Cédric Blanpain
Université libre de Bruxelles

Mechanisms controlling tumor heterogeneity in squamous cell carcinoma.

Squamous cell carcinoma is the second most frequent skin cancer affecting more than 500,000 patients each year in the world. It is the most frequent tumor type in oral cavity, head & neck, as well as esophagus cancers. Using state of the art genetic approaches in mice, we will define the influence of the cancer cell of origin in regulating tumor heterogeneityand we will investigate the relation between tumor initiating cells, cancer stem cells, and tumor propagating cells. We will study the cellular and molecular mechanisms that control tumor heterogeneity and epithelial-mesenchymal transition (which leads to the acquisition of invasive properties) and their importance in controlling metastasis. Finally we will assess how tumor heterogeneity influences the response to medical therapy. The answer to these questions will have important implications for the development of future strategies to treat invasive cancers in humans.

Alain Chariot
Université de Liège

Dissecting oncogenic pathways

Cancer is a highly heterogeneous disease characterized by thousands of mutations affecting tumor cells. These genetic alterations ultimately impact on a dozen of oncogenic pathways that sustain cell proliferation, survival, dedifferentiation and invasion. Hence, understanding why those oncogenic pathways are constitutively activated in cancer is of paramount importance to define new therapeutic targets and to circumvent resistance to targeted therapies. We will focus on yet largely unknown oncogenic pathways. We will focus on molecular components of these pathways and assess how their genetic inactivation slows down tumor development. We will also explore whether and how these oncogenic proteins promote resistance to targeted therapies.

Jean-François Collet
Université catholique de Louvain

Discovering the molecular mechanisms involved in the protection of the bacterial cell envelope from stress: a step towards the design of new antimicrobial drugs.

Gram-negative bacteria are surrounded by a complex cell envelope, a barrier essential for cell shape and growth. Proteins important for its integrity are attractive targets for new antibiotics. However, developing new drugs targeting the envelope requires a deep understanding of the biology of this cellular compartment. Over the last 10 years, our laboratory has made important contributions to the unraveling of the pathways involved in the assembly and protection of the envelope. We want to understand the molecular details of stress-sensing mechanisms that allow bacteria to monitor envelope integrity. Our work will contribute to the development of new antibiotics which are urgently required as new bacterial strains, resistant to current antibiotics, emerge.

Alban de Kerchove d'Exaerde
Université libre de Bruxelles

Genetic Identification of the neural circuits involved in Attention deficit/ Hyperactivity disorders (ADHD).

Attention-deficit/hyperactivity disorder (ADHD) is a chronic condition that affects millions of children and often persists into adulthood. Symptoms include difficulty staying focused, lack of inhibitory control and hyperactivity. The origin and pathophysiology of ADHD remain largely unkown. The pharmacotherapeutics of ADHD are essentially based on the administration of psychostimulants. These drugs which normally stimulate arousal in healthy individuals, have opposite calming effects in ADHD patients. Importantly, the neural mechanisms underlying these paradoxical alleviating effects are poorly understood limiting new strategies to improve therapeutic efficiency.
We will study the neural circuits involved in ADHD and in the mechanisms of action of psychostimulants. We aim at identifying functional circuits responsible of ADHD and involved in the calming effect of psychostimulants. Our work should contribute to the understanding of the pathophysiology of ADHD and identify new, better targeted, therapeutic approaches, avoiding the side effects associated to psychostimulants (growth impairment, addiction, psychosis).

Yves Dufrêne
Université catholique de Louvain

Staphylococcus aureus biofilms: understanding bacterial adhesion and developing new anti-adhesion strategies.

Staphylococcus aureus is an important bacterial pathogen which is a leading cause of biofilm-associated infections on indwelling medical devices. Biofilm infections are difficult to eradicate because many cells within the biofilm are dormant and resistant to multiple antibiotics (*e.g.* methicillin-resistant *S. aureus* strains). Our goal is to answer the following questions: what are the molecular mechanisms underlying biofilm formation by *S. aureus*? How can we optimise the use of anti-adhesion compounds to inhibit biofilm formation? To this end, we will use a new tool from nanotechnology, *i.e.* the atomic force microscope, combined to microbiology methods. The results will pave the way to the discovery of a new anti-adhesion therapies targeting biofilms, as a complement to antibiotics.

Decio L. Eizirik
Université libre de Bruxelles

Beta cell splicing signature of diabetes.

Most eukaryotic genes are composed of multiple coding regions (exons) interrupted by non-coding regions (introns). To transform the pre-mRNA into a mature mRNA, introns must be removed and exons ligated. This is called splicing. Many genes exhibit alternative splicing , which occurs only at the level of a selection of specific intron-exon boundaries. Alternative splicing affects more than 95 % of human genes. Recent findings by our group indicate that splicing is modified in pancreatic beta cells in the early stages of type 1 diabetes, an autoimmune disease where the immune system “goes wrong” and starts attacking the insulin-producing beta cells.
We will use advanced bioinformatics and molecular biology techniques to define the regulatory splicing networks that modulate beta cell alternative splicing under basal and inflammatory conditions. We will characterize inflammation-induced splice variants as beta cell biomarkers or as modulators of cell survival. We will develop novel approaches to modulate alternative splicing in pancreatic beta cells, with the aim to prevent their destruction in early diabetes.

Benoît Van den Eynde
Université catholique de Louvain.

Finding new immunotherapy targets in the tumor microenvironment by in vivo shRNA pool screening in autochthonous melanomas and by studying hypoxia-driven immunosuppression.

Oncology is currently living a true revolution thanks to a new therapeutic approach called immunotherapy, which increases immune responses against cancer cells. These new therapies already save lives of advanced cancer patients afflicted with melanoma or lung cancer. However, these responses only occur in 20 to 40% of patients. The aim of this project is to understand the mechanisms developed by cancer cells to resist immune rejection. To this end, we will study a mouse melanoma model that faithfully reproduces the features of the human disease. We hope to identify resistance mechanisms that we can subsequently neutralize using pharmacological agents. This should help increase the number of cancer patients who can benefit from immunotherapy.

Pierre Vanderhaeghen
Université libre de Bruxelles

Using human pluripotent stem cells to understand brain diseases and for the design of novel brain repair therapies.

Understanding the mechanisms of human brain development constitutes a fascinating and crucial challenge in biology and medicine.Novel tools and approaches need to be developed in order to tackle its complexity in health and disease.
The advent of pluripotent stem cell (PSC)-based reductionist models provides novel opportunities to model brain diseases and, in a longer prospect, for brain repair therapies. Taking advantage of our pioneering work on cortical neurogenesis from PSC, the present project aims to discover new mechanisms of human neurodevelopmental diseases, in particular malformations of the cerebral cortex and autistic disorders, and to determine how PSC-derived neural cells can contribute in an efficient way to the repair of damaged brain circuits.

Emile Van Schaftingen
Université catholique de Louvain

Metabolite repair and metabolic diseases.

Due to spontaneous reactions or to side-activities of enzymes, some classical metabolites are slowly converted to abnormal metabolites that may have toxic effects. Our work has demonstrated the importance of a process that was until then largely unknown : metabolite repair. Living cells have ‘metabolite repair’ enzymes serving to eliminate at least some of these abnormal compounds. The deficiency of such enzymes may cause cellular dysfunction and, in humans, metabolic diseases such as L-2- hydroxyglutaric aciduria (a rare neurometabolic disease). The aim of our project is to discover other metabolic repair enzymes. One of our approaches will be to identify the function of putative enzymes, of unknown function, that are mutated in some genetic diseases. Our work can help understanding human diseases and develop therapeutic approaches. It can also contribute to the improvement of bioengineering processes.

Miikka Vikkula
Université catholique de Louvain

Development of diagnostic tools for lymphedema.

Primary lymphedema is a chronic, debilitating pathology, characterized by swelling, most commonly of the limbs, due to lymph accumulation. It affects 1-2 million individuals in Europe. Current treatments are limited to lymphatic drainage, mostly performed manually and repeatedly, and surgery. There is no cure. Thus, there is an important need for improved patient care. To achieve this, we need a better understanding of the underlying causes of this pathology.
The etiology of primary lymphedema is complex, with currently at least 23 genes implicated. Yet, in two thirds of the patients the cause remains unknown.
We will use high-througput sequencing to identify and characterize genetic alterations and to analyze the mechanisms by which these alterations induce primary lymphedema. The data will directly improve differential diagnostics, prognostics and thereby, patient care. It will also pinpoint targets for personalized therapies. Moreover, the project will help uncover the molecular mechanisms controlling lymphangiogenic processes and function, important for several other disorders in which the lymphatic system plays an important role.

Christophe Desmet
Université de Liège

Study of the regulation of hematopoiesis and T cell fate through translational control.

Cell differentiation is driven by changes in the cell gene expression program. These changeare generally assessed at the level of gene transcription, which is technically the most amenable. Yet, burgeoning evidence suggests that translational control of gene expression is as prominent as transcription in determining the composition of the cell proteome.
We aim to assess the consequences of impairing specific enzymatic modules of translational control on the differentiation of hematopoietic cells and classical T cells. Hematopoietic progenitors ensure the production of blood cells throughout life, whereas classical T cells are essential cells of the adaptive immune system that contribute to protection against pathogens and cancer development. Both cell systems represent some of the best-characterized models of physiologic cell differentiation.
This project should identify radically novel mechanisms regulating cell differentiation and open wide perspectives of basic and clinical development in immunology/hematology.

Isabelle Migeotte
Université libre de Bruxelles

Role of mechanical forces and cytoskeletal rearrangements in epithelial-mesenchymal transition and cell migration at mouse embryo gastrulation.

Epithelial-mesenchymal transition (EMT) is a fundamental cell transformation process during embryo morphogenesis. It is also responsible for fibrosis, as well as cancer invasion and metastasis. We use the mouse embryo gastrulation as a model to study the cellular and molecular mechanisms of EMT followed by cell migration. We focus on the cytoskelet reorganization during EMT, on the role of proteins involved in this reorganization and on the role of mechanical constraints.
Our data suggest that cell rounding during mitosis may be a driving force for cell ingression through the primitive streak (the site of gastrulation). We will test that hypothesis through multiphoton and light sheet confocal life imaging of embryos. We will develop computer tools to refine our analysis of cell rearrangements and trajectories during gastrulation. We will study the gene expression pattern associated to this transformation. Our work will contribute to the understanding of congenital malformations and to the unraveling of complex mechanisms associated to cancer development.

Kristel Van Steen
Université de Liège

DESTINCT: DEtecting STastistical INteractions in Complex Traits.

Our understanding of human diseases biology progresses through the identification of genetic variation associated to the investigated phenotypes. These associations are often complex and involve gene-gene interactions (epistasis). Model organisms indicate that heritability attributed to gene-gene interactions may be as high as 80% for certain traits. There is no reason to assume that this would not be the case for humans. Given the increased complexity of human biology compared to the biology of model organisms, our project will invest in sophisticated epistasis detection methods, define consensus criteria for their evaluation, and bring awareness about pros and cons of each method. Large-scale epistasis studies can give new clues to genetic mechanisms and to a better understanding of the underling biology of complex human diseases, contributing to the development of personalized medicine and to diseases' risk calculation.

Valérie Wittamer
Université libre de Bruxelles

Ontogeny of microglia, the resident macrophages of the central nervous system.

Neurodegenerative diseases such as Parkinson's or Alzheimer's diseases, are often associated with neuroinflammation. The microglia cells represent a potential target for the development of novel therapeutic approaches. The microglia is indeed a population of resident macrophages in the central nervous system, which constitutes the primary immune defense of the Central Nervous System. Our project aims at characterizing microglia origin. The first steps of microglia development (ontogeny) occur early during development. We will study this process in a non invasive way in transgenic zebrafish embryos, taking advantage of their transparency. We will use state-of-the-art molecular, genetic and live imaging techniques to determine the cellular and molecular requirements for the establishment and maintenance of the microglial network in the brain parenchyme. We will utilize new and existing fluorescent transgenic lines to directly visualize in real time the emergence and fate of microglial progenitor cells (cells at the origin of the microglia). By providing new insights into the genetic control of microglia ontogeny and differentiation, our work should open new perspectives in the treatment of neuroinflammation and neurodegenerative diseases.

Interested in one of these programmes ?

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