been leading a research group towards the development of prophylactic and therapeutic vaccines against genital human papillomavirus (HPV) infections and cancers. She has been recipient of the Leenaards Foundation (1999) and a SNSF-professor fellowship (2000-2006). Since 2009, she is heading the Urology Research Unit of Prof. Jichlinski’s Department and her research projects have extended to diverse immunotherapeutic approaches for treating urogenital cancers, including immune regulators (see Derré’s lab).

Research interests

Nardelli’s lab has focused on the use of mucosal approaches and vaccination routes with a special interest in the induction and analysis of immune responses at the mucosal urogenital sites in both murine models and humans, and including the direct translation of immunotherapeutic strategies developed in mice to clinical trials in patients.
Recent scientific contributions

For inducing efficient anti-tumoral responses, we are using different routes of immunization and are administering diverse molecular or bacterial agents to target and increase anti-tumoral CD8 T cells at the site of the tumor. We had demonstrated previously that an intravaginal immunostimulation with CpG after vaccination greatly improved regression of HPV genital tumors in an animal orthotopic model of cervical cancer. We have now determined that either subcutaneous or intravaginal immunization is able to induce regression of established bladder tumors, though only in half of the mice. Our preliminary data showed that intravesical immunostimulation with a bacterial vaccine, but not with CpG, is able to increase both CD8 and CD4 T cells numbers at the tumor site, resulting in regression of bladder tumors in 90% of the mice. These data showed that a strategy combining vaccination with local immunostimulation may be beneficial for treating bladder cancer in the patients. This is currently being tested in a clinical trial with the MAGE-A3 vaccine (GSK) combined to BCG intravesical immunostimulations (PI and sponsor: Prof. Jichlinski).

In addition, immune monitoring of bladder cancer patients during BCG therapy shows specific immune infiltrations that may correlate to BCG efficacy (see Derré’s lab). Mouse data also indicate that BCG may be replaced by a safer bacterial vaccine.

Our prostate cancer projects are led by Dr. Tawadros, who is currently investigating the effect of the lipid diet on bone metastasis in a mouse prostate cancer model.

SELECTED PUBLICATIONS


Future focus and expectations

- Extension of immune monitoring of bladder to kidney and prostate cancer patients
- MAGE-A3/BCG clinical trial outcomes (coll. GSK-Ludwig at UNIL)
- Outcome of bacterial intravesical therapy in a murine bladder cancer model and initiation of a clinical trial in bladder cancer patients
- Initiation of a collaborative project combining vaccination with immune regulators against HPV cervical and head and neck cancers in orthotopic and genetic mouse models (coll. EPFL-CHUV-Torino)
- Investigation of human prostate cancer microenvironment
Olaia NAVEIRAS

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Funding sources
- SNSF
- Fondation Pierre Mercier pour la Science
- Fundacio Josep Carreras contra la leucèmia
- European Hematology Association

Key research collaborations
- EPFL Bioscreening, Flow Cytometry, Histology Cores
- Prof. Matthias Lutolf, EPFL-IBI (CH)
- Prof. George Coukos, Dr. Dominique Vanhecke, CHUV (CH)
- Dr. Pierre Bourquin, Hematology, Kinderspital Zürich (CH)
- Dr. Vincent Kindler, Hematology, HUG (CH)

Biography
Prof. Naveiras originally trained as a Medical Doctor in Spain, then studied Immunology at the Pasteur Institute and Harvard University. Attracted by the potential of cell therapies, she joined the laboratory of Prof. George Daley at Harvard Medical School, where she made important contributions to the understanding of the hematopoietic stem cell microenvironment, as well as to the process of instructive hematopoiesis from pluripotent stem cells. She arrived in Switzerland in 2009 and joined the Laboratory of Stem Cell Bioengineering at EPFL, while pursuing Internal Medicine and Hematology training at the CHUV. She started her own lab in 2014 thanks to a SNF Professorship grant.

Research interests
Prof. Naveiras is interested in understanding the regulation of the reversible transition between mammalian yellow (adipocytic) and red bone marrow (hematopoietic), as this naturally occurring process can be enhanced to increase safety and efficacy of hematopoietic stem cell (HSC) transplantation, and, possibly, to slow the progression of myelodysplasia or even aplastic anemia into overt leukemia.
Recent scientific contributions

Our laboratory was established in January 2014. Since then, we have optimized complex models of hematopoietic stem cell (HSC) transplantation extending to, thanks to our collaborators, single cell transplants and NSG human-into-mouse xenotransplantation. We have established a high-throughput screening platform for mesenchymal stem cell differentiation based on digital holographic microscopy (DHM), adapted for the study of bone marrow adipogenesis, and have developed quantitative methods to assess the red-to-yellow and yellow-to-red bone marrow transitions upon bone marrow transplantation. Aside from method-development, following up on the work initiated by our group at the Laboratory of Stem Cell Bioengineering, postdoctoral fellow Dr. Nicola Vannini has demonstrated the capacity of specific mitochondrial modulators within the NAD pathway to accelerate the yellow-to-red bone marrow transition upon HSC transplant in mice, opening the possibility of translating these findings to reduce the mortality associated to HSC transplant in patients suffering from leukemia or lymphoma.

SELECTED PUBLICATIONS


Future focus and expectations

Future work will concentrate on characterizing the mesenchymal stem cell (MSC) and preadipocyte populations in relationship to the expanding hematopoietic compartment, as well as identifying small molecule inhibitors of the yellow-to-red bone marrow transition that may be used in the context of HSC transplantation and aplastic anemia. A special emphasis will be placed on developing in vivo screening tools for microenvironments capable of mediating hematopoietic progenitor expansion.
Esat Mahmut OZSAHIN

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Funding sources
- Accuray Inc.
- Ablatech S.A.

Key research collaborations
- Prof. Bochud, Dr Moeckli, Dr Vallet, Dr Germond, Institute of radiophysics, CHUV
- EORTC Radiation Oncology, and Head and Neck Groups
- Rare Cancer Network
- Prof. D. Azria, Service of Radiotherapy, Montpellier (FR)

Biography
Prof. Ozsahin obtained his medical degree in 1985 from the Ege University, Izmir, Turkey. He obtained his PhD degree in radiation biology from the ETH (Zurich, Switzerland) in 1996. He held various positions in Turkey, France, and Switzerland prior to taking up his current position. His main interests are head and neck cancer, lung cancer, colorectal cancer, hematological malignancies, rare cancers, combined modality treatment, and modern radiotherapy techniques including intensity-modulated radiation therapy, stereotactic RT, and helical Tomotherapy. His biology research topics include radiation-induced normal tissue damage, and predictive assays in radiotherapy. He is a member of several scientific societies and groups, including ASTRO, ESTRO, SASRO, SGSMP, SFRO, Turkish Society of Radiation Oncology, Turkish Society of Hematology, EORTC Radiation Oncology (chairman of the HN working party) and Head and Neck groups, AROME (vice-president), and the Rare Cancer Network (president).

Research interests
Prof. Ozsahin’s research interests include clinical research in head and neck cancer, lung cancer, colorectal cancer, hematologic malignancies, rare cancers, modern radiotherapy techniques, as well as translational research in predictive assays for normal tissue radiosensitivity.
Recent scientific contributions

Prof. Ozsahin contributed as principal investigator or scientific collaborator to various projects that were published including:

- Nomograms predicting locoregional recurrence in the subtype era of breast cancer.
- Adenosquamous carcinoma of the head and neck: report of 20 cases and review of the literature.
- Intrinsic radiosensitivity: predictive assays that will change the daily practice.
- Radiotherapy options after breast-conserving surgery: How can selection of patients be refined?
- Prognostic factors in adult soft tissue sarcoma treated with surgery combined with radiotherapy: A retrospective single-center study on 164 patients.

SELECTED PUBLICATIONS


Future focus and expectations

Being a collaborator of Prof. Jean Bourhis’ team, Prof. Ozsahin participates actively in new research programs in Radiation Oncology at the CHUV as follows:

- Establishment of the CHUV radiation oncology as an Accuray International flagship reference site and international training center
- Development of advanced 4D radiotherapy (Dr Péguret)
- Development of new clinical trials of high precision radiotherapy in rectal and bladder cancer (Dr De Bari)
- Participation in the development of Flash-Beam radiotherapy
- Participation in the predictive assay program and Radiogenomics Consortium for the prediction of radiation-induced late toxicity (Dr Vozenin, CHUV; Prof. Azria, Montpellier; and Prof. Rosenstein, Mount Sinai)
Jean Yannis PERENTES

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Funding sources
- Swiss National Science Foundation
- UNIL-FBM Young Scientific Grant
- Swiss Society of Surgery Grant

Key research collaborations
- Pr Paul Dyson, Institute of Chemical Science and Engineering, EPFL
- Pr Norbert Lange, Institute of Pharmacological Science, UNIGE (CH)
- Pr Ivan Stamenkovic, Institute of Pathology, CHUV
- Pr Tatiana Petrova, UNIL

Biography
Dr JY Perentes completed his medical studies at the University of Lausanne in 2003. He then performed his PhD in Tumor Biology at the Edwin Steele Laboratory at the Massachusetts General Hospital of Boston, USA under the mentorship of Professors RK Jain and Y Boucher. There, he worked on the different projects involving real time imaging of tumors by intravital microscopy in living rodents. From 2007, Dr Perentes started his General Surgery training at the CHUV and Sion Hospitals and obtained his General Surgery Board in 2012. He joined the Department of Thoracic Surgery in 2013 where he is training to obtain his Thoracic Surgery Board. In parallel, Dr Perentes has taken over the Thoracic Surgery Tumor Biology Laboratory. He is interested in methods to enhance drug penetration in tumors to improve the effect of chemotherapy and subsequent surgery.

Research interests
The group is interested in methods to enhance tumor vascular transport and improve the distribution of chemotherapy for a better tumor response using Swiss-medic approved drugs. Multiplex quantitative analysis of vessel morphology/function as well as drug distribution is made possible by intravital microscopy and other techniques on orthotopic and heterotopic animal models.
Recent scientific contributions

We had shown that the pre-treatment of lung and pleural tumors by low-dose Photodynamic Therapy (PDT) enhanced the subsequent administration of chemotherapy. However, the exact mechanism for these findings was unknown. Using the same model as well as others, we assessed how low-dose PDT affected tumor/surrounding lung interstitial fluid pressure, tumor blood flow and chemotherapy distribution. We found that low-dose PDT caused a significant decrease in tumor but not lung interstitial fluid pressure while leaving tumor blood flow unaffected. These findings suggested that low-dose PDT enhanced tumor blood vessel convection which improved the transport and distribution of chemotherapy. We are now looking into the precise changes in vessel structure that could explain these findings as well as the length of the improved drug transport window induced by low-dose PDT. In parallel, we are testing the application of such an approach in mini pigs as a first step for the clinical translation of this therapy for the management of pleural cancers.

Future focus and expectations

We plan to determine the exact mechanism responsible for tumor interstitial fluid pressure drop as well as the length of the improved vascular transport window induced by low-dose PDT. We will focus, in particular, on the changes induced on pericyte coverage and tumor vascular chemokine expression induced by low-dose PDT. Also, we will determine how vascular transport is affected by a single low-dose of PDT over one month. Finally, we will assess the feasibility of such an approach in minipigs, a first step for clinical translation.
Solange Peters
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Biography
Solange Peters is in charge of the thoracic malignancies program in the Department of Oncology of the University of Lausanne since 2006. In parallel, she is active in building a translational program in collaboration with the molecular oncology laboratory directed by Prof. D. Hanahan and Prof. E. Meylan. She is co-chair of the Swiss lung cancer research group (SAKK), and Scientific Coordinator as well as Chair of the Informatics Committee of the European Thoracic Oncology Platform (ETOP). She has been ESMO-elected Executive board Member since 2014. She recently was elected the youngest member ever of the IASLC Board of Directors 2013-2017, the most honorific position in the lung cancer community. She is the president of the Swiss education organization Forome, dedicated to cancer multidisciplinary professionals.

Research interests
Our field of interest is NSCLC (non small cell lung carcinoma) new biomarker discovery and validation in preclinical and clinical settings. We are taking part in several translational trials in lung cancer in Europe, chairing or taking in charge their translational part, based on our solid network. We are also heavily involved, at the national level, in the development of multimodality trials for locally advanced NSCLC, leading Swiss and European clinical programs in stage III lung cancer. In the neighborhood of the LICR and in collaboration with EPFL, Dr. Peters is involved in the development of promising new immunological approaches for the treatment of thoracic malignancies.

Funding sources
- Pharma dedicated and unrestricted grants
- ETOP and SAKK
- Gateway Foundation
- Swiss National Science Foundation
- Swiss Cancer League

Key research collaborations
- Prof. Etienne Meylan, ISREC-EPFL
Recent scientific contributions

Dr. Peters has been actively involved in and responsible for a wide range of projects and trials including:

- Database and subprojects in the ETOP Lungscape Project which consists of a Retrospective analysis of about 2600 completely resected NSCLC with at least 3 years of follow-up from 15 sites.
- ETOP-sponsored phase III trial EMPHASIS (Erlotinib Maldi TOF Phase III Signature in Squamous cell non-small cell lung cancer)
- SAKK trial: SAKK 16/08 Pre-operative chemotherapy and radiotherapy concomitant to Cetuximab in non-small cell lung cancer (NSCLC) patients with IIIB disease. A multicenter phase II trial
- ETOP/EORTC SPLENDOUR trial (A randomized phase III trial evaluating the addition of denosumab to standard first-line anticancer treatment in advanced NSCLC. Survival improvement in Lung cancer induced by Denosumab therapy)
- ETOP STIMULI trial (A randomized phase II trial of consolidation ipilimumab vs observation in stage I-III (“limited disease”) small cell lung cancer after chemo-radiotherapy)
- Diagnostic and clinical development of SPECTALUNG prospective molecular characterization led by EORTC in collaboration with ETOP (budget in preparation/charity funds and pharma companies)
- Roche phase III randomized ALEX trial, (BO28984), a randomized phase III study comparing the effect of alectinib with crizotinib in ALK positive NSCLC patients, in preparation for 2014.

SELECTED PUBLICATIONS


Future focus and expectations

We aim to:
- Develop new strategies in immunotherapy for the treatment of NSCLC (check point inhibitors anti PD1 or anti PDL1 respectively in combination with radio/chemotherapy) in stage III/IV
- Develop Phase IB/II Study of Combination Treatment with Carboplatin/Paclitaxel and the Copper Chelator, Tetrathiomolybdate in Patients with Advanced Solid Tumors (CATAtEm)
- Set up the whole translational study in the RANKL inhibition phase III randomized trial SPLENDOUR
Tatiana PETROVA

Funding sources

- Swiss National Science Foundation
- Oncosuisse
- EU FP7

Key research collaborations

- Owen Sansom, Beatson Institute (UK)
- Mauro Delorenzi, SIB
- Stefan Schulte-Merker, Hubrecht Institute (NL)

Biography

Tatiana Petrova received her M.Sc in chemistry from Moscow State University in 1990 and a Ph.D. in biochemistry from the University of Geneva in 1996. She did a postdoctoral work at Northwestern University in Chicago from 1997 to 1999, and then moved to a second postdoctoral position at the University of Helsinki, Finland. In 2004, she became a group leader at Molecular Cancer Biology Program at the University of Helsinki, and in 2008 joined CHUV and University of Lausanne as an SNSF professor.

Research interests

Our group studies molecular mechanisms of cancer progression with an emphasis on the transcriptional regulation, the role of blood and lymphatic vessels and the cross-talk of cancer stem cells and tumor microenvironment. Our goal is to identify key molecular regulators, which could be used as targets for treatment or diagnostics of cancer.
Recent scientific contributions

We explored the mechanisms underlying the resistance of metastatic colon cancer stem cells to metabolic stress, such as hypoxia and low nutrient conditions.

Using genetic mouse models, we investigated signaling pathways down-stream of VEGF pro-angiogenic signaling in tumor blood and lymphatic endothelial cells, and established their differential contribution to the growth of primary tumors or organ-specific metastasis.

We identified a novel endothelial-specific regulator and established a mouse model, which will allow us to study its role in tumor (lymph) angiogenesis and cancer progression.

Future focus and expectations

Our focus is to develop concepts and approaches for targeting metastatic colon cancer cells and to validate them using both genetic models and patient-derived material.

We also aim to further characterize the interactions of metastatic colon cancer stem cells with their microenvironment, in particular blood vessels, and to study how such interactions contribute to tumor resistance to current anti-angiogenic therapies.

Moreover, we plan to establish closer collaborations with clinicians, chemists and engineers to evaluate the potential use of novel endothelial specific protein, identified in the group, for cancer diagnostics and treatment.

SELECTED PUBLICATIONS

John PRIOR

John Prior
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Biography
John O. Prior obtained a MSc in electrical engineering (ETHZ Zurich, 1989) followed by a PhD in biomedical engineering (UTSW Dallas, 1993), a MD federal diploma (UNIL Lausanne and specialized in nuclear medicine in Lausanne (2005) with a 2-year fellowship at the UCLA (2002–2004) as visiting associate professor. Academically, Prof. Prior was appointed MER (teaching and research) in 2005 and PD (privat docent) in 2006. Since 2004, he has been working as nuclear medicine physician at CHUV and was appointed full professor and Head of the Nuclear Medicine at CHUV in 2010.

Research interests
Prof. Prior’s research interests include: clinical trials for molecular imaging and therapy using radionuclides of glioma, angiogenesis imaging, bombesin imaging; preoperative imaging by PET/CT or SPECT/CT for tumor targeting; development of instrumentation for image-guided biopsy and surgery, compact probes for radiotracer-guided surgery; patient-specific delivery of selective interstitial radiation therapy (SIRT) of liver tumor and metastases; delivery of antibody- and peptide-targeted radiation therapy.

Funding sources
- Swiss National Science Foundation
- CTI-KTI
- Oncosuisse
- EU FP7
- Swiss Heart Foundation
- Leenaards Foundation
- Swiss Group for Clinical cancer Research
- Lionel Perrier Foundation

Key research collaborations
- Switzerland: CHUV, HUG, PSI, ETHZ, EPFL, SAKK
- Europe: CERN-Medicis, CERIMED.NET, ADACAP, Forimtech, Technische Universität München
- Worldwide: Ottawa Heart Center, Fred Hutchinson Cancer Research Center Seattle, Turku PET Center
Recent scientific contributions

Reviewing of currently observed long-term progression free survivals of indolent non-Hodgkin lymphoma over 8 years, after radioimmunotherapy and immunotherapy, suggests that these patients have been possibly cured thanks to their T cells immune response.

In collaboration with CERN Medicis and based on bombesin and neurotensin targeting radiopeptides and micro-PET-SPECT-CT imaging, we explore new therapy approaches that can lead to curative treatments. Such preclinical models with a direct strategy to cure are currently missing.

We also developed a fast (200ps) time-of-flight endoscopic probe for image-guided biopsies of cancer of the pancreas and prostate with a 13-partner consortium financed by the EU FP7 grant (€ 5.5M).

In addition, we developed a β+ detection probe for radioguided surgical oncology (project financed by a “science-to-market” CTI grant).

SELECTED PUBLICATIONS


Future focus and expectations

Clinical trials have been approved and will start in 2014 on the use of a β+ detection probe for radioguided surgical oncology, PET/CT imaging with novel tracer for prostate cancer (bombesin), as well as angiogenesis imaging with Ga-68-based targeting of αvβ3 in 12 selected cancer types. We will pursue the project in collaboration with the CERN-Medicis for a preclinical model of peptide targeted radiation therapy with alpha-emitters towards a curative approach in a prostate cancer xenograft model. We will set up the FNS/UNIL-FBM funded micro-PET/SPECT/CT (kCHF 977) in Nuclear Medicine and will continue to deliver SIRT therapy service with individualized dosimetry.
Freddy RADTKE

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Funding sources

- Swiss National Science Foundation
- Swiss Cancer League
- OptiStem
- EuroSyStem
- Notch IT

Biography

Freddy Radtke graduated from the University of Zürich in molecular biology in 1994. His postdoctoral fellowship at Genentech Inc., USA, in 1995-1996 was followed by a postdoctoral position at ISREC Switzerland in 1997-1999. He was Assistant Member of the Ludwig Institute for Cancer Research from 1999 to 2004 and was promoted to Associate Member in 2004. Freddy Radtke joined ISREC as Senior Scientist in 2006, before joining EPFL in August 2006 as associate professor and was appointed full professor in 2012.

Research interests

The Radtke lab use mouse genetics to study the molecular mechanisms controlling self-renewal and differentiation of normal and cancer cells. These processes have to be under stringent control mechanisms to ensure life-long tissue homeostasis. Their deregulation can lead to organ failure and/or cancer. Current attention is focused on developmental signaling pathways, which play pleiotropic roles in different self-renewing tissues and cancer.
Recent scientific contributions

We continue to use mouse genetics to study how deregulation of developmental signaling pathways (Notch or Wnt signaling) contributes to cancer, with a particular focus on hematological malignancies and skin cancer including melanoma. Moreover, the lab further optimizes and validates potential drug development candidates targeting developmental signaling pathway to assess their mode of action and efficacy in pre-clinical cancer models and primary human tumor samples. The laboratory also studies how inflammation can promote or inhibit tumor progression. In this context of skin carcinogenesis we showed how certain cytokines influence the immune system to adapt a tumor protective role, while their blockage tips the balance towards a tumor promoting type of inflammation.

The laboratory is currently studying mouse models for T cell acute lymphoblastic leukemia (T-ALL), Chronic lymphoblastic leukemia (CLL), Squamous cell carcinoma and melanoma.

SELECTED PUBLICATIONS


Model for the role of the immune system in controlling inflammation and cancer upon loss of Notch signaling in the adult murine skin. Notch receptors are expressed in the suprabasal layer of the epidermis. Skin specific loss of Notch signaling leads keratinocytes to secrete high levels of TSLP that trigger massive inflammation and the development of an AD-like disease. Inflammation is characterized by dermal recruitment of mast cells, eosinophiles, CD11b+Gr1+ myeloid cells, and CD4+ and CD8+ T cells. Genetic removal of TSLPR in Notch mutant mice causes the development of skin tumors. T cells are absent from the tumor microenvironment whereas CD11b+Gr1+ myeloid cells accumulate. Together with stromal fibroblasts, CD11b+Gr1+ myeloid cells sustain Wnt dependent tumorigenesis.
Eric RAYMOND

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Funding sources
- Nelia and Amadeo Barletta Foundation

Key research collaborations
- Prof. Valérie Paradis, Paris 7 Diderot University (FR)
- Prof. Anne Janin, Paris 7 Diderot University (FR)
- Dr Laurent Desaubry, University of Strasbourg (FR)

Biography
Eric Raymond was appointed Head of Medical Oncology and Full Professor at CHUV-UNIL in 2014. He graduated in 1995 in Medical Oncology. In 1993-1995, he was Chief Doctor at Saint-Antoine Hospital in Paris (with Prof de Gramont) before doing a PhD and Fellowship at University of Texas (with Prof. Von Hoff) working on phase I and translational programs on telomere/telomerase inhibitors. Then, Eric Raymond developed first in human phase I trials at Institute Gustave-Roussy (1997-2003) with sunitinib and everolimus. He was nominated Professor of Oncology at Paris 7 Diderot and created the service of Medical Oncology at Bichat/Beaujon Hospitals in Paris in 2003.

Research interests
Our group is interested in developing novel anticancer agents with original mechanisms of action, with potential for combination, and with non-overlapping toxicity or resistance mechanisms with other drugs.

We aim to develop research programs abolishing frontiers from preclinical to clinical cancer research making a continuum from bench experiments to bedside patient care.
Recent scientific contributions

We have focused our drug and translational research on proteins involved in EMT that are frequently expressed in tumors becoming resistant to targeted agents. TGF-beta receptor, HGF/MET, and CXCR4 inhibitors were tested in the clinic and in the lab along with drugs that could restore apoptosis.

Our translational research aimed to develop culture conditions to maintain alive tumors that have been biopsied or explanted surgically. This \textit{ex vivo} testing allows various biomarkers and evaluation of drug concentrations in tumors with their preserved stroma.

In 2013, our group finalized the center of excellence for pancreatic and hepatobiliary tract tumors at Beaujon University hospital. This three-year project was made in close collaboration with the Department of Pathology at Paris 7-Diderot University. Associated with the launching of this center, we organized our first international conference on Cutting Edges in Pancreatic and Liver Tumors that gathered top speakers in Paris for a two-day meeting. Details on the conference can be found at (www.beaujon.conference.fr)

Future focus and expectations

We aim to develop translational research using novel target agents at CHUV in 2014. This will be made using the facilities of the Center for Experimental Therapeutics, together with close collaborations with the Institute of Pathology, the Department of Medical Imaging, and Surgery at the CHUV. For instance, we will set up a novel technology at CHUV allowing the evaluation of new drugs in freshly explanted tumors from patients, which are maintained alive \textit{ex-vivo} for few days.
Alexandre REYMOND

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Biography
Alexandre Reymond carried out his thesis at the Swiss Institute for Experimental Cancer Research and received his Ph.D. from the University of Lausanne in 1993. After completion of his postdoctoral training with Dr Roger Brent in the Department of Molecular Biology, Massachusetts General Hospital in Boston, he moved to the Telethon Institute of Genetics and Medicine in Milan in 1998 to lead a research group. In 2000, he joined the Department of Genetic Medicine and Development, University of Geneva Medical School. He moved to the Center for Integrative Genomics in October 2004.

Research interests
We assessed the functional impact of genome structural changes and demonstrated that expression levels of genes within and neighboring rearrangements are changed. Using mouse models, we further showed that some phenotypes were caused by structural changes per se rather than by gene dosage. We provided initial evidence that copy number variants shape tissue transcriptomes on a global scale and thus represent a substantial source for within-species phenotypic variation.

Funding sources
- Swiss National Science Foundation
- SystemsX.ch
- National Institute of Health (USA)

Key research collaborations
- T. Hubbard & J. Harrow, Wellcome Trust Sanger Institute (UK)
- E.T. Dermitzakis, UNIGE (CH)
- N. Katsanis, Duke University (USA)
- A. Metspalu, Estonia Genome Center
- E. Eicher, University of Washington, Seattle (USA)
Recent scientific contributions

In 2013, Prof. Reymond has been actively involved as principal investigator in a wide range of projects including:

• MLL2 mutation detection in 86 patients with Kabuki syndrome: a genotype-phenotype study.

• RGASP Consortium: Assessment of transcript reconstruction methods for RNA-seq.

• Structural variation-induced expression changes are paralleled by chromatin architecture modifications.

• Coordinated effects of sequence variation on DNA binding, chromatin structure, and transcription.

• Identification and removal of low-complexity sites in allele-specific analysis of ChIP-seq data.

SELECTED PUBLICATIONS


Future focus and expectations

We have started to map chromatin interaction using chromatin-conformation capture of the promoters of genes associated with common diseases to demonstrate a link between perturbation of chromatin loops and the observed phenotypes.
Hans-Beat Ris
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Biography
After obtaining his MD at the University of Bern, Switzerland, Dr. Ris underwent training in general surgery and specialized in thoracic and vascular surgery. In 1989, he was board certified for Surgery FMH. He then took on research training in thoracic surgery centers in the USA including NIH in Bethesda and MGH in Boston. Associate Professor at the University of Bern, he headed the Thoracic Surgery Unit and co-directed the Inselspital Vascular Surgery Unit before becoming Full Professor at the University of Lausanne and Chief of Thoracic and Vascular Surgery Service at the CHUV, Lausanne in 1999. Prof. Ris developed internationally renowned research in thoracic surgery, especially in lung oncology. He is a member of numerous societies of Surgery and Thoracic Surgery.

Research interests
Prof. Ris focuses his research on:
- Intrapleural low-dose photodynamic therapy as a mean to selectively improve the uptake of conventionally available approved cytostatic drugs in pleural malignancies (photo-induction).
- Combined treatment modalities with extended resection after neoadjuvant radio-chemotherapy for locally advanced [T4 N0-2M0] non-small cell lung cancer
- Complex tracheo-carinal reconstructions by use of pedicled muscle flaps after extended resections of pretreated malignancies.

Key research collaborations
- Prof. Paul Dyson, EPFL - ISIC (CH)
- Dr. Norbert Lange, School of Pharmaceutical Sciences, UNIGE-UNIL (CH)
- Prof. Ivan Stamenkovic, IUP, CHUV (CH)
- Dr. Georges Wagnières, EPFL-ISIC-LCOM (CH)
- Dr. Solange Peters, Medical Oncology, CHUV (CH)
- Prof. Tatiana Petrova, CHUV UNIL (CH)
- Dr. Lana Kandalaft, Department of Oncology, CHUV (CH)

Funding sources
- SNSF
- Swiss Cancer League
- Andreas P. Naef Foundation
Recent scientific contributions

Malignant pleural disease is a frequently observed clinical entity that has an important social, medical and economic burden. It causes significant morbidities, such as cough, chest pain, dyspnea, and ultimately death. Quality of life is compromised due to these debilitating symptoms and therapy is therefore considered in virtually all patients. Current treatment is based on systemically administered chemotherapy, but success is limited due, in part, to the poor penetration of cytostatic agents into tumors. Experimental studies show that tumor drug penetration can be improved using vessel-targeted pretreatment protocols. This enables sufficient concentrations of approved and putative drugs to selectively enter the tumors and thereby improve treatment outcome.

In different pleural tumor models, we have shown that the tumor microenvironment properties are a major barrier for drug distribution, which partly explains the chemoresistance observed in clinical practice. We found that the vascular architecture and permeability cause elevated interstitial fluid pressure which impair fluid convection between the intra- and extra-vascular spaces and thereby hinder chemotherapy transport. Using light-activated sensitizers, we were able to “normalize” tumor vessels, decrease interstitial fluid pressure and enhance convection and chemotherapy distribution in tumors. This vascular pretreatment was specific for tumor vessels and did not affect normal tissues (SNF320030-135197, SNF310030-118222, SNF3200-055818, SNF3200-032547). These results are currently being translated into a clinical phase I trial for malignant pleural effusions.

SELECTED PUBLICATIONS


Future focus and expectations

Based on previous encouraging findings, we propose to assemble a multidisciplinary platform that will focus on developing methods to modulate the tumor microenvironment and improve the distribution of approved cytostatic drugs into chemoresistant tumors. The platform synergistically bridges clinicians, basic scientists and bioengineers to rapidly develop clinical solutions for this devastating disease. The platform will be of benefit to medical doctors, industry and researchers interested in the development of new vascular modulating approaches to improve chemotherapy distribution in tumors, with the following specific aims:

1. Selectively increase the uptake of SWISSMEDIC approved drugs into pleural malignancies using a tumor vascular modulation pretreatment step.
2. Delineate and optimize the mechanisms by which pharmacological pretreatments of the tumor vasculature lead to a selective increase of drug uptake and distribution of conventional cytostatic agents to solid tumors.
3. Obtain a new tumor vascular modulation pretreatment protocol for pleural diseases that will enter a phase I clinical trial using conventional chemotherapy.
4. Establish a state-of-the-art, long-term translational medicine platform for the evaluation of new therapeutic strategies for the treatment of pleural and other malignancies.
Carlo RIVOLTA

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Funding sources

- Swiss National Science Foundation
- European Union
- The Gebert-Ruef Foundation
- Fond’Action contre le cancer

Key research collaborations

- Harvard Medical School, Boston
- Hôpital Ophtalmique Jules-Gonin, Lausanne

Biography

Carlo Rivolta obtained his Master’s degree in Genetics and Molecular Biology at the University of Pavia, Italy, in 1994. He then moved to Lausanne where he got a PhD in Genetics at UNIL in 1999. After a postdoctoral training at Harvard Medical School (HMS) from 1999 to 2003, he became Instructor at HMS between 2003 and 2004. He came back to Lausanne to take up the position of Junior Group Leader at UNIL (2004-2008) followed by the position of Tenured Group Leader (2008-present).

Research interests

We are interested in studying the genetic basis of human diseases, mostly via the use of combined and large-scale approaches. In Switzerland, we have pioneered the use of next-generation sequencing in the context of the human pathological genome.
Recent scientific contributions

Our scientific contributions in 2013 followed the path that was previously set concerning the analyses of the genetic basis of human diseases via the use of whole-genome (as opposed to whole-exome) sequencing. The most important contribution within this context has been the publication of an article in PNAS, detailing the identification of mutations in non-coding regions of the human genome and causing recessive retinal degenerations. Along those lines and within the cancer thematic area, we have performed, in 2013, a full-genome sequencing of cancer vs. blood DNA in a patient with choroidal melanoma, as a proof of concept that such an endeavor can produce important (and new) data in the field of cancer genetics. Indeed, thanks to whole-genome information, we could identify not only classical coding mutations, but also directly non-coding DNA aberrations and even aneuploidies. Based on these positive findings, a set of 35 tumor-blood DNA pairs is currently being sequenced and will be analyzed in 2014.

SELECTED PUBLICATIONS


Future focus and expectations

As mentioned above, during this current year, we expect to generate and analyze a consistent amount of data on choroidal melanoma, which should provide enough material for several downstream investigations (genetics, cell biology, etc...).
Pedro ROMERO

Funding sources

- Swiss National Science Foundation
- Swiss Cancer League
- MEDIC Foundation
- ISREC Foundation

Key research collaborations

- Nicholas Restifo, Luca Gattinoni, NIH/NCI (USA)
- Daniel Speiser, LICR@UNIL
- Dietmar Zehn, Swiss Vaccine Research Institute (CH)

Biography

Pedro Romero, born in Guateque, Colombia, did medical studies at the School of Medicine of the National University of Colombia in Bogota. Then he performed experimental work in the field of immunology of malaria and malaria vaccines, at the Institute of Immunology, Faculty of Medicine, National University of Colombia in Bogota and as postdoctoral fellow at New York University School of Medicine. He joined the Lausanne branch of the Ludwig Institute for Cancer Research in 1989. He is currently a Member of the Ludwig Center for Cancer Research, leads the Translational Tumor Immunology Group at the Ludwig Center and is Director of the Division of Fundamental Oncology at the Lausanne University Hospital and is the Editor-in-Chief of the Journal for Immunotherapy of Cancer.

Research interests

The Romero group studies tumor antigens, human anti-tumor T cell responses and the development of immunotherapy of cancer. It combines the use of mouse models with studies in cancer patients, mainly melanoma. A major focus is on the study of molecular events regulating T cell expansion and differentiation.
Recent scientific contributions

We addressed the role of molecularly defined adjuvants, TLR agonists, in modulating the ratio of antigen specific effector to regulatory T cells upon immunization with long synthetic peptides containing both MHC-I and MHC-II restricted tumor antigens. We found that two TLR agonists, poly(I:C) engaging TLR3 and CpG-ODNs, engaging TLR9, are very efficient at driving a high ratio, in favor of a strong effector T cell response, whereas QuilA or peptide alone injection leads to lower ratios as a result of increased regulatory T cell expansion.

In a separate study, we identified miR-155 as a key miRNA in controlling specific CD8 T cell immunity to viral infections, peptide vaccination and cancer. The expression of this miRNA is upregulated soon after TCR engagement by antigen in naïve T cells. Its expression contributes to the accumulation of responding CD8 T cells via both promotion of T cell division, proliferation and decreased activation induced T cell death. A relevant mRNA target turned out to be SOCS-1, leading to an increased sensitivity of activated lymphocytes to signaling through the γ-common chain cytokine receptors, e.g. IL-2R and IL-15R. Importantly, we could show that overexpression of miR-155 in tumor antigen specific CD8 T cells greatly enhances their therapeutic potential in an adoptive cell transfer therapy setting.

Future focus and expectations

This year the focus is on extending the miR-155 research in two directions: (i) assess the expression levels and clinical relevance of miR-155 in CD8 tumor infiltrating T lymphocytes in patients with melanoma, in different clinical settings, (ii) seek proof-of-principle in pre-clinical models that addition of miR-155 to CAR-encoding retroviral vectors improves the therapeutic efficacy of reprogrammed human CD8 T cells against xeno-grafted human tumor cell lines.

We will also focus on assessing the role of mTOR signaling on tumor specific CD8 T cell differentiation and on the role of innate lymphoid cells in human cancer.

SELECTED PUBLICATIONS

Nathalie Rufer
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Funding sources
- Swiss National Science Foundation
- Swiss Cancer League
- Emma Muchamp Foundation
- ISREC Foundation
- Instituts de recherche en santé du Canada (IRSC)

Biography
Dr. Nathalie Rufer received her PhD from the University of Geneva in 1996. She carried out post-doctoral work in the laboratory of Peter Lansdorp (Terry Fox Laboratory, Vancouver, Canada), before joining in 2001, the Swiss Institute for Cancer Research as an associate scientist within the Lausanne Oncology program. Since 2009, she has been appointed by the Lausanne University Hospital Center (CHUV) and affiliated to the Ludwig Center for Cancer Research. In 2012, Nathalie Rufer finished her full education in clinical medicine at the University of Lausanne and joined the newly formed Department of Oncology led by Prof. George Coukos.

Key research collaborations
- CHUV-UNIL: D. Speiser, P. Romero, I. Luescher, O. Michielin
- UNIL: M. Thome
- T. Schumacher, Netherlands Cancer Institute (NL)

Research interests
The Rufer lab studies T-cell responses against tumor antigens in cancer patients following therapeutic vaccination and naturally occurring immune responses, with the major goals to identify the most efficient anti-cancer T cells, to advance our knowledge of T-cell mediated protection from human diseases and to improve T-cell based therapy in the fight against cancer.
Recent scientific contributions

The Rufer group investigates on approaches to optimize the T-cell receptors (TCR) with the aim to increase their affinity for cognate tumor antigens. We recently generated tumor-specific T lymphocytes expressing sequence-optimized TCRs and showed that T-cell responses against cancer cells could be specifically improved. Remarkably, we found an unexpected functional attenuation of T-cells expressing very high TCRs affinities, related to the presence of inhibitory regulators restricting cell activation and signaling (1). Understanding T-cell regulation and identifying optimized tumor antigen-specific TCRs directly contributes to the rational development of adoptive cell therapy (2). Additional research topics include assessing the memory and cell-survival attributes using the long-lived and protective Epstein-Barr virus model. We developed a highly sensitive and specific assay for single T-cell gene expression profiling (3) and identified a memory-associated gene expression signature characterizing the persisting virus-specific T-cell clonotypes (4).

SELECTED PUBLICATIONS


Future focus and expectations

We are pursuing our efforts to characterize the mechanisms controlling T cell activation and signaling in affinity-optimized tumor-specific T cells, with a special emphasis on TCR-mediated proximal signaling molecules and regulators. Using a large database of well-defined anti-cancer T cell clonotypes from melanoma patients, we are also studying the causal link between TCR affinity, T cell selection/amplification, T cell function and T cell survival against tumor cells.
Marc-Olivier SAUVAIN

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CHUV

Biography

After medical studies at the Universities of Lyon Nord (France) and Geneva where he graduated in 2001, Marc-Olivier Sauvain defended his PhD in 2009 at the EPFL, Lausanne, on lentiviral-mediated transgenesis. He then was a resident at the University Hospital of Zurich in various divisions or units including Visceral and Transplant Surgery, Gynaecology, Intensive Care Unit, Thoracic Surgery. He was appointed Chief resident from 2009 to 2010 at the Walenstadt Hospital in St-Gallen, and from 2011 to 2013 at the General Surgery Clinic of the HFR Fribourg-Kantonsspital. He currently is a surgeon in the Service of Visceral Surgery under the direction of Prof. Nicolas Demartines.

Research interests

Currently, the TNM classification is used to stratify oncological patients into classes of risks based on the histo-pathological features of tumors. However, it offers only a limited predictive value of tumor response to therapy. In addition, the TNM classification cannot be applied pre-operatively on tumor biopsies. Growing evidence shows that a new score based on the immune contexture around and within the tumor has a prognostic value superior to and independent from the TNM classification for CRC. This score also requires the analysis of the surgical specimen. We assume that the combination of a limited immunoscore on pre-operative tumor biopsies of CRC combined with the analysis of the level expression of five immunogenes will result in a new pre-operative score with good predictive value. This new score will help to identify sub-classes of high-risks patients who will benefit most from neoadjuvant therapies.
Recent scientific contributions

The histo-pathological examination of tumors shows an important infiltrate of inflammatory and lymphocytic cells. These cells reside not only within but also around the tumor where tertiary lymph nodes are formed. These intricate interactions reflect the importance of the immune system in controlling tumor spreading. It is known that colorectal cancers inducing a potent lymphocytic reaction are associated with improved long-term prognosis. Interestingly, this increase in survival seems independent of patient characteristics or other related molecular variables including KRAS mutation or the number of tumor containing lymph nodes. A recent study revealed a non-random distribution of immune cells within and around the primary tumor.

In 2013, we launched our retrospective analysis of patients with primary American Joint Committee on Cancer (AJCC) stage I to IV who underwent primary tumor resection with curative intent within 6 months of diagnosis during the years 2006 to 2013. As the immunoscore is a new method not yet available at the CHUV, we developed a protocol with the collaboration of the service de pathology and Prof J. Galon that allows rapid quantification of the immunoscore on paraffin-embedded tumor slices. As the immunoscore could become part of the routine oncological work-up performed on oncological patients, we calibrated our protocols to be as automated as possible without interfering with the guidelines published by the international immunoscore task force in 2012. To date, the immunoscore was validated on post-surgical specimen but not on tumor biopsies. Thus, we performed the immunoscore on tumor biopsies using the same protocol with encouraging results. However, the use of immunoscore on tumor biopsies does not reach the predictive value of the immunoscore on surgical specimen. Thus, we combined the immunoscore with the quantification of selected gene activation, developing a RT-PCR protocol from RNA extracted from the tumor and from the microenvironment separately in old paraffin-embedded samples. Our preliminary data shows that selected genes of interest are expressed in the microenvironment and not within the tumor.

SELECTED PUBLICATIONS


Future focus and expectations

We aim to focus on:
- The definitive validation of our immunoscore technique by Prof. J. Galon
- The analysis of our cohort of patients with primary American Joint Committee on Cancer (AJCC) stage I to IV who underwent primary tumor resection with curative intent within 6 months of diagnosis during the years 2006 to 2013. This analysis will contain the immunoscore on surgical specimen and biopsies when available. Moreover, quantification of genes of interest will be performed on biopsies.
- The immunoscore on surgical samples will be compared to overall and disease free survival of our cohort.
- The quantification of genes of interest will be further investigated on surgical samples following the observed differential expression pattern of genes within and around the tumor.
Markus SCHÄFER

Key research collaborations

- Dr. Pu Yan, Pathology University Institute, CHUV (CH)
- Dr. Anna Wagner, Service of Medical Oncology, CHUV (CH)

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Biography

Markus Schäfer got a broad surgical and scientific training at the university hospitals of Berne and Zurich before he started in 2009 as a senior consulting surgeon (team leader) for upper GI and pancreas surgery in Lausanne. He made major contributions to the successful development of oncological surgery in Lausanne to a leading national cancer center. In addition, he is the program director of the surgical resident program, as well as the head of clinical research of the Department of Visceral Surgery. He published over 100 papers and he is member of important national and international societies and Editorial Boards.

Research interests

Clinical cancer research is focused on perioperative risk factors and tumor characteristics determining outcome and the role of neoadjuvant treatment in pancreatic and esophageal cancer. Tailored approaches for an individualized cancer treatment represent ultimate goals.

A further interest is the perioperative stress response and the possibilities to control it by nutritional interventions and drugs.
Recent scientific contributions

**Pancreas:**
Current TNM classification considers tumor size only to distinguish T1 vs. T2 tumors. We showed that tumor size is also important in T3 tumors, meaning that “small T3” (<20mm) have significantly better survival than “large T3” (>20mm). We also could demonstrate that severe postoperative complications, especially in patients at risk for early tumor recurrence (e.g. R1/2) shorten survival. Finally, we contributed to the ERAS guidelines on pancreatectomy.

**Esophagus:**
We could demonstrate that active smoking is the single most important factor that negatively impacts on postoperative complications after oncological esophagectomy. In addition, we showed that increasing the number of risk factors (malnutrition, alcohol consumption) is associated with an increased postoperative morbidity.

**Health care economics:** We could demonstrate that ERAS programs for colorectal surgery are highly cost-effective. We also proved the cost-effectiveness of immunonutrition in GI cancer patients.

**SELECTED PUBLICATIONS**


**Future focus and expectations**

Regarding the pancreas, the role of major venous tumor infiltration on survival rate and preoperative MRI to precisely predict tumor margins to identify patients at risk for incomplete resections are actually under investigation.

For esophagus, the role of down-staged lymph nodes is being investigated. PET-CT is analyzed regarding the prediction of tumor characteristics.
Viesturs SIMANIS

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Funding sources
- Swiss National Science Foundation

Biography

Viesturs Simanis was awarded a degree in Biochemistry from Imperial College London. He carried out his doctoral studies with David Lane at Imperial College, London University, and postdoctoral studies with Paul Nurse (London and Oxford). He has been a group leader at ISREC since 1988. In 2006 he was appointed Associate Professor in the School of Life Sciences at EPFL.

Research interests

The laboratory is interested in the regulation of cell division in the mitotic cycle and meiosis. All cells arise by division. Failure to coordinate cell cycle events properly and execute them with high fidelity can lead to death of the progeny of a division event, or alterations of the genome which can contribute to the genesis of tumors. We use a simple model system, the fission yeast S. pombe, to study how cell division (cytokinesis) is coordinated with chromosome segregation (mitosis). As these are mechanistically conserved processes, our findings should be applicable to understanding how division is controlled in human cells.
Recent scientific contributions

As part of a SINERGIA collaboration with the labs of Ioannis Xenarios (UNIL-SIB) and Michael Unser (EPFL), we developed a semi-automated image analysis method to study the behavior of proteins that regulate cytokinesis. This work was published as Schmitter et al.

We also contributed to a study conducted by the Hagan lab in Manchester UK, which addressed how localized activity of key mitotic regulatory protein kinases contributed to determining the timing of mitotic commitment, and morphogenetic switches in dividing cells. This work was published as Grallert et al.

SELECTED PUBLICATIONS


Future focus and expectations

We are analyzing the role of regulators of cell division in meiosis, where they control “cellularization” at the end of meiosis. Our data indicate that their wiring and interactions are significantly different from those in the mitotic cycle, and we will be trying to understand the molecular basis underlying this.

Analysis of cytokinesis regulators in time and space

The image shows sequential frames of the mid-section of a dividing cell. The green signal is myosin regulatory light chain; the red signal is a regulator of cytokinesis. Note that the regulator lags behind the leading edge of the contractile ring, where it is presumed to coordinate the process of laying down membranes and dividing the cell.
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Funding sources
- Swiss National Science Foundation
- Commission for Technology and Innovation
- Novartis
- Dreyfuss
- UNIL-FBM

Biography
Christian Simon obtained his medical degree from Medical School University of Hamburg Germany, in 1996. After a postdoctoral fellowship at M.D. Anderson Cancer Center, USA, from 1996 to 1998 and a residency in Otorhinolaryngology at the University of Tuebingen, Germany, he was a fellow in Head and Neck Surgical Oncology at M.D. Anderson Cancer Center and Washington University, Saint-Louis, USA, from 2002 to 2004. Then, he has been consultant surgeon in the Department of Otorhinolaryngology at the University of Heidelberg, Germany, for 8 years. Fellow in Otology and Neurootology at the University of Minnesota, USA, in 2008-2009 and vice-chairman of the Otorhinolaryngology Department, University of Heidelberg, he became Chairman of the Service of Otorhinolaryngology at CHUV-UNIL in 2012.

Research interests
Prof. Simon’s research interests focus on:

a. Surgical trials in Head and Neck Cancer
b. Techniques for head and neck surgical reconstruction
c. Minimally invasive surgical approaches to Head and Neck Cancer (i.e. TORS, TLM)
d. Biology of invasion and metastasis of head and neck cancer
e. Biology of recurrence after surgical interventions
Recent scientific contributions

An oncological research platform has been developed within the service (see HNCR-Lab), which aims at deciphering mechanisms and cell populations underlying recurrence formation of HNSCCs after surgery including the role of the immunological and non-immunological microenvironment using various animal models.

In a collaborative activity with various services in the CHUV (CHV, OBG, URO) and the Hospital La Source, a robotic surgery platform has been developed, which allows for trans-oral robotic surgery and other robotic ORL-procedures.

Through synchronizing large patient databases in the service, a common ORL-Oncology patient database has been created, that includes data on all complex reconstructions and that will contain quality-of-life and symptom-burden data.

Future focus and expectations

Analysis of data from synchronized databases in the service will provide evidence on strengths and weaknesses of current oncological practice. Clinical (windows) trials in collaboration with EORTC and GORTEC will help to define the role of trans-oral surgery and targeted therapies in the neo-adjuvant setting of surgical patients. Novel treatment approaches developed in the HNCR-Lab through regulating signaling pathways in control of invasion and metastasis will be tested on this trial platform.

SELECTED PUBLICATIONS

4. Behren A. et al. Phenotype-assisted transcriptome analysis identifies FOXM1 downstream from Ras-MKK3-p38 to regulate in vitro cellular invasion. Oncogene. 2010
Daniel SPEISER

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Funding sources

- Swiss National Science Foundation
- Swiss Cancer League
- ISREC, Kummer & Tossizza Foundations
- European Community
- Campbell Family Institute, Canada
- Cancer Research Institute, USA

Key research collaborations

- Dirk Busch, Technical University (DE)
- Patrick Hwu, MD Anderson CC (USA)
- Pam Ohashi, Ontario Cancer Institute (CA)
- Melody Swartz, ISREC EPFL (CH)
- Michel Gilliet, Dept. Dermatology CHUV
- Alfred Zippelius, University of Basel (CH)

Biography

Daniel Speiser, born in Zürich Switzerland, graduated in 1982 and received a Doctorate in Medicine in 1986 at the Univ. of Zürich. He is a board certified clinician in internal medicine including immunology and (hemato-) oncology. In research, he specialized in infection and tumor immunity, starting with 5 yrs training in the laboratory of Rolf Zinkernagel. Then he extended his experience to basic and clinical immunology and habilitated at the University of Geneva in 1995. During his career, Daniel accomplished many R&D projects, for example by developing experimental immunotherapy in mouse models with naturally arising pancreatic tumors, with Pam Ohashi and Tak Mak at the Ontario Cancer Institute, Univ. of Toronto, Canada.

Research interests

The Speiser group develops novel strategies for clinical trials and patient investigation. The studies assess very large numbers of biological parameters (molecular, cellular, in situ, clinical), providing insights in basic mechanisms, and in mutual interdependence of oncogenic, angiogenic, inflammatory and immunologic pathways, and their impact on clinical outcomes.
Recent scientific contributions

Based on our studies identifying novel oncogenic drivers in human melanoma, we discovered new therapy resistance mechanisms. We found that multiple escape pathways to oncogene (mutated BRAF) inhibition were operational even within one single patient. Of high clinical relevance is the fact that escape is less a problem with immunotherapy, likely because it can be designed to target large numbers of antigens. For the first time, we have shown that “checkpoint targeting” with anti-CTLA-4 antibody induces T cells with novel specificities in melanoma patients. This broadening to more antigens is likely important for the long-term success of anti-CTLA-4 therapy. By further studying T cell biology, we obtained solid evidence that effector T cells in tumor tissues are functional, despite that they display the hallmarks of “exhaustion”. Further, we developed a novel T cell receptor for adoptive cell therapy, targeting the highly specific tumor antigen SSX-2. We performed clinical studies with vaccination and with an immune-cytokine showing promising anti-tumor activities. In our studies, we are generating extra-ordinarily broad and detailed data from the melanoma patient’s tumor and immune biology. The results allow characterizing the therapy effects in detail, based on which we design novel combination therapies that have high potential for clinical efficacy with limited toxicity.

Future focus and expectations

Lymphoid structures are exploited by tumor cells and immune cells, pointing to multiple roles in tumor biology. In ongoing clinical studies and research, we elucidate the roles of lymphangiogenesis in the tumor microenvironment and draining lymph nodes. We develop new techniques for the analysis of myeloid and lymphoid human cells. Our recent molecular screen suggested novel roles for transcription factors that we are verifying in animal models. In parallel, we explore powerful human anti-viral vaccines, with the aim to identify key mechanisms that can further enforce tumor-specific immune responses in patients.

SELECTED PUBLICATIONS

12. S. Gillessen, Eur J Cancer 49, 35.
15. T. Fagerberg, PLoS ONE 8, e65590
17. J. Laurent, J Transl Med 11, 5.
Olivier SPERTINI

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Biography
Olivier Spertini is born in Switzerland and received a diploma of Medicine (1981) and a MD degree (1983) from UNIL. He was trained in internal medicine and Hematology at CHUV (FMH in internal medicine and hematology in 1990, FAMH in hematology in 2001). He worked at the Dana Farber Cancer Institute (Division of Tumor Immunology, Harvard) from 1989 to 1991 and joined the Service of Hematology as clinician in 1991. He developed research focused on normal and malignant leukocyte adhesion and participated in international clinical trials on acute leukemia, chronic myeloid leukemia and myelodysplastic syndromes.

Research interests
Our laboratory studies the mechanisms which control leukocyte adhesion to vascular endothelium and adhesive interactions of hematological malignancies with bone marrow microenvironment promoting cell proliferation, survival and drug resistance. These studies are aimed at elucidating mechanisms which contribute to promote leukemia and multiple myeloma cell dissemination and growth, and to identify new therapeutic targets.
Recent scientific contributions

Our laboratory continued to investigate the mechanisms which control the interactions of multiple myeloma and acute leukemia cells with endothelial selectins. We identified several ligands of E-selectin which support leukemia and multiple myeloma cell rolling and initiated studies to investigate whether these ligands generate intracellular signals which promote cell proliferation and survival.

In addition, we analyzed PSGL-1 structure-function relationships by constructing mutants by swapping CD44 and PSGL-1 extracellular or cytoplasmic domains and generating deletion mutants devoid of highly evolutionary conserved sequences of the cytoplasmic domain with goal to identify PSGL-1 sequences controlling PSGL-1 export from the endoplasmic reticulum to cell surface as well as motives involved in regulating MAPK and Src family kinase pathway activation.

Future focus and expectations

We will keep investigating selectin ligand-induced signaling in leukemia and multiple myeloma cells with the goal of identifying new targets promoting cell proliferation, survival and drug resistance.

We plan to identify PSGL-1 sequences involved in Src family kinase pathway activation and PSGL-1 export to cell surface.

SELECTED PUBLICATIONS

Ivan STAMENKOVIC

Funding sources

- Swiss National Science Foundation
- Oncosuisse
- ISREC Foundation
- MEDIC Foundation

Key research collaborations

- Miguel Rivera, Mario Suva, Bradley Bernstein, Dept. of Pathology MGH (USA)
- Paolo Provero, San Raffaele Institute (IT)
- Shyamala Maheswaran and Daniel Haber, MGH Cancer Center (USA)

Biography

Ivan Stamenkovic received his MD from the University of Geneva (1978). After specializing in internal medicine and pathology (1978-1985), he did a postdoctoral fellowship at the Massachusetts General Hospital, in the Department of Genetics, Harvard Medical School. From 1988 to 2001 he was on the faculty of the Department of Pathology at Harvard Medical School and served as Director of Experimental Pathology at MGH. He currently directs the Experimental Pathology Service at CHUV/University of Lausanne and served as Vice-Dean of research of the Faculty of Biology and Medicine of the University of Lausanne (2007-2012).

Research interests

We investigate sarcoma development and progression using mouse models and primary human tumor xenografts. Our aim is to understand sarcoma origins and pathogenesis with the goal of developing novel mechanism-based therapeutic strategies. We are also studying the role of mesenchymal stem cells in tumor-host interactions in a variety of cancer types.
Recent scientific contributions

We are investigating the pathogenesis of Ewing and synovial sarcoma, focusing on the mechanisms whereby the fusion proteins associated with these tumors promote transformation, nuclear reprogramming and the emergence of a cellular hierarchy that includes cancer stem cells. Understanding of these mechanisms should lead to the design of rational, mechanism-based therapies that can be introduced to the clinic. In addition, we are studying metabolic differences among tumor cell subpopulations, focusing on Ewing sarcoma and glioblastoma in an effort to determine metabolic distinctions between cancer stem cells and the bulk tumor cell population. A third area of investigation is the tumor microenvironment where we are addressing the role of myeloid derived suppressor cells in the dissemination of tumor cells of diverse histotypes; and that of mesenchymal stem cells in the progression of a variety of tumors, including lung and bladder cancer as well as sarcomas.

SELECTED PUBLICATIONS


Future focus and expectations

Currently, we are focusing on: epigenetic mechanisms that underlie cancer stem cell emergence in Ewing and synovial sarcoma; regulators of OXPHOS and glycolysis in glioblastoma subpopulations; MSC regulation of lung cancer progression and cancer stem cell maintenance.
Margot THOME-MIAZZA

Funding sources
- Swiss National Science Foundation
- Oncosuisse
- Swiss Cancer League

Key research collaborations
- Georg Lenz, Charité, Berlin (DE)
- Louis Staudt, NCI, Bethesda (USA)

Biography
Margot Thome-Miazza studied Biochemistry at the University of Tübingen (Germany) and the University of Arizona (USA), and carried out her PhD work on lymphocyte activation in the laboratory of Oreste Acuto at the Pasteur Institute (Paris, France). As a postdoctoral fellow with Jürg Tschopp (University of Lausanne, Switzerland), she identified human and viral FLIP proteins as key apoptosis regulators. Since 2009, she has been Associate Professor at the University of Lausanne. Her present work focuses on the study of signaling pathways that control lymphocyte activation and the development of B-cell lymphomas.

Research interests
Our main research interest is the identification of novel signaling mechanisms that control lymphocyte proliferation and the development of B-cell malignancies.
Recent scientific contributions

In 2013, we published that the protease MALT1 is activated by monoubiquitination, and showed that this mechanism is relevant for the growth of diffuse large B-cell lymphomas of the activated B-cell subtype (Pelzer et al., 2013). In addition, we generated a mouse model to assess the therapeutic usefulness of catalytic MALT1 inactivation (Jaworski et al., submitted).

We also contributed to studies of the laboratory of Georg Lenz, which revealed key roles for the anti-apoptotic protein MCL1 in therapy resistance of diffuse large B-cell lymphomas (Wenzel et al., 2013) and an essential role for the atypical IkB family member IkB-zeta in the ABC subgroup of diffuse large B-cell lymphoma (Nogai et al, 2013).

Future focus and expectations

The main focus of our research in 2014 is to identify proteins that are critical for the regulation of MALT1 activity, and to characterize novel MALT1 substrates that are essential for lymphocyte proliferation in the immune response and development of B-cell malignancies.

SELECTED PUBLICATIONS


Experiment addressing the requirement of MALT1 activity and monoubiquitination for the growth of the lymphoma cell line OCI-Ly3. Cell growth of MALT1-deficient cells (green curve) was restored upon expression of wild-type MALT1 (red curve), but not upon expression of catalytically inactive (C464A) or monoubiquitination-deficient (K644R) MALT1 mutants (blue curves). *From Pelzer et al., Nature Immunol. 2013*
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Funding sources
- Swiss National Science Foundation
- Novartis Foundation

Key research collaborations
- Prof. Gian-Paolo Dotto, Department of Biochemistry, UNIL
- Prof. Tatiana Petrova, Department of Biochemistry, UNIL
- Prof. Pedro Romero, LICR@UNIL
- Prof. Vladimir Kalinichenko, Cincinnati Children’s Hospital Medical Center (USA)

Biography
Genrich Tolstonog, born in Tashkent, Uzbekistan, received a M.Sc. degree in Biochemistry from Russian State N.I. Pirogov Medical University, Moscow (1993), and a Ph.D. in Cell Biology from Heidelberg University, Germany (1997). He worked at Max Planck Institute for Cell Biology in Ladenburg, Germany from 1994-2003 as graduate student and then as senior scientist, and from 2003-2012 at Heinrich-Pette-Institute, Leibniz Institute for Experimental Virology, Hamburg, Germany as project leader. He has been Head of Research in the Department of Otorhinolaryngology and Head and Neck Surgery at the CHUV since 2012.

Research interests
The Head and Neck Cancer Research (HNCR) Lab investigates in oral orthotopic mouse models the molecular and cellular mechanisms underlying invasive and metastatic behavior of head and neck cancer, aiming to develop efficient therapeutic strategies to prevent loco-regional recurrence at the primary tumor site and in the neck.
Recent scientific contributions

The HNCR lab has established xenogeneic and syngeneic mouse models of HNC to identify critical subpopulations of tumor cells (recurrent tumor initiating cells (R-TIC)) that give rise to post-surgical recurrence. Mice with established orthotopic tumors are treated as the regular patients using specifically designed microsurgical setup for ablative procedures in the floor-of-mouth/neck region. Research is dedicated to provide in vivo disease models resembling the various stages of HNC, allowing to evaluate the response to current and future treatments and treatment combinations, thus helping to individualize therapy. Aiming to improve loco-regional control the following properties of HNC are studied in the HNCR lab: invasive and metastasizing properties of orthotopically transplanted tumor cells; tumor-supporting properties of cancer-associated fibroblasts; immune surveillance; molecular determinants of HPV-induced oropharyngeal squamous cell carcinoma; tumor heterogeneity and field cancerization.

SELECTED PUBLICATIONS


Future focus and expectations

The main focus of research is, firstly, to test targeting signaling pathways involved in regulation of tumor invasive phenotype and post-surgical recurrence, and, secondly, to combine a set of distinctive anti-cancer treatments in pre-clinical mouse models, searching to identify mechanisms-based strategies, regimens, and agents that will improve control of tumor recurrence of patients with head and neck cancer.
Sheila UNGER

Key research collaborations

- Prof. Vincent Mooser, Department of Laboratories and Service of Biomedicine, CHUV (CH)
- Prof. George Coukos, Department of Oncology, CHUV (CH)
- Dr. Pierre Chappuis, Service of Oncology, HUG (CH)

Sheila Unger
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Biography
Sheila Unger received her undergraduate medical training and completed her residency in medical genetics in Canada. She did specialist certifications in medical genetics in Canada, the USA and Germany. Since 2011, her main clinical focus has been hereditary predisposition to cancer and genetic counseling and testing for patients and their families.

Research interests
Dr. Unger’s main research interest is the application of genetic testing to understand personal and population risks of cancer. By using the rapidly expanding genetic knowledge and advances in technology, she would like to better stratify people according to their personal cancer risk and offer appropriate and timely cancer surveillance.
Recent scientific contributions

Currently, my research is developing in two main directions: population screening and targeted therapy for mutation carriers.

I am interested in the field preventive oncology. This would involve screening the general population to understand the contribution of inherited genetic factors to cancer predisposition and then implementing appropriate prevention/screening strategies for patients and their families.

We have requested funding for a pilot project that would screen biobank samples for cancer predisposition genes.

We are now seeing the introduction of therapies targeted for women who are carriers of BRCA1/BRCA2 mutations, and together with Dr. Anita Wolfer, we are identifying and screening women to determine eligibility for PARP-inhibitor trials.

Quote from a BRCA1 mutation carrier:

“I don’t want to be a victim. I made a decision. I decided that... well, I’ll block its [the gene’s] path. I know that I carry the gene, OK, then I am not going to wait. No. Not this kind of fatalism. I will not end up like them [family members who died from cancer]. I’ll live my own life.”

(Anissa, 42)

SELECTED PUBLICATIONS


Future focus and expectations

The focus will be on research and implementation of personalized medicine in preventive oncology. This implies not only understanding someone’s genetic risk but also for those who develop a cancer understanding the genetics of the tumor and creating a therapy tailored to their germline and somatic mutations.
Anna Dorothea WAGNER

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Biography
After completion of her training in internal medicine at Martin-Luther University Halle/Saale, Germany in 2001 and hematology and medical oncology at the University Hospital of Jena, she joined the Multidisciplinary Oncology Center in CHUV in 2008. In 2004 and 2005, supported by a grant from the medical faculty, she worked at the Coordinating Centre for Clinical Trials at Halle as research physician, conducting Meta-analyses (Cochrane Reviews) and developing clinical trial protocols in oncology. She was nominated PD and Associate Doctor in 2013, and is responsible for the Gastrointestinal Cancer Clinic since 2011. Her research activities encompass the elaboration of clinical trial protocols and meta-analysis on gastro-intestinal cancers.

Research interests
Dr. Wagner’s clinical research interests focus on:

a. Gastroesophageal cancer
b. Hepatobiliary and pancreatic cancer
c. Colorectal cancer
d. Clinical and translational research
e. Meta-analyses

Funding sources
- German Ministry for Education and Research (BMBF)

Key research collaborations
- EORTC
- Korean Cancer Study Group
- Prof. A. Grothey, Mayo Clinic, Rochester, Minnesota (USA)
Recent scientific contributions

Elaboration of a clinical research proposal for the European Organization for the Research and Treatment of Cancer (EORTC 1203, “INNOVATION”-trial) for the perioperative treatment of HER-2 positive gastric cancer. 20% of gastric cancers are HER-2 positive. A significant survival benefit of targeted treatment with trastuzumab and pertuzumab has been shown for HER-2 positive, advanced gastric cancer, as well as for trastuzumab in the treatment of early breast cancer. EORTC 1203 is the first randomized study on targeted treatment for early HER-2 positive gastric cancer. This trial will be performed in collaboration with the Korean Cancer Study Group and is supported by an educational grant of from Roche to EORTC of 6.7 million Euros. It includes a translational research program and a separate imaging sub-study (supported by an academic grant from EORTC of 200,000 Euro), which addresses the predictive value of the early metabolic response test for the histopathologic response.

Future focus and expectations

We will finalize the protocol for EORTC study 1203 and inclusion of the first patients in Q4 2014 (see Figure for trial design). Furthermore, updates of the meta-analyses for chemotherapy on gastric cancer and anti-angiogenic treatments for colorectal cancer are in progress or planned for 2014. A title for a new meta-analysis on targeted therapies for esophageal cancer has been registered in the Cochrane library.

SELECTED PUBLICATIONS

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Funding sources
- Swiss National Fund
- Swiss Cancer League

Key research collaborations
- Olivier Michielen, SIB
- Curzio Rüegg, University of Fribourg (CH)
- Monilola Olayioye, University of Stuttgart (DE)

Biography
Christian Widmann obtained in 1991 his PhD at the department of biochemistry at the University of Lausanne. He then did a first post-doc in the laboratory of Prof. Bernard Thorens in Lausanne and then a second one in the laboratory of Prof. Gary Johnson at the National Jewish Center in Denver. He came back to Switzerland in 1999 where he started his own lab as an independent group leader at the CHUV. In 2002, he got an assistant professorship position in the Department of Cell Biology, UNIL. Since 2006, he is an Associate Professor within the Department of Physiology, UNIL.

Research interests
Our core research interest is to understand how cells sense stress and how the ensuing signals determine cell fate such as cell survival, adaptation, or apoptosis. We have characterized in particular a stress-sensing module composed of the caspase-3 protease and one of its substrates, the p120 RasGAP protein. Relevant to cancer research is our discovery that some of the RasGAP fragments produced by caspase-3 bear potent tumor sensitizer and anti-metastatic activities.
Recent scientific contributions

We have identified a short peptide within one of the RasGAP fragments produced by caspase-3 (fragment N2) that increases cell adherence to their substratum and that potently inhibits cell migration and invasion in vitro and that hampers the metastatization process in vivo.

We have discovered that DLC1, a tumor suppressor that is deleted in cancers nearly as often as p53, is the target of the anti-invasive activity of the RasGAP-derived peptide.

The identification of the peptide’s target allows us now to look for small molecules that bind DLC1 as the peptide does and to determine if these small molecules have anti-metastatic activity in vivo.

Future focus and expectations

We will further characterize the structural mode of interaction of TAT-RasGAP\textsubscript{317-326}, the RasGAP-derived peptide, with DLC1. This will be accomplished by performing hand-to-hand \textit{in silico} modeling and mutagenesis of selected residues in DLC1 and TAT-RasGAP\textsubscript{317-326}. Once sufficient information is acquired on the structural requirement for DLC1/ TAT-RasGAP\textsubscript{317-326} interaction, structure-based and ligand-based approaches will be employed to rationally design small molecules that bind DLC1 binding like TAT-RasGAP\textsubscript{317-326} does. This will be coupled to parallel assessment of the anti-invasive properties of the designed small molecules.

SELECTED PUBLICATIONS

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### Biography

After obtaining her medical diploma from the University of Lausanne in 1998, she spent three years in basic science working at the Ludwig Institute for Cancer research on elucidating the role of Notch1 during murine T cell development. She then went back to clinical medicine to train in internal medicine and medical oncology until she moved to Boston in 2006. There she spent four years as a postdoctoral fellow at the MGH Cancer Center studying the underlying biology of poor outcome gene expression signatures in oncology. She has been back in Lausanne since 2010, where she has been working as “cheffe de clinique” in gynecological malignancies and also been leading a small research group interested in understanding the role of MYC in metastasis.

### Research interests

Breast cancer is the most frequent cancer and the leading cause of cancer death in women in Switzerland. Death from cancer is usually due to the dissemination of the cancer into other organs of the body, different from the one where it originally arises. This is called metastatization and our group is interested in understanding the mechanisms underlying this process in order to develop methods to control it and propose new treatments for women with advanced breast cancer.

### Funding sources

- MEDIC Foundation
- Oncosuisse
- Mercier Foundation for Science
- San Salvatore Foundation
- Leenaards Foundation
Future focus and expectations

We are currently expanding the number of cancer cell lines with MYC knock-down to study its effects on proliferation and invasion in vitro, as well as on metastasis in vivo in xenograft models. In the next step, we will analyze these cell line pairs on a genome-wide level for RNA, miRNA and protein expression. In addition, we are studying RGD-peptides targeting tumor vessels conjugated to different cytotoxic molecules in order to target the therapy and decrease systemic effects while increasing delivery to the tumor itself.

SELECTED PUBLICATIONS


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Funding sources

- The SIB, UNIL/EPFL/UNIGE/UNIFR/UNIBE fund in part Vital-IT’s infrastructure and additional funding is provided by other national and international funding bodies, including industry.

Key research collaborations

- CHUV-UNIL: George Coukos, Vincent Mooser, Olivier Michielin, Thierry Buclin, Jean-François Delaloye
- EPFL-ISREC: Michele De Palma, Viesturs Simanis, Pierre Gönzcy
- LICR-SIB: Mauro Delorenzi

Biography

Ioannis Xenarios manages the Vital-IT and Swiss-Prot groups, which are two major groups of the SIB Swiss Institute of Bioinformatics. Trained as an immunologist and as a bioinformatician, he has a long experience in data analysis –omics related data as well as in maintenance and development of computational and bioinformatics resources.

Research interests

With a multi-disciplinary team of more than 50 scientists and technical staff with education backgrounds covering biology, biochemistry, medicine through to physics, computer science and business administration, Vital-IT has the unique capability to support research projects by providing informatics resources and analysis expertise to scientific partners from various Swiss universities and research laboratories worldwide.
Recent scientific contributions

Vital-IT provides a wealth of IT hardware resources and software services to partners and users. Per year, more than 3700 compute cores and 2.5 Petabytes of distributed storage (incl. HSM) are made available to the research community, and Vital-IT users run more than 10 million jobs and consume more than 5 million CPU hours.

Vital-IT bioinformatics service and support were provided to various collaborators in Switzerland and worldwide through joint research projects. Vital-IT enables and supports life and medical science research in multiple domains such as behavior, ecology, genetics, genomics, metagenomics, pharmacodynamics, phylogeny, population genetics, proteomics, structural biology, systems biology, amongst others. Some of the on-going projects are listed on Vital-IT's web site:
http://www.vital-it.ch/projects/project_list.php


SELECTED PUBLICATIONS


Future focus and expectations

Given the increasing amount and complexity of biological data generated among the different scientific groups, there is a growing need for training highly qualified personnel and for developing, coordinating and maintaining high-performance level computational resources enabling (Big Data) large-scale data analysis and management. Through its active participation to the European infrastructure for biological information ELIXIR, Vital-IT will contribute to building a sustainable support for life science research in Europe.
15. PUBLICATIONS 2014


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