CRCL
CENTRE DE RECHERCHE EN CANCÉROLOGIE DE LYON

Research Teams and Technological Platforms

Lyon 1

Inserm
La science pour la santé
From science to health

cnrs

CENTRE DE LUTTE CONTRE LE CANCER LEON BERARD
Chercher et soigner jusqu'à la guérison

CANCER RESEARCH CENTER OF LYON

Director
Dr Patrick Mehlen
CNRS Research Director

Member of the French Academy of Science

"One of our main goal is to support the development of a strong research to enable patients to rapidly benefit from the latest breakthroughs. This is rendered possible thanks to the strong collaboration between clinicians and pathologists of the CLB and HCL and scientific teams of the CRCL, creating a continuity between basic research and clinical applications."

4 GOVERNING BODIES
INSERM CNRS UCBL CLB

1 CLINICAL PARTNER
Hospices Civils de Lyon

24 RESEARCH
Teams

500 STAFF
150 Researchers

7 RESEARCH LABS
From Centre Leon Berard

11 TECHNOLOGICAL
Platforms

>300 PUBLICATIONS
Per year

60 PATENTED
Technologies

SCIENTIFIC ORGANIZATION

TERI

TUMOR ESCAPE, RESISTANCE AND IMMUNITY

11 TEAMS

- Oncopharmacology — Breast cancer
- Tumor immunology — Cancer and development
- Cancer cell plasticity — Melanoma
- TGF-beta — Drug design
- Molecular regulation — Cancer immunity
- Integrated analysis — Immuno-regulation

CITI

CANCER INITIATION AND TUMOR CELL IDENTITY

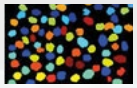
13 TEAMS

- Hepatitis viruses — Chronic liver disease
- Childhood cancers — Glioblastomas
- Senescence — Cancer and aging
- Inflammasome — Tumor microenvironment
- Cancer cell death
- Ribosome — Translation and cancer

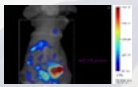
Basic Research


Cytometry


Single Cell

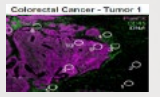

Cell Imaging


Bioinformatics


Animal Facility

Translational Research


Center for Drug Discovery


Research Pathology

Clinical Research


3DONCO


Cancer Genomics


Tumor Bank


Ex-Vivo Platform

CITI DEPARTMENT : CANCER INITIATION AND TUMOR CELL IDENTITY

Cellular senescence, cancer and aging

David Bernard


Cell death and childhood cancers

Marie Castets & Jean-Yves Blay

Glioblastoma metabolism and heterogeneity, in 3D organoids

Erika Cosset

Signaling, metabolism and tumor progression

Germain Gillet


Stemness in gliomas

Mathieu Gabut & François Ducray

Reprogramming, stem cells and oncogenesis

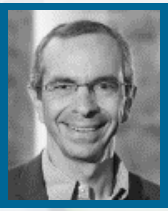
Fabrice Lavial

Epigenetics, microenvironment and liver cancer

Massimo Levrero

BMP, Ecosystem, Stemness and Dynamic in Cancer

Véronique Maguer-Satta



Hepatitis Viruses and Pathobiology of Chronic Liver Diseases

Fabien Zoulim

Genetics, Epigenetics and Biology of Sarcomas

Franck Tirode

Inflammasome and cancer

Virginie Petrilli

Cancer cell death

Gabriel Ichim

Ribosome, translation and cancer

Jean-Jacques Diaz

TERI DEPARTMENT : TUMOR ESCAPE, RESISTANCE AND IMMUNITY

Adhesion and signaling in metastatic melanoma

Julien Ablain

Tumor immune surveillance and therapeutic targeting

Christophe Caux

Molecular regulation of cancer immunity

Yenkel Grinberg-Bleyer


Endocrine resistance, methylation *and breast cancer*

Muriel Le Romancer & Olivier Tredan

Apoptosis, cancer and development

Patrick Mehlen


Cancer cell plasticity in melanoma

Julie Caramel & Stéphane Dalle


Oncopharmacology

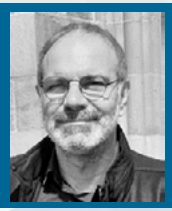
Lars-Peter Jordheim & Charles Dumontet

Small molecules for biological targets

Isabelle Krimm

TGF-beta and immune response

Julien Marie



Targeting non-canonical protein functions in cancer

Toufic Renno

Integrated analysis of the dynamics of cancer

Pierre Saintigny

TECHNOLOGICAL PLATFORMS


Cell Imaging Platfrom

Frédéric Catez & Christophe Vanbelle


Flow Cytometry Core Facility

Christophe Vanbelle & Thibault Andrieu

Cancer Genomics Platform

Qing Wang

BIological sample management platform

Séverine Tabone-Eglinger

3D-ONCO Organoids Platform

Stéphane Giraud


Research Pathology Platform

Sylvie Lantuejoul & Nicolas Gadot


Laboratory of Immunotherapy of Cancer of Lyon

Christophe Caux & Uzma Hasan


Gilles Thomas Bioinformatics Platform

Alain Viari & Anthony Ferrari


Ex-Vivo Platform

Séverine Tabone-Eglinger & Sophie Léon

Center for Drug Discovery and Development

Stéphane Giraud

Small Animal Platform - P-PAC

Isabelle Goddard

TRANSLATIONAL RESEARCH TEAMS FROM CLB


Experimental Surgery Institute

Michel Rivoire & Stéphan Langonet

Prevention Cancer Environment Department

Béatrice Fervers

Imaging and Radiotherapy (creatis)

David Sarrut

Prevention and Genetic Epidemiology Unit – LBBE
Public Health Prevention Department – Centre Léon Bérard

Christine Lasset

Human and social sciences department

Véronique Christophe

Medical Evaluation and Sarcoma/rare cancers teams (EMS)

Isabelle Ray-Coquard

Department of translational medicine

Pierre Saintigny

CENTRE DE LUTTE CONTRE LE CANCER LEON BERARD

David Bernard
david.bernard@lyon.unicancer.fr

Cellular senescence, cancer and aging

Senescent cells accumulate during aging or during exposure to stresses that promote aging (cigarette smoke, obesity, radiation, etc.) and the pathologies associated with it. These senescent cells stop to proliferate and secrete many factors that regulate the environment. They can induce fibrosis and inflammation, thus promoting many pathologies associated with aging, including cancer.

The objectives of the team are (i) to identify and characterize new mechanisms regulating cellular senescence using various cell models and inducers of senescence and (ii) to describe the role of the identified mechanisms in the occurrence of alterations / pathologies associated with aging such as fibrosis, inflammation and cancer. For these latter approaches, we use different pre-clinical mouse models.

Our work, beyond helping to better understand the biology of cancer and of aging, allows us to describe new molecular targets whose targeting could help to prevent certain pathologies, including cancer.


Marie Castets
marie.castets@lyon.unicancer.fr
Jean-Yves Blay
jean-yves.blay@lyon.unicancer.fr

Cell death and childhood cancers

Despite progress made over the last 30 years, nearly 80,000 children and adolescents die of cancer each year worldwide. In addition, 2/3 of the children and adolescents who are cured suffer from long-term sequelae related to the disease itself but also to the treatments received.

Cancers in children, adolescents and young adults therefore remain a major therapeutic challenge, making cancer the leading cause of death in young people over the age of one in France.

It is therefore urgent to propose new strategies to improve the clinical management of patients, taking into account the specificities of pediatric cancers, both in biological and epidemiological terms.

The «Cellular Death and Pediatric Cancers» team is actively part of this momentum, through different actions:

1. The creation of a national collaborative impulse, essential to efficiently progress on rare pathologies at the research level. The team thus initiated a national network of basic research in pediatric oncology React4kids, which unites French researchers. We are also leading a multi-omics data warehouse project in pediatric oncology, Share4Kids, recently financed by INCa (1M€), which will allow researchers to access a repository of data from sequencing of patients and models.
2. The development of pediatric cancer models, reproducing them in their specificity and complexity. In particular, we are currently finalizing organoid models of rhabdomyosarcoma and brain tumors, reproducing intra- and inter-tumor heterogeneity. In parallel, we are developing orthotopic graft models of sarcomas and brain tumors, to mimic the ontogenic context in which these tumors develop, and in particular the immaturity of the immune system. These models are essential to understand the etiology of pediatric cancers, but are also essential tools to test new strategies in pre-clinical and even personalized medicine approaches. In collaboration with the epidemiologists of the Léon Bérard Center, we also use them to define the role of pollutants on the occurrence of pediatric cancers.
3. Finally, we seek to identify new therapeutic targets by dissecting the oncogenic mechanisms at the origin of pediatric cancers. To this end, by combining the integration of omics data with the use of CRISPR-Cas9 strategies on organoids, we focus our efforts on the idea that developmental pathways, activated during embryogenesis, may be co-opted by tumor cells and support tumor initiation and escape.

Erika Cosset
erika.cosset@lyon.unicancer.fr

Glioblastoma metabolism and heterogeneity, in 3D organoids

Recently created at the CRCL, our team focuses on:

-the cellular and molecular mechanisms underlying cancer cell and cancer stem cell addiction to different metabolic pathways,

-the development of new cellular model (such as organoids) and new therapeutic approaches to exploit these metabolic (and non-metabolic) vulnerabilities to halt cancer progression (especially glioblastoma).

To do so, we developed innovative tools and cellular (in 2D and in 3D) model-derived from glioblastoma patients, in one hand, and pluripotent stem cell-differentiation, one the other hand. Therefore, we have developed a tissue engineering in vitro approach to generate a pluripotent stem cell-derived human brain-like tissue and organoid in 3D. We demonstrated that GBM cells proliferate and develop into these brain-like tissues, generating a mixed tissue that mimics critical and important features of the in vivo host/tumor interaction. This system represents a relevant and unique mini-brain model that can be used not only to study and understand molecular and cellular mechanisms underlying the interaction between the human neural tissue but also to screen bank of therapeutic molecules thus serving as a powerful preclinical model (as shown in our previous studies).

Germain Gillet
germain.gillet@lyon.unicancer.fr

Signaling, metabolism and tumor progression

The molecular mechanisms involved in tumor progression leading to metastasis development are still poorly understood. Epithelial-to-Mesenchymal Transition (EMT) is an embryonic trans-differentiation process frequently reactivated during cancer progression and metastasis. EMT is characterized by a spectacular increase in cell migration and invasion capacities.

Our research project aims at a better understanding of the molecular mechanisms underlying EMT reactivation and tumor progression during mammary gland tumorigenesis.
Based on animal models (zebrafish and mice) and cellular assays, our work mainly focuses on three different axes:

1- the TGFß pathway and its role in EMT,

2- the perturbations of glucose metabolism that characterize cancer cells and their consequences for tumor progression,

3- the regulation of calcium fluxes by the Bcl-2 family members.


Mathieu Gabut
mathieu.gabut@lyon.unicancer.fr

François Ducray
françois.ducray@chu-lyon.fr

Stemness in gliomas

Our team is managed by a duo composed of a neuro-oncologist, Pr. François DUCRAY and a molecular biology researcher, Dr. Mathieu GABUT.
We are primarily interested in characterizing how the most aggressive brain tumors (gliomas and glioblastomas) evolve and resist to conventional treatments resulting too often in very dark prognoses, including short survival expectancies.

To this end:

1- We first combine different approaches including multi-omics analyses of primary gliomas (transcriptomics, methylomics and proteomics) to identify new Achilles' heel to target in specific tumor subgroups.

2- We explore the molecular mechanisms underlying the activity and survival of a specific population of tumoral cells, which display undifferentiated phenotypes, and enhanced resistance to treatment: the glioma stem cells.

3- We finally develop mini brain tumor models in vitro (brain tumoroids) directly from patient-derived tumor samples and microfluidic tools to characterize and model the behavior of glioma stem cells in response to treatment or environmental changes.

What are we aiming for?

1- We are interested in further developing the microfluidics system and image analyses solutions (live imaging microscope and neural networks) used to phenotype glioma cells in order to reach single cell isolation and manipulation.

2- We will use the brain tumoroid models to test novel therapeutic approaches to target glioma stem cells and their ability to adapt to different tumor environments.

Fabrice Lavial
fabrice.lavial@lyon.unicancer.fr

Reprogramming, stem cells and oncogenesis

My lab is interested in understanding how cellular identity is controlled during development and disease. Embryonic development leads stem cells to differentiate into specialized cellular identities, characterized by specific transcriptional and epigenetic programs, and defects in the orchestration of those programs can have dramatic consequences for developing organisms.

Moreover, while cellular identities were long thought to be irreversibly established in adult organisms, recent advances indicate that those identities can be directly manipulated in vivo for regenerative purposes, for example to repair a damaged tissue. In addition, erasure of cellular identities emerged recently as an initial and critical step of the formation of a variety of cancers, for example in the lung. In that context, we combine different approaches in vitro, ex vivo and in vivo to decipher how (i) the identity of stem cells evolves naturally in the mammalian peri-implantation embryo but also how (ii) cellular identity is impacted during reprogramming to pluripotency and oncogenic transformation.

We conduct comprehensive analyses of the early molecular and phenotypic changes by combining multi-omics approaches at the single-cell level with the ultimate goal of identifying major determinants that may become targets of regenerative and/or anti-cancer therapies interfering with cellular identity.

Massimo Levrero
massimo.levrero@inserm.fr

Epigenetics, microenvironment and liver cancer

The team of Massimo Levrero has been at the forefront of the research on the epigenetic control of hepatitis B virus (HBV) cccDNA minichromosome activity, the identification of novel viral/host targets for HBV cure, the identification of viral and immunological determinants of HBV persistence and the impact of HBV viral proteins on host gene expression in chronic HBV infection and hepatocellular carcinoma (HCC) development.

Our current research efforts aim at deciphering the epigenetic changes that precede and accompany HCC development and progression in virus- and non-virus-related HCC and, in particular:

- the epigenetic changes that precede and accompany HCC development and progression with a focus on the role of histone methyltransferases in liver transformation, their interaction with long non-coding RNAs (lncRNAs) and the gut/liver microbiome, their modulation to reshape the liver microenvironment and boost the response to immunotherapy and multi-kinase inhibitors;
- the interaction of HBV, hepatitis delta virus (HDV) and hepatitis C virus (HCV) with the host epigenome.

Furthermore, our translational research program focuses on the identification of novel serological biomarkers (viral circulating RNA, circulating miRNAs) for prediction of HBV functional cure, liver disease outcome and/or HCC development.

Véronique Maguer-Satta
Veronique.maguer-satta@lyon.unicancer.fr

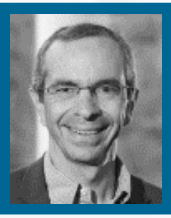
BMP, Ecosystem, Stemness and Dynamic in cancer

-What we do in the team:

We study the dialogue between stem cells and their microenvironment (mesenchymal stem cells, endothelial cells, extracellular matrix) in the mechanisms of tumor initiation, dormancy (quiescence) during chronic phases of the disease (with or without treatment) and tumor escape mechanisms. We focus on the developmental pathway of the Bone Morphogenetic Protein-BMP, environmental pollutants and biomechanics. We study pre-transformed states, myeloid leukemias (adult and pediatric) and breast cancers.

-What you might be interested in:

We have developed a fully standardized, easy-to-use, 3D microphysiological study system of human bone marrow that can be transposed to all laboratories and can be used to test the in situ targeting of cancer (stem) cells (leukemia or metastatic cells in bone). We have set up an innovative long-term cell confinement system to study the importance of biomechanics. We use samples from patients at different stages of the disease and/or under treatment, and from healthy donors thanks to physicians who are members of our team. We have thus developed numerous models for studying human cancer stem cells and cells of their microenvironment, representative of primary cells.



Fabien Zoulim
fabien.zoulim@inserm.fr

Hepatitis Viruses and Pathobiology of Chronic Liver Diseases

Hepatocellular Carcinoma (HCC) is the 5th most frequent cancer worldwide and ranks 3rd in terms of cancer mortality. Globally, chronic HBV and HCV infections are the main cause of liver disease leading to HCC, while hepatitis Delta virus (HDV) co-infection with HBV significantly accelerates disease progression. Alcohol-induced liver injury and nonalcoholic steatohepatitis (NASH) are frequent and increasing causes of HCC especially in Western countries.

Chronic HBV infection is the most prevalent chronic infectious disease worldwide with more than 250 million individuals concerned and, therefore, the first cause of HCC and a major public health issue. HBV infection is a model of viral persistence, as most infected patients never clear the viral minichromosome and bear viral sequences integrated into the host DNA. Clinical resolution of infection requires the control of persisting viral genomes and residual infected cells by the immune system. Current treatment of chronic HBV mono-infections with nucleoside analogues achieves only viral suppression, and the management of HBV/HDV co-infected patients is limited by the low response rate to interferon therapy.

As for HCV infection, although a therapeutic revolution was seen in the last few years, which largely allows patient remission, a residual risk of HCC development remains. Possible mechanisms involved in HCV-induced HCC include HCV reprogramming of liver metabolism, chronic cellular stress and inflammation, and other modulations of cell signaling pathways. The knowledge generated by studies with HCV may become relevant for the understanding of alcohol- or NASH-induced liver disease and HCC.
In this context, during the current 2021-2025 contract, research priorities based on two main axes will be developed:

1) Biology of HBV cccDNA, the viral minichromosome: towards functional silencing or degradation (B. Testoni & F. Zoulim group)
2) Molecular pathogenesis of liver diseases and predisposition to HCC (B. Bartosch, F. Lebossé & R. Parent groups)

Franck Tirode
franck.tirode@lyon.unicancer.fr

Genetics, epigenetics and biology of sarcomas

Sarcomas are a heterogeneous group of aggressive malignant tumors of mesenchymal origin that affect approximately 4,000 people per year in France. Despite their relatively low number in adults, sarcomas are responsible for more than 20% of cancer-related mortality in children and young adults.

Our team studies sarcomas on 3 levels:

1) Due to their great heterogeneity (more than 75 different histological types and more than 200 molecular subtypes) the precise diagnosis of sarcoma is often difficult. Our goal is to provide the most comprehensive molecular characterization of sarcomas using high-throughput RNA sequencing from paraffin-embedded tumor samples.

2) Some new alterations identified by RNAseq allow the discovery of new oncogenic mechanisms. We were able to show the existence of a close link between some pathognomonic fusion genes and chromatin remodeling processes. Thanks to the development of specific cellular models (mouse PDX or transgenic zebrafish) we are able to study the effects of the aberrant genes on these mechanisms, in their natural context.

3) Functional studies of some pathognomonic alterations also allow us to consider the development of targeted therapeutic approaches that we can test in our in vivo models.

Strengths: Unique collection of sarcoma expression data (+2500 RNAseq samples), expertise in bioinformatics analysis of RNAseq, expertise in epigenetics, unique animal or cell models.

Virginie Petrilli
virginie.petrilli@lyon.unicancer.fr

Inflammasome and cancer

Virginie Petrilli's team studies the links between cancer and the inflammatory response. In particular, the team has long-standing experience in the innate immune complex expressed by myeloid cells and called the inflammasome. This complex is formed when an innate immune receptor, for example NLRP3, detects a pathogen or danger signal. Its purpose is the activation of caspase-1, an enzyme responsible for the maturation and secretion of two proinflammatory cytokines IL-1 and IL-18, and for triggering an inflammatory death called pyroptosis. The team studies the mechanisms that regulate the activation of the inflammasome by developing technological approaches, and is also interested in its regulation by the circadian clock.

The team has also identified a new function for NLRP3 in lung epithelial cells. This receptor is part of the defense system against DNA damage in cells. Indeed, NLRP3 controls the activation of the ATM kinase in response to DNA double-strand breaks. Dysfunction of this pathway can lead to the accumulation of mutations that can promote the transformation of normal cells into cancerous cells. The team is currently studying how NLRP3 modulates DNA double-strand break repair pathways, and testing its anti-tumor role.

Gabriel Ichim
gabriel.ichim@lyon.unicancer.fr

Cancer cell death

Dr. Gabriel Ichim is a team leader who recently joined CRCL (2016) and INSERM (2017) to establish his own research team as part of the Laboratoire d'excellence (LabEX) DEVweCAN. Following a post-doctorate as an EMBO Long Term Fellow and EMBO Advanced Fellow at the Beatson Institute in Scotland, Dr. Ichim gained expertise in mitochondrial-driven apoptosis, caspase activation and early tumorigenesis while becoming familiar with different microscopy techniques (Ichim et al., Mol Cell, 2015; Tait and Ichim, Nat Rev Cancer, 2016; Melo, Ichim et al., Nat. Prot., 2017).

The Cancer Cell Death team focuses on investigating how cell death fuel the oncogenic process. This happens by either promoting the proliferation of bystander cancer cells (Roumane et al., BMC Cell Biology, 2018), boosting the aggressiveness of cancer cells undergoing failed apoptosis (Berthenet et al., Cell Reports, 2020; Castillo-Ferrer et al., FEBS J, 2020) or by sustaining cancer stem cell survival (Fanfone et al., Cancers, 2020).

The team is also greatly interested in addressing non-canonical functions of pro-apoptotic effectors such as caspase cysteine proteases and mitochondria: one team project deals with a novel role of caspase-3 in sustaining melanoma aggressiveness, while another investigates how proteins usually involved in maintaining mitochondrial shape can have a shadow function in epigenetic transcriptional regulation.
Overall, the Cancer Cell Death team aims at describing how cancer, aside from actively blocking cell death, can actually use apoptosis and its effectors (caspases and mitochondria) to reinforce some of its hallmarks.

Jean-Jacques Diaz
jean-jacques.diaz@lyon.unicancer.fr

Ribosome, translation and cancer

Fourty years after the demonstration that ribosomes were the effectors of translation, new evidence suggests that we are entering an exciting novel ribosomal era. Not only does it appear that ribosomes are direct effectors of translation but also that ribosomes themselves can be used in the clinic. First, recent studies revealed unexpected roles for the eukaryotic ribosome in selective translational regulation including in cancer pathology. These observations led to the concept of specialized ribosomes. This team published ground-breaking studies recognized in the “ribosome field” demonstrating that ribosomal RNAs (rRNAs) are major actors of ribosome specialization. They unraveled rRNA plasticity induced by chemical modifications (2’Ome) and demonstrated that this plasticity provides functional specificity to human cancer ribosomes favoring the translation of several genes playing key roles in cancer. By demonstrating that cancer ribosomes display specific compositions and functions, they offer novel perspectives for clinical applications. Ribosomes can be used as promising biomarkers as well as therapeutic targets.

Second, it is now clearly established that cancer cells are addicted to ribosome biogenesis, which sustains a high protein synthesis rate and thus cancer cell growth and proliferation. Several anti-cancer molecules have been developed that inhibit ribosome biogenesis and have shown strong efficacy in phase I/IIa clinical trials. The team of JJ Diaz is currently working at evaluating these molecules in aggressive adult and pediatric cancers, and developing new therapeutic approaches targeting additional ribosome biogenesis factors, as well as the mTOR signaling pathway.

The Team has a long-standing experience in basic and translational research with key know-how and actively contributes to the development of innovative technologies (RiboMETH-seq for rRNA 2’Ome, polysome profiling for whole-exome translational reprogramming, puromycilation assays for global protein synthesis, medium through-put RTqPCR dedicated to quantify ribosome biogenesis factors, molecules targeting ribosome biogenesis). JJ Diaz has deposited several international patents and the Team is involved in clinical trials to evaluate anti-viral as well as anti-cancer molecules.

Selected publications:

Diaz JJ and Roufa, DJ. A fine structure genetic map of human ribosomal protein S14. Mol Cell Biol, 12, 1680-1686 (1992).

Diaz JJ, Duc Dodon M, Schaerer-Uthurralt N, Simonin D, Kindbeiter K, Gazzolo L and Madjar JJ. Post-transcriptional transactivation of human retroviral envelope glycoprotein expression by herpes simplex virus Us11 protein. Nature, 379, 273-277 (1996).

Julien Ablain
julien.ablain@lyon.unicancer.fr

Adhesion and signaling in metastatic melanoma

The goal of the “Adhesion and Signaling” Team is to discover new vulnerabilities of cancer cells by better understanding the mechanisms underlying tumor metastasis, the leading cause of mortality in patients with cancer.

We focus on melanoma, the deadliest form of skin cancer, where the presence of metastases is associated with poor prognosis. We are particularly interested in how signals from the tumor microenvironment, such as secreted factors or the presence of other cell types, influence the adhesion and dissemination of cancer cells, and how these mechanisms can be targeted therapeutically.

To that end, we leverage the powerful genetics and unparalleled imaging capabilities of zebrafish to manipulate genes involved in the sensing of external signals and to visualize the behavior of cancer cells in situ in a well-established zebrafish model of melanoma.

In addition, the zebrafish offers a unique platform for high-throughput drug screens, which facilitates the discovery of inhibitory treatments.

We thus hope to better understand the mechanisms by which microenvironmental cues affect the behavior of cancer cells and to create new therapeutic opportunities against metastatic tumors.


Julie Caramel
julie.caramel@lyon.unicancer.fr
Stéphane Dalle
stephane.dalle@chu-lyon.fr

Cancer cell plasticity in melanoma

Our research team is dedicated to studying metastatic melanoma, the treatment of which has been recently revolutionized by targeted and immune-therapies. However, a significant number of patients still develop resistance, and melanoma is the proof-of-concept tumor model for studying resistance mechanisms. Our lab focuses on non-genetic mechanisms of resistance to treatment, which rely on melanoma cell adaptation, through transcriptional and epigenetic mechanisms. Based on our previous results exposing EMT-inducing transcription factors as major regulators of melanoma phenotype plasticity and intra-tumor heterogeneity, our projects aim at further characterizing the mechanisms underlying the adaptation of melanoma tumors, viewed as complex ecosystems, and the acquisition of resistance to targeted therapies and immunotherapies. Based on the complementary expertise of basic researchers and physicians, the team leads basic, translational and clinical research at the international level. The oncodermatology clinical unit (headed by Pr S Dalle) has reached a significant international visibility, associated with high-impact clinical trial publications. The team has proven its capacity to launch phase 1 clinical trials and translational works are facilitated by a privileged access to large cohorts of melanoma samples (1st rank in France). Based on J. Caramel's recognized expertise in cancer cell plasticity (Caramel et al., Cancer Cell 2013; Puisieux et al., Nat Cell Biol 2014; Richard et al, EMBO Mol Med, 2016) and thanks to a strong collaborative network (epigenetics, immunology), we use innovative methods in vitro and in vivo in mouse models, as well as in human samples, to:

(i) further investigate the molecular mechanisms sustaining the plasticity of cancer cells, including the identification of transcriptional networks and epigenetic regulators (ChIP-seq);

(ii) decipher the crosstalk between tumor cells and their immune microenvironment, the mechanisms of immune evasion and resistance, including a detailed characterization of intra-tumor heterogeneity in patient samples (Digital Space Profiling technology, Nanostring; scRNAseq of fresh samples; spatial multi-immunofluorescence analyses);

(iii) develop original strategies to target cancer cell plasticity in order to overcome melanoma resistance to current therapeutic strategies, which will in turn provide a strong rationale for the development of new combination therapies in the treatment of malignant melanoma.

Christophe Caux
christophe.caux@lyon.unicancer.fr

Tumor immune surveillance and therapeutic targeting

Our team conducts a translational research in Breast, Ovarian and Colon carcinoma aiming at the identification of immune escape mechanisms and the development of therapeutic strategies to restore anti-tumor immune responses. The team contributed to showing the critical role of dendritic cells (DC) in T cell activation and pioneered several escape mechanisms from immune surveillance in cancer such as altered conventional DC (cDC) physiology, selective plasmacytoid DC (pDC) functional alteration, and dominant local Treg activation. Our observations identified pDC/Treg interactions as pivotal local immuno-suppressive pathways, and identified targets for immune intervention (ICOS, CD73).

The team has recently initiated a research axis to define early immuno-surveillance mechanisms that remain largely underexplored. Using both supervised biology-driven and unsupervised systems biology approaches, we are seeking cell intrinsic innate detection mechanisms of cell transformation and extrinsic sensing mechanisms propagating immune alert through DC, neutrophils, B cells and macrophage (Mph) populations. Understanding mechanisms of early immune detection of cell transformation overridden in advanced tumors will lead to the discovery of important novel escape mechanisms. Thus, defining strategies to restore immune surveillance processes will enable potent therapeutic approaches initiating both specific anti-tumor immune response and immune memory that will prevent relapse.

Thanks to its strong link with clinicians, our team is conducting basic and translational research programs aiming at target identification and therapeutic innovations in order to eradicate the tumor and to induce anti-tumor immune memory preventing relapse.

Methodologies used:

-High dimension and spectral flow cytometry
-High dimension spectral multi-fluorescence imaging
-Preclinical spontaneous, sporadic tumors models in animals
-ELISA multiplex
-RNA seq and data mining
-Single cell transcriptomic and in situ analysis
-Bioinformatics applied to immunology

Recent publications

1-Hubert M, Hubert M, Gobbini E, Couillault C, Manh TV, Doffin AC, Berthet J, Rodriguez C, Ollion V, Kielbassa J, Sajous C, Treilleux I, Tredan O, Dubois B, Dalod M, Bendriss-Vermare N, Caux C*, Valladeau-Guilemond J* (*co-last authorship). cDC1 produce IFN-λ in human primary tumors and are associated with a good prognosis. Science Immunology, 5(46):eaav3942, 2020

2-Ramos RN, Rodriguez C, Hubert M, Ardin M, Treilleux I, Ries CH, Lavergne E, Chabaud S, Colombe A, Trédan O, Guedes HG, Laginha F, Richer W, Piaggio E, Barbuto JAM, Caux C*, Ménétrier-Caux C*, Bendriss-Vermare N* (*co-last authorship). CD163+ TAMs accumulation in breast cancer patients reflects both local differentiation signals and systemic skewing of monocytes. Clinical & Translational Immunology, 9(2):e1108, 2020


Lars-Peter Jordheim
lars-petter.jordheim@univ-lyon1.fr
Charles Dumontet
charles.dumontet@chu-lyon.fr

Oncopharmacology

The Oncopharmacology team focuses on improving our understanding of the mechanisms of resistance to approved anticancer agents and the development of novel compounds, including small molecules and antibodies. This team develops and characterizes preclinical models of resistance representative of several solid tumor models (breast, lung, melanoma, sarcoma, bladder, kidney, colorectal) as well as hematological malignancies (leukemias, myeloma, lymphomas), both in vitro and in vivo. These observations are secondarily validated on relevant clinical samples associated with the required clinical annotations.

The team is also closely associated with several small and large pharmaceutical companies for the development of novel agents, at different stages: preclinical package before clinical trials, companion diagnostic development during early clinical trials, analysis of resistance mechanisms after approval. The team has directly been involved in the creation of three start-ups (Antineo, Mablink Pharma, Hephaistos Pharma).

Yenkel Grinberg-Bleyer
yenkel.grinberg-bleyer@lyon.unicancer.fr

Molecular regulation of cancer immunity

Effector T lymphocytes (Teff cells) are immune cells that exhibit critical functions in diverse biological settings. While their main function is to fight against infectious agents, they have also been shown to play beneficial roles in the clearance of tumors; conversely, Teff cells generally exert a deleterious effect in autoimmune diseases. Thereby, understanding the intracellular pathways that orchestrate their function is of the utmost interest for the development of novel immunotherapies. Our lab focuses on the NF-kappaB (NF-kB) family of transcription factors. Whereas NF-kB-targeted therapies were historically aimed at inhibiting the whole family, we hypothesize that each member (or subunit) exhibits selective contributions in the biology of Teff cells in autoimmunity and cancer. To investigate this, we have developed mouse models carrying conditional ablation of NF-kB subunits in T cells and CRISPR/Cas9-edited human T cells. Our published reports and preliminary data suggest that NF-kB subunits play specific roles in each disease context, thus pavingthe way toward NF-kB-subunit-targeted therapies.

Specific aims :

-Dissect the molecular programs driven by NF-kB subunits in Teff biology during autoimmunity and cancer, using omics approaches.

-Design T cell-targeted, NF-kB-subunit inhibitors, using high-throughput screening assays and antibody-drug conjugate approaches.

Isabelle Krimm
isabelle.krimm@univ-lyon1.fr

Small molecules for biological targets

Our team's objectives are to discover and optimize small molecules as protein inhibitors or protein modulators. The small molecules are used to decipher the role of potential therapeutic targets or establish a pharmacology validation of a therapeutic target. We are also generating novel leads as future drug-candidates (allosteric, bivalent, protein-protein interaction inhibitors). We can develop de novo inhibitors (where no starting chemical matter is available or known), or perform hit-to-lead optimization.

Our main methodology is based on fragment-based and structure-based approaches. Our multidisciplinary team offers the opportunity to include methods such as molecular modeling, virtual screening, medicinal chemistry, molecular biology, biochemistry, molecular interactions, biophysics, structural biology, cellular biology.

Muriel Le Romancer
muriel.leromancer@lyon.unicancer.fr

Olivier Tredan
olivier.tredan@lyon.unicancer.fr

Endocrine resistance, methylation and breast cancer

The strength of our team lies in its co-direction by a researcher and a clinician, which allows us to rapidly transfer knowledge from bench to bedside. Our aim is to understand how steroid hormone signaling is involved in treatment resistance in breast cancer. We focus mainly on estrogen and glucocorticoid. These hormones play an important role in the initiation and development of breast tumors. We study the expression of proteins and how post-translational modifications (with a focus on lysine and arginine residue methylation) regulate their activity. We are continually developing innovative technologies to study protein/protein interactions in cell lines and in breast cancer samples. We also seek to understand the mechanisms by which proteins move between the nucleus and the cytoplasm, a process that is dysregulated in cancers. We can study the expression of proteins of interest in breast tumor cohorts through our privileged access to a breast database that indexes patient data. We can thus perform statistical analyses of the correlation between biomarker expression and clinical parameters and patient survival owing to close our collaboration with the different departments of the Léon Bérard Center.

Julien Marie
julien.marie@inserm.fr

TGF-beta and immune response

By focusing on the physiological context, the lab of Julien Marie assesses how the cytokine TGF-beta affects the immune responses, both in mice and patients.

The immune system has to be tolerant towards self-cells and the microbiota to avoid autoimmunity and chronic inflammation. However, it should also be able to eliminate self-cells that are noxious for the organism such as tumor cells. Transforming Growth Factor beta (TGF-β) is a highly conserved cytokine present in all mammals. TGF-β has been described as a key regulatory cytokine of the immune system. Interestingly, this cytokine is strongly produced by the tumor micro-environment and is also known to contribute to tumor growth. Our previous works revealed that within the immune system the target cells of the regulatory effects of TGF-β are T lymphocytes (Immunity 2006) and that TGF-β signaling represses their activation against self-cells. We reported that TGF-β influences the differentiation of memory T cells (Nature Com 2014, Immunity 2012), NKT (J. Exp Med 2009, Blood 2012) and thymic development (Nature Com 2019). We also revealed that TGF-β prevents auto-antibody development by regulating T follicular helper cell differentiation (J. Clin invest 2014). Our works also revealed a key role for TGF-β in Foxp3 regulatory T cell biology (Tregs) (J. Exp. Med 2009, Immunity 2015, Nature Immun 2020) and in anti-tumor response (Cancer Res 2020). One particularity of TGF-β is that it is secreted by the tumor micro-environment (TME) as an inactive form. Our recent work revealed that Tregs are the main cells expressing the Integrin capable of activating TGF-β in the TME.Subsequently, absence of this Integrin on Tregs as well as neutralization of its action ex-vivo on patient turmors allowed a massive activation of the CD8 T cell response and control of tumor growth (Nature Com 2021).

Our lab developed several innovative tools to study the molecular and cellular mechanisms responsible for the control of peripheral T cell tolerance to self-cells by TGF-β and to analyze their effects on autoimmune diseases and tumor development. In addition to compounds with the ability to control TGF-β we developed a unique technology which allows us to address the effects of different compounds (or doses of a same compounds) on the TME of a given patient in which the immune system and its interactions with the tumor tissues occurred live.

Patrick Mehlen
patrick.mehlen@lyon.unicancer.fr

Apoptosis, cancer and development

The team “Apoptosis, Cancer and Development” led by P. Mehlen is internationally known for its work on the concept of dependence receptors. Such receptors have a dual signaling ability: when bound to their specific ligand they induce various pathways leading to cell migration, proliferation or differentiation, whereas they induce an active signal of cell death in the absence of their ligand. This pro-death activity was demonstrated to be a mechanism negatively controlling tumor progression, and aggressive tumors select the production of ligands of dependence receptors to survive. Based on this basic fundamental research on cell biology mechanisms, the team has transferred its discoveries into translational/preclinical developments with the generation of therapeutic tools blocking the ligands/dependence receptor interaction in tight partnership with a spin-off biotech company NETRIS Pharma. This has led to the clinical evaluation of NP137 in a phase 1 and a large ongoing phase 2 clinical trial assessing its ability to interfer with the binding of netrin-1 to its dependence receptors. The aim being to use this antibody either in monotherapy or in combination with chemotherapy and/or immunotherapy in patients with advanced solid cancers. Additional candidate drugs are under preclinical development. The team encompasses a large set of expertise covering the analysis of cell death mechanisms, the analysis of tumor plasticity, the preclinical assessment of anti-tumor activity in various animal models, and the regulatory preclinical development of biologics.

Toufic Renno
toufic.renno@lyon.unicancer.fr

Targeting non-canonical protein functions in cancer

Since 2006, our lab has described several non-canonical functions of proteins. For instance, we showed that in addition to their well-known activities in innate immunity, MyD88 and TLR3 play important roles in Ras signaling via the interaction with Erk, and induction of apoptosis of cancer cells, respectively. These findings have led to several publications and patents, leading to the creation of two startups.

More recently, we identified:

- a new protein-protein interaction-dependent role for the Erk MAPK, independently of its kinase activity;
- a novel molecular link between Erk and GCN2, independently of the latter's amino acid-sensing function;
- a hitherto unknown role for the phosphoribosyltransferase QPRT in Ras transformation, independently of its enzymatic activity.

The team's goal is to better understand the cellular and molecular mechanisms underlying these non-canonical activities, and how they could be implicated in tumor initiation and/or progression. We are actively exploring whether these proteins or their newly-identified partners are potential therapeutic targets in cancer. In that case, we will use our proven know-how in transfer research (target validation, molecule screening and optimization…) to develop novel therapeutic agents in cancer.

Pierre Saintigny
pierre.saintigny@lyon.unicancer.fr

Integrated analysis of the dynamics of cancer

The team '*Integrated analysis of the dynamics of cancer*' mainly focuses on head and neck, lung and to a lesser extent, breast cancer. Combining experts from different backgrounds (MDs, PharmDs, molecular biology, immunology, biochemistry, and bioinformatics), we aim at studying early stages of tumorigenesis and the heterogeneity of established tumors, to understand how tumor cell plasticity impacts phenotypic diversity under various selective pressures, and to identify new therapeutic targets emerging from a non-genetic biological process driving cancer cell plasticity. Multi-omics studies, single cell RNAseq, multiplex immunofluorescence, spatial transcriptomics, animal and patient-derived modeling of the disease and proteomics are among the approaches we use.

The team offers complementary skills, both in wet lab and bioinformatics, and has recognized expertise in translational research. It has close interactions with clinicians at Centre Léon Bérard, as well as multiple collaborations both at the CRCL, nationally and internationally, with both academic labs, pharma and biotechs. Finally, the team is strongly involved in the education and training of students.

Frédéric Catez
frederic.catez@lyon.unicancer.fr

Christophe Vanbelle
christophe.vanbelle@lyon.unicancer.fr

Cell Imaging Platform

The Cell Imaging Platform (CIP) is open to the entire academic and private scientific community (Consult the academic / private sector rates).

The equipment allows the imaging of cells, tissues, organoids, living or fixed, on different supports (slide, petri dish, 6, 12, 26, 96, 384 wells plate) and in different modalities (epifluorescence, confocal, bright field and cross polarization).

The platform offers scientific support during the setting up and/or the realization of your projects, at the level of sample preparation, data acquisition strategies and the analysis and quantification of your fluorescence images.

The equipment can be used independently or with assistance.

Theoretical and practical training is regularly given to allow the use of the equipment in autonomy. The assistance of a staff is always possible. The platform also provides training courses adapted to the specific needs of an academic or private public, with a certificate to benefit from the financing of training organizations.

The platform has the Columbus software on a calculation server allowing the analysis and quantification of small and large volumes of data.

Sylvie Lantuejoul
sylvie.lantuejoul@lyon.unicancer.fr

Nicolas Gadot
nicolas.gadot@lyon.unicancer.fr

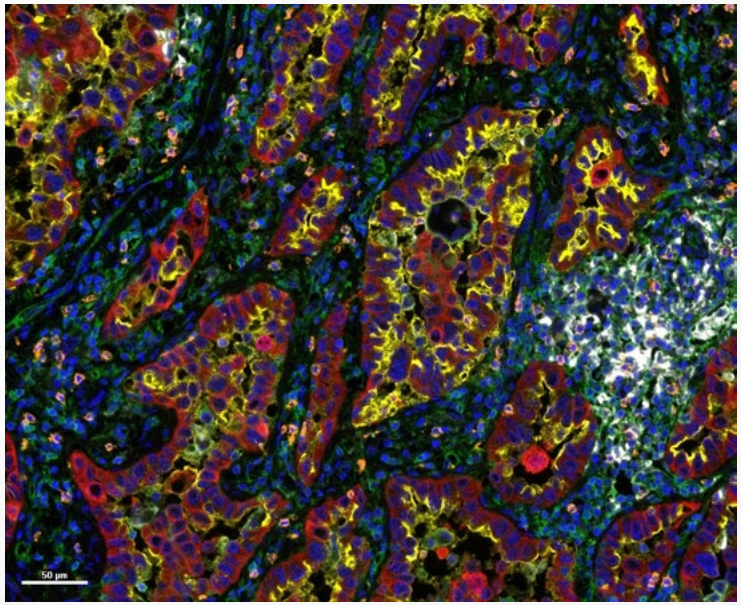
Research Pathology Platform

The Research Anatomopathology platform provides CRCL and CLB researchers, and private companies, with standard and innovative histopathological techniques for in situ molecular detection of proteins and mRNA on human or animal samples, as well as experimental models such as organoids, 3D cultures, etc. It promotes collaborations between researchers, clinicians and pathologists from the Léon Bérard Centre, the HCL CHU Lyon-Est and VetAgroSup. Coordination with other platforms allows them to analyze their samples or prepare sections for genomic NGS or spatial transcriptomic (visium) analyses.

The platform was recently equipped with automated machines to perform 6 to 8 fluorescent multiplex immunostaining on a single FFPE tissue section, based on a sequential immunohistochemistry methodology allowing the deposition of tyramide-fluorochrome complexes. The Vectra Polaris scanner is able to perform image acquisition on 9 fluorescent channels. Spectral quantification and labeling analysis can then be done with Inform or Halo software.

The platform also has a GeoMx Digital Spatial Profiling (DSP) NanoString.

This is an innovative technology that allows spatial quantification of up to 96 proteins or 18,000 RNAs in previously identified regions of interest ranging from a few cells to 600 µm in diameter on a single FFPE tissue section. It combines several techniques: 1- a morphological and immunohistochemical approach to determine the regions of interest, 2- an IHC or HIS technology for the hybridization of antibodies or probes coupled to oligonucleotides, 3- a quantification step of these markers to obtain a precise evaluation of the abundance of each protein or RNA.



Christophe Vanbelle
christophe.vanbelle@lyon.unicancer.fr

Thibault Andrieu
thibault.andrieu@lyon.unicancer.fr

Flow cytometry core facility

The Lyon-Est Cytometry Platform (Cyle) has all the human and material resources necessary to carry out all flow cytometry projects for analysis and cell sorting in basic and translational research, from panel design to report writing. The platform also offers à la carte training in all areas of cytometry (theory, practice on equipment, data processing and analysis). To carry out all these services, the platform relies on 3 specialized staff: 1 research engineer, 1 study engineer and 1 assistant engineer. Adapted premises accommodate the equipment (3 conventional analysis cytometers, 1 full spectrum analysis cytometer, 2 conventional sorters and 1 full spectrum sorter). This equipment allows us to perform analysis and sorting experiments based on 1 to 32 fluorescent labels on vesicles, cells in culture and tumors. As the platform is open to the entire academic and private scientific community, it also have recognized expertise in the fields of neuroscience, nutrition and virology. The partnerships established with the major players in cytometry, both equipment and antibodies, allow privileged access to their portfolio, facilitating and accelerating the implementation of projects, mainly during the set-up phases.


Christophe Caux
christophe.caux@lyon.unicancer.fr
Uzma Hasan
uzma.hasan@lyon.unicancer.fr

Laboratory of Immunotherapy of Cancer of Lyon

The main objective of LICL is to identify predictive immune parameters in response to immunotherapy and define mechanisms of primary or acquired resistance to discover new therapeutic targets. The LICL provides expertise in tumor immunology, innovative tools, and knowledge to analyze immune parameters in blood and tumors from cancer patients enrolled into basic, translational, and clinical research projects. We welcome projects and partnerships from academic groups, clinicians, and private companies. Each LICL axis has been developed by a scientific principal investigator and works in tight partnership with other CRCL platforms (see figure).

We provide the following services:

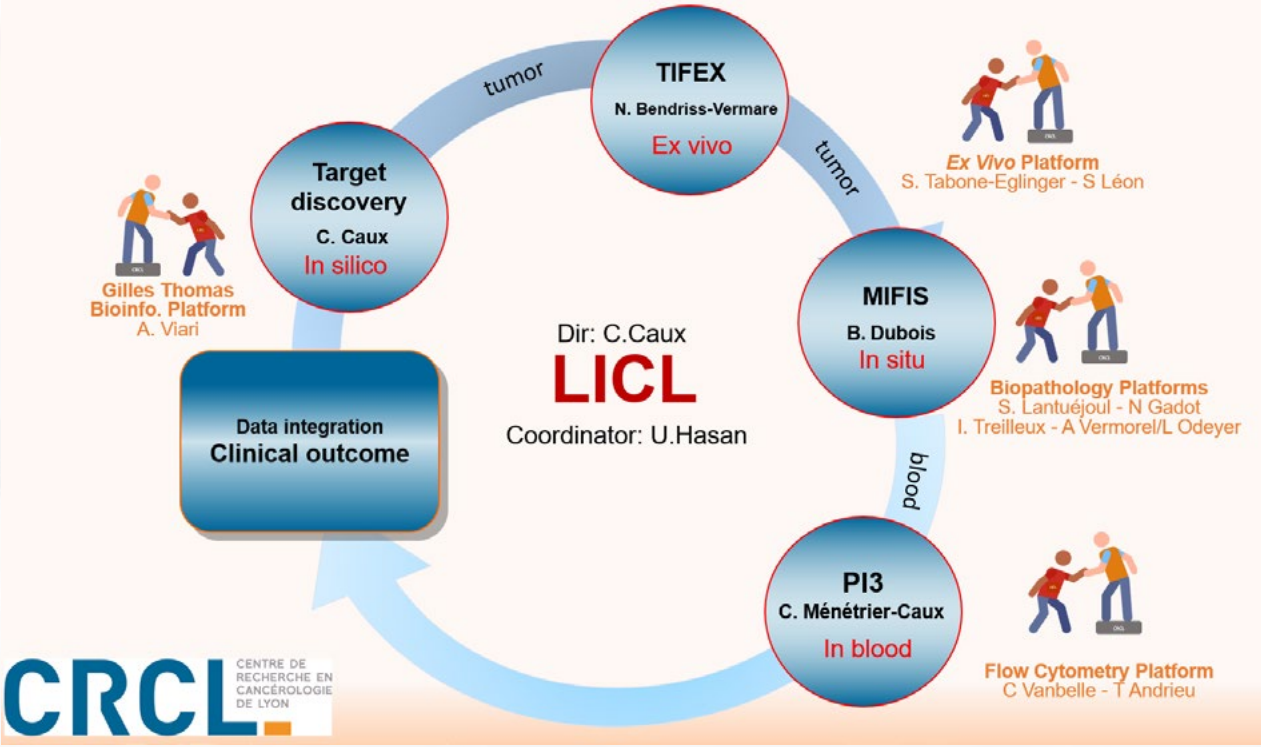
- Target discovery/validation- Bioinformatics expertise in immuno-oncology is used to analyze immune signatures from bulk transcriptomic signatures and scRNAseq data from cohorts of patients.

- Multiplex immunofluorescence in situ (MIFIS) - Simultaneous detection of multiple markers in tumor tissue in a single section is performed to deepen the understanding of the tumor immune microenvironment.

- Clinical trial immuno-monitoring by multiparametric flow cytometry (Pi3) – We aim to identify in the blood immune cell profiles as biomarkers of successful treatments and guide therapy decisions for cancer patients.

- Tumor Immune Functions EX vivo (TIFEX)- Analysis from tumor tissue fragments (under development). An ex-vivo platform aiming at analyzing drug activity in sections from fresh patient primary tumors

Various requests for platform use are possible with a preference for collaborative projects.



Qing Wang
qing.wang@lyon.unicancer.fr

Cancer Genomics Platform

The Cancer Genomics platform offers a wide range of technologies dedicated to the molecular biology of cancers. With more than 25 years of experience in this field, since 2011 it has implemented the next-generation sequencing (NGS) technology which is capable of analyzing the entire human genome.

With a specialized team and high performance sequencing systems, the platform carries out analyses that contribute to fundamental, translational and clinical research in oncology, in participating in research projects at international, national and institutional levels.

Many applications are available to clinicians/researchers. For DNA, sequencing of a panel of genes, or the entire coding sequence (WES) or entire human genome (WGS) allows the identification of genomic alterations that drive carcinogenesis or the identification of actionable biomarkers that can be therapeutic targets or predictors.

On the RNA level, study of gene expression and fusion transcripts are very frequently carried out in cancer research and personalized cancer treatment.

Other technologies/experiments are also implemented, such as epigenetic analysis (DNA or RNA), study of gene interactions, and transcription of a panel of genes with HTG technology (EdgeSeq system).

Recently, the platform developed technologies for single-cell analyses, making it possible to characterize more precisely the cellular heterogeneity or the spatial cellular expression of genes within a tumor. This technology offers new perspectives to extend knowledge on cancer development and progression.

For more details please refer to https://www.crcl.fr/les-plateformes/plateforme-de-genomique-des-cancers/

Alain Viari
alain.viari@inria.fr

Anthony Ferrari
anthony.ferrari@lyon.unicancer.fr

Gilles Thomas Bioinformatics Platform

Since 2009, the platform has been actively involved in cancer genomics research programs within the International Cancer Genome Consortium (ICGC) that undertook the systematic study of more than 25,000 cancer genomes, from 50 different types, at the genomic, epigenomic and transcriptomic levels. In this context, the platform participated in 3 INCa/INSERM funded programs: HER2-amplified breast cancer, prostate cancer and gynecological carcinosarcoma. It also provides some help and guidance to other French ICGC programs such as retinoblastoma.

During the past ten years, the platform has developped several projects at the national and regional (CRCL) levels and gained a strong expertise in the analysis of transcriptomics (bulk and single cell) and epigenetics data.

The platform also has an expertise in the field of genome-wide association studies (GWAS) and is in charge of the statistical analyses of two major national Breast Cancer cohorts: CANTO (UniCancer and Labex GenMed partnership) and PHARE/SIGNAL (INCa funded program).

In addition, the platform is leading the bioinformatics developments and analyses in several precision medicine initiatives. It participates, since 2013, to the Lyric ProfiLER collaborative effort with the CLB clinical department to explore the therapeutic impact of molecular profiling (gene panel sequencing) in routine setting for patients.

More recently, in 2017, it was committed to the French national healthcare Plan France Médecine Génomique 2025. The platform coordinates the bioinformatics operations (with the CHUGA in Grenoble) for the AURAGEN national sequencing platform, generating thousands of Whole Genome Sequences (WGS) per year in a clinical setting for cancer and rare diseases.

Séverine Tabone-Eglinger
severine.tabone-eglinger@lyon.unicancer.fr

Biological sample management platform

At the interface of diagnosis and research, the PGEB is an essential structure which puts its skills at the service of the medico-scientific community and of innovation.
Under the scientific responsibility of Séverine Tabone-Eglinger (pharmacist and PhD), a dynamic team of 14 people manages the biological samples intended for the medico-scientific community of the center, as well as its academic and industrial partners (**certified NF S96-900 and ISO9001 ; performance 3CR label**).

- Sample management within the framework of **clinical trials.**
  More than 300 clinical trials are active (local or industrial promotion) with more than 21,000 biospecimens collected and processed each year.
- Institutional collection of the **Center for Biological Resources**
  Main collections: Breast, Ovary, Lung, Intestine, Sarcoma…
  Biospecimens available: 10,000 frozen tumor samples, 9,450 whole blood, 3,600 PBMC, 19,600 Plasmas, 8,300 sera, 16,200 DNA, 4,700 RNA…
  Sample traceability and clinical data implemented in specifically developed software.
- **Extraction of the nucleic acids** necessary to carry out numerous molecular studies in close connection with the genomics platform.
  Extraction automatons: Chemagic Prime, Biomek I5, Maxwell 16, Qiacube.
- **Hosting** of external collections (UNICANCER and MESOBANK).
- Provision of **fresh tissues** to research teams, at the interface with the Ex vivo platform and the Biopathology department.

Séverine Tabone-Eglinger
severine.tabone-eglinger@lyon.unicancer.fr
Sophie Léon
sophie.leon@lyon.unicancer.fr

Ex-Vivo Platform

The translational research platform Ex-Vivo created in 2015(PEXVIVO@lyon.unicancer.fr) is the direct interface between clinical services and research departments. It supports academic and industrial preclinical research projects.
Through our missions and expertise, we support you to find the most relevant experimental approach to achieve your objectives:

You need fresh human tissue samples for the development of your preclinical projects ?
The platform coordinates the clinical services to organize this provision of fresh tissue. A multidisciplinary committee (CMT) will evaluate your project in advance in order to respect the ethical and legal issues.

You want to strengthen the proof of concept of your drug candidate for transfer to clinical trials ?
We propose predictive tests evaluating the response to therapeutic agents on organotypic sections of human or animal tissue. This innovative and relevant technology in the context of personalized medicine mimics the patient's therapeutic response by preserving the intact architecture of the tumor and its microenvironment.
Possible applications: Histology, IHC, flow cytometry, single cell in connection with the CLB and CRCL platforms and research teams.

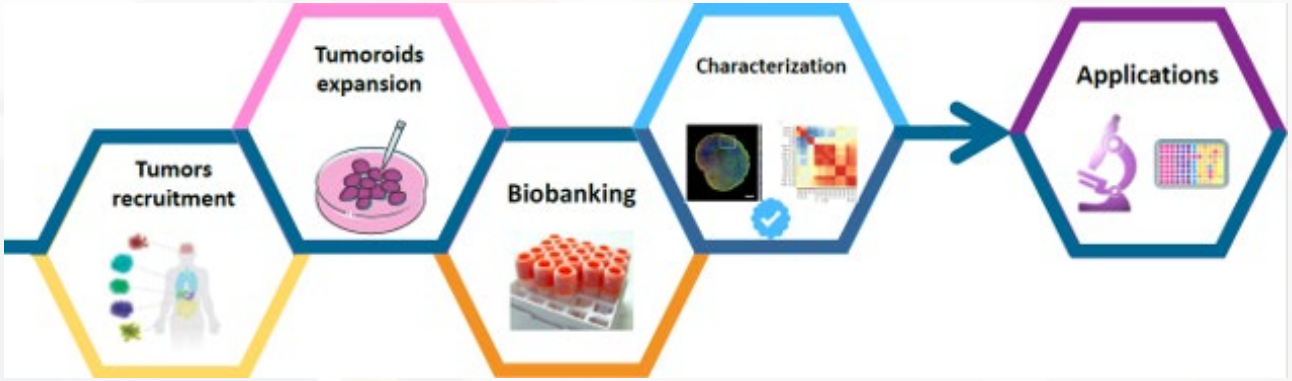
You need fresh tissue preparations for single cell or cytof ?
The platform performs automated tumor dissociation with gentle MACS technology, cell counting, viability...

Stéphane Giraud
stephane.giraud@lyon.unicancer.fr

3D-ONCO Organoids Platform

Historically, in vitro cultures have been limited to monolayers on flat (2D) supports, which is physiologically non-relevant. In recent years, three dimensional (3D) models, closer to physiology have emerged: organoids. These in vitro structures have architectures and functionalities which are similar to those of the tissues and organs from which they are derived. In oncology the 3D structures derived from tumors are called tumoroids. These models recapitulate more faithfully the genetic and physiological characteristics of the tumor from which they originate.

The aim of 3DONCO is to provide the research teams and pharmaceutical companies with a strong expertise 100% focused on the development of 3D models. The major axes of the activity are the production, the molecular characterization and the biobanking of tumoroids models from different pathologies.



Our goals

- Development and characterization of tumoroids models; optimization and standardization of culture protocols
- Creation of a bio-bank
- Support the research teams in their 3D projects
- Establishment of partnerships between academic and private research

Our specificity: Access to a large panel of tumors thanks to our partnership with the CLB and the University Hospitals of Lyon (HCL).

Stéphane Giraud
stephane.giraud@lyon.unicancer.fr

Center for Drug Discovery and Development

The C3D platform, Center for discovery and development is an academic drug discovery platform localized at the Léon Bérard hospital site. Based at the interface between basic research and the clinic C3D relies on a high scientific environment:

- The Centre Léon Bérard (CLB) a hospital that is dedicated 100% to cancer care and research. Its intention is to offer excellent care and to be a referral center for people with cancer.
- The Cancer Research Center of Lyon (CRCL), affiliated with the University Claude Bernard Lyon 1, the national health and research bodies (Inserm and CNRS), the Léon Bérard Comprehensive Cancer Centre (CLB). The CRCL comprises 23 teams dedicated to research in oncology.

The aim of C3D is to develop new cancer therapies (antibody or new chemical entities). Strongly supported by the fundamental research, the missions of C3D are to identify, characterize and develop new clinical candidates. The C3D works from the early stages of discovery, up until the entry into clinical trials.

C3D offers the opportunity to accelerate the transfer of academic research programs towards the clinic and to patients, and to create developmental partnerships between academic and industrial research.

Skills and activity :

Biology	- In vitro assays: HTRF, enzymatic activiy. - Cell based assays: high Content Screening; phenotypic assays - Disease relevant assays (biochemistry, cellular biology, molecular biology)
Medical chemistry	- Compounds design - Structure Activity Relationship study - Synthetic chemistry management - Activity, PK and Safety optimization based on biology and ADMET
ADMET	- Charge (pKa), lipophylicity (logp/logD), solubility, - Permeability - Metabolism (liver microsomes, hepatocytes) - CYP450 inhibition; cardiac toxicity (in vitro hERG)

Isabelle Goddard
isabelle.goddard@lyon.unicancer.fr

Small Animal Platform - P-PAC

P-PAC is the in vivo platform of the CRCL. Within the P-PAC facility, two departments P-PAC Tumor Models and P-PAC Imaging propose custom-made experiments.

P-PAC Tumor Models offers studies in oncology using three technologies:

1) transgenic mice predisposed to the development of cancer,

2) PDXs (Patient-Derived Xenografts),

3) CDXs (Cell line-Derived Xenografts).

These models are used to test drug candidates. P-PAC Imaging offers as imaging modalities, X-ray scanner, fluorescence, ultrasound/photoacoustic and bioluminescence. All these imaging systems are complementary and non-invasive. The main applications proposed are anatomical and longitudinal monitoring of the whole body, organs and the development of tumors/metastases, monitoring the biodistribution of cell populations, drugs, antibodies or labeled nanoparticles and finally interventional imaging.

Michel Rivoire
michel.rivoire@lyon.unicancer.fr

Stéphan Langonet
stephan.langonet@lyon.unicancer.fr

Experimental Surgery Institute

The Experimental Surgery Institute of the Léon Bérard Center is a transfer research platform which allows researchers to develop and test new surgical techniques on relevant animal models in an adapted and safe operating room before they can be made available for patients.
This is a joint unit between CLB and Inserm U1032 LabTAU.
The major theme of our lab, “tumor destruction by physical agents” consists in developing new techniques of tumor destruction (both physical and chemical) usable in surgery and interventional radiology.
Our other themes are: Visceral oncology surgery, Therapeutic Ultrasound (HIFU ...), Tumor targeting, Focused tissue destruction, Multimodal therapies, Irradiated tissues reconstruction, surgical endoscopy and on demand Model Development.
Fully trained and experienced staff with all the regulatory authorizations supervise the experiments under the best conditions and under the latest European baselines.
The multidisciplinary team is composed of:

- Lab Animal specialized veterinarian
- Biology Research Engineer
- Surgeon in charge of the transfer
- The CLB clinical teams
- The Unit 1032 researcher teams
- Two animal technicians

Our lab benefits from recognized clinical expertise (Surgery, Oncology, Radiology ...), rich research environment (LabTau, LyriCAN, CRCL, BEC ...), scientific supervision (Anesthesiology, Biology, Biostatistics, Pathology...) and hospital logistics support (Pharmacy, sterilization ...).
Available animal models are rabbit, regular pig and minipig. Available tumor models are VX2 and Rabbit hepatocarcinoma. We also offer possibilities of developing innovative animal and tumor models to meet the goals of each project involved.
The structure is composed of a "Clean conventional" registered animal facilities and 2 fully equipped surgical blocks. Instrumentation includes Respirators, Gas Anesthesia, Chemical Anesthesia, electrosurgical units, Monitoring, Ultrasound scan, …
The lab also has a reactive Ethics Committee (registered with authorities) and strong expertise in Project Development, Protocol Writing, Project Authorization, Biostatistics, Anesthesiology, Oncology and Interventional radiology.
Applications that can be developed within our lab includes all types of surgery on pigs and rabbits, imaging (ultrasound, MRI, Scanner, PET ...), Specific model Development (surgical, tumoral, ...). All the expertise developed in 15 years of experience through our own projects can be put to the service of external projects through collaborations, services, trainings and competence transfers.

Béatrice Fervers
beatrice.fervers@lyon.unicancer.fr

Prevention Cancer Environement Department

Created in 2009 and coordinated by Prof. B. Fervers, the Prevention Cancer Environment Department (DPCE) develops interdisciplinary research programs on environmental exposures, nutrition and cancer, combining epidemiological, geographical and molecular approaches. The DPCE also develops interventional research projects, both in physical activity using innovative technologies, in particular connected tools in the field of tertiary prevention and a program to support patients after cancer treatment. This work provides tangible answers to the challenges of prevention and personalized management of cancer risk factors - before, during and after the disease.

Nearly 40% of cancers are attributable to individual lifestyles. The DPCE has developed several actions to inform the general population on cancer risks (with dynamic and participative awareness campaigns, conferences, an interactive exhibition, a complete information portal dedicated to a large population www.cancer-environnement.fr). Research projects to prevent cancer risk in high-risk populations such as caregivers are also being developed.

The DPCE has also implemented in France a systematic process to identify occupational cancers in collaboration with the Hospices Civils de Lyon professional pathology consultation centre.

Through the diversity of its projects and research programmes, the DPCE acts at all stages of prevention and develops partnerships as close as possible to the territories.

David Sarrut
david.sarrut@creatis.insa-lyon.fr

Imaging and Radiotherapy (CREATIS)

The CREATIS laboratory is a research unit in medical imaging encompassing approximately 200 people. Members of two of the Creatis teams, Tomoradio and Magics, representing about 25 people, are located within the Léon Bérard Center and develop several transdisciplinary projects in close collaboration with clinicians and medical physicists.

The research areas cover in particular: 1) inverse problems in imaging, in particular tomographic reconstruction (radiography, nuclear medicine, spectral scanner, etc.), 2) simulation and imaging in radiotherapy and nuclear medicine, 3) identification of biomarkers for precision oncology via quantitative MRI and radiomics as well as treatment planning in radiotherapy by MRI, 4) artificial intelligence methods (deep learning) applied to the treatment and analysis of medical images.

The collaborations are mainly with the departments of radiotherapy, nuclear medicine and radiology. Recent industrial collaborations include: Philips, Siemens, Elekta, IBA, Kitware, Capgemini engineering, Therapanacea, etc.

Christine Lasset
christine.lasset@lyon.unicancer.fr

Prevention and Genetic Epidemiology Unit – LBBE
Public Health Prevention Department – Centre Léon Bérard

The Prevention and Genetic Epidemiology Unit (UPEG) is a research group certified by the UCBL mixed research unit and is supported by two clinical units linked to prevention (Addictology Pole and Clinical Genetic Oncology Unit). It is associated with a database management unit (hospital databases and national co-horts) and is integrated into the CLB DATALAB. It is a certified research team within the mixed research unit 5558 of the CNRS. https://lbbe-web.univ-lyon1.fr/fr/equipe-biostatistiques-sante

The role of DATALAB (CLB-CRCL site) is to help clinicians and researchers develop their research projects, either through methodological support or through the production of analyses.

The research group conducts work in genetic epidemiology and data sciences in the field of cancer with a predictive approach to risk or tumor progression.

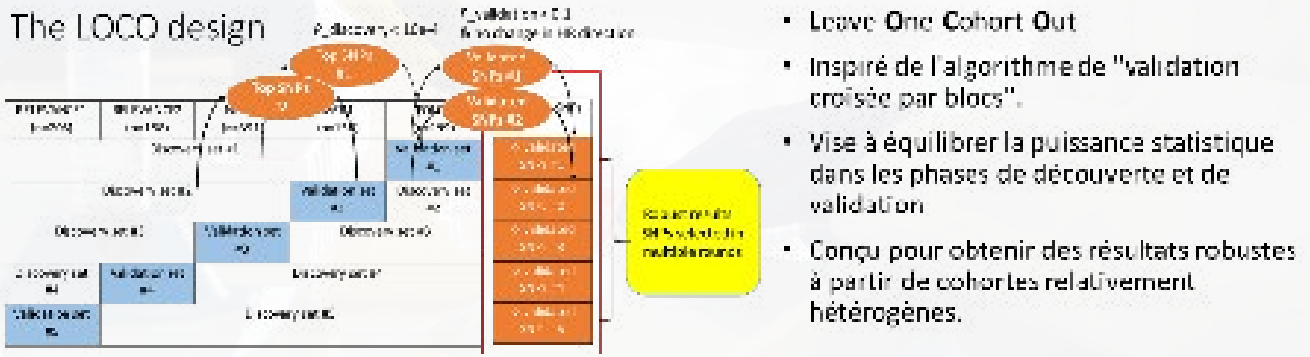
The main recent or ongoing works are the following.

AXIS 1: Implementation of innovative statistical methods for the processing of large data in oncology.

The explosion of available data in oncology (biomics, imaging, etc.) offers tremendous opportunities to develop and accelerate translational research. The inter-pretation and diffusion of these large data requires the implementation of new statistical methods able to simultaneously exploit all of the multi-omics and clinical data in an integrative approach. Our team is in charge of the design and implementation of statistical analysis in several large-scale projects, including:

- GWAS CONPIL (PI : H. Ghesquières, HCL, Grant INCa PRT-K16-167)
  - Primary Objective: Identification of constitutional genetic variants associated with event-free survival (EFS) in follicular lymphoma (FL) patients treated with «immunochemotherapy.»
  - 1140 patients included: largest international study on follicular lymphoma. 4 cohorts involved: MER (US), FOL05 (IT), PRIMA (FR), RELEVANCE (FR)
  - Collaboration with the Mayo Clinic (Pr. James Cehran, Rochester, USA)

  => We developed a new study design called «LOCO» (presented at the INTERLYMPH 2021 international congress, illustration below), which identified robust results.



Christine Lasset
christine.lasset@lyon.unicancer.fr

Prevention and Genetic Epidemiology Unit – LBBE
Public Health Prevention Department – Centre Léon Bérard

- METABOLOMIC-CANTO
  - Primary Objective: The identification of predictive metabolites of chemotherapy toxicity in breast cancer (multiple outcomes of interest, including neurotoxicity).
  - 1,000 patients of the CANTO cohort included.
  - Collaboration with the «Exploration of Metabolism» platform (PFEM, Clermont-Ferrand) - Université Clermont Auvergne (UCA).

  => We develop methods of analysis adapted to these large data (>2,000 metabolites).

AXIS 2: Research in Cancer Genetic Epidemiology

=> More than 15 years of research in hereditary Lynch and Breast-Ovarian syndromes

=> The team has recognized expertise in genetic epidemiology.

Among the ongoing projects:

- The OFELY2 project: Estimating the risk of developing cancer in Lynch syndrome from the national FR3LyS/OFELy registry.
  - In connection with a database supported by INCa comprising >1,500 families (>33,000 individuals). It is the largest European database on Lynch syndrome.

  => Our team coordinates the project, is in charge of data base management and performs statistical analyses.
- The LI-FRAUMENI project: Estimating the risk of developing cancer in de Li-Fraumeni syndrome.
  - In connection with a national database of 180 families (>3,400 individuals).

  => Our team conducted the statistical analyses.
- The GENERISK R package project

  => Our team created an R package pooling the programs developed by the team for likelihood calculation from family data.

Collaborations: INSERM 1245, IRIB, Université de Rouen; INSERM, U900, Université PSL Paris; Melbourne University, School of Population Health; IARC, Nutrition and Metabolism Section, Lyon

Véronique Christophe
veronique.christophe@lyon.unicancer.fr

Human and social sciences department

The mission of the Human and Social Sciences Department (SHS) of the Léon Bérard Center is to develop and promote international level research in the field of cancer, to ensure a transfer of expertise to the medical and scientific teams on site, and to ensure training and awareness of SHS methodologies. The researchers of the department develop research in the fields of sociology, economics, geography and health psychology.
https://www.centreleonberard.fr/professionnel-de-sante-chercheur/la-recherche-contre-le-cancer-au-coeur-du-centre-leon-berard/sciences-humaines-et-sociales

The research carried out in the Department revolves around the question of the social and human stakes of innovations in oncology and is organized around three axes:

Axis 1: Analysis of diagnostic, therapeutic and organizational innovations in oncology.
The aim is to analyze how the technological, epistemic and therapeutic changes of precision oncology are modifying the current and historical relationship between medicine and science. How these innovations promote a new organization of cancer care.

Axis 2: Health systems and access to innovations.
The objective here is to study the relationship between innovation and the conditions for maintaining the functionality of existing healthcare infrastructures. Inequalities in access to innovations and the economic and social viability of health systems in a context of continuous innovation are also part of the research programs of this axis.
This question of access is a major issue both for ethical reasons and for the representativeness of the results of clinical trials. It is therefore necessary to understand the social, organizational and medical issues surrounding patient access to clinical research. In terms of skills, it is necessary to conduct mixed multicenter studies (qualitative and quantitative) in adults and children

Axis 3: Quality of life and experience of care with regards to innovations.
This axis aims at evaluating the temporal evolution of quality of life related to mental and physical health, emotional distress, sequelae and/or survival of patients included in «standard» clinical trials as well as precision medicine clinical trials, including immunotherapy and targeted therapies.

Another aspect of research in this axis is to identify the determinants of the decision to participate in early phase or precision medicine clinical trials from a systemic perspective (patients and/or investigators and/or relatives).

Isabelle Ray-Coquard
isabelle.ray-coquard@lyon.unicancer.fr

Medical Evaluation and Sarcoma/rare cancers teams (EMS)

Created in 2005, the Medical Evaluation and Sarcoma/rare cancers team (EMS) is specialized in the management of reference networks and transversal research programs dedicated to rare tumors, with the goal of improving patient care by understanding the biology of rare cancers and defining novel predictive factors and/or biomarkers. The team is composed of two coordinating physicians, one team leader, 8 project managers with complementary expertise, 2 data managers and 8 clinical research associates. The team collaborates with CLB technological platforms (CRB, genomics, bioinformatics…), other departments (biopathology, IT, clinical department…) and CRCL teams, as well as many institutions at national, European and international levels.

Reference networks: The team manages the French sarcoma reference network (NetSarc+) and its national database (>114 000 patients), and collaborates within the French rare gynecological tumors reference network (TMRO-TMRG) and the French mesothelioma network (Mesopath). At the international level, the team leads and/or participate in several networks including the European Reference Network on rare adult solid cancers (EURACAN) involving 18 countries and >70 centers, and SELNET (European-Latin-American Sarcoma Network, >40 centers) among others.

Translational research: The EMS team coordinates and participates in various research programs (both with academic and industrial partners and/or funding bodies): translational projects (e.g. T-cell therapy in sarcoma), real-life registries (e.g. the European registry of actionable fusions, registry of PDGFR D842V gastrointestinal tumor patients), geographical inequalities in access to care, epidemiological and cost-effectiveness studies. Additionally, the team also coordinates translational research programs on gynecological cancers and rare gynecological cancers including ROCSANbio (NCT03651206), COLIBRI (NCT04256213), PAOLAbioMic (NCT02477644), ALIENORbio (NCT01770301).

Expertise: Data collection, project management, extraction, processing, cross-referencing (real-world data, SNDS, health data hub winner project, European registry, artificial intelligence); network/consortium coordination; set up of registries and real-world evidence programs; geographical inequalities in access to care; epidemiology; translational program coordination and set up; regulatory processes; scientific analysis and valorization.

Pierre Saintigny
pierre.saintigny@lyon.unicancer.fr

Department of translational medicine

Department of Translational Medicine:

The Department of Translational Medicine has recently been created at OECI-certified cancer center Centre Léon Bérard (CLB). It has emerged in the context of LYriCAN, one of the eight integrated cancer research sites (SiRIC), certified by the National Cancer Institute (INCa), the Ministry of Solidarity and Health, Inserm and ITMO Cancer AVIESAN (National Alliance for Life Sciences and Health). Positioned at the crossroad between clinical research, core laboratories and research teams, its role is to foster excellent translational research. Our main goals are :

1 - to accelerate collaborations between Centre Léon Bérard and pharma companies/biotechs by taking advantage of our know-how in multidimensional characterization of human samples and data management;

2 - to build multidisciplinary programs involving clinical, basic and translational as well as social sciences and humanities research teams,

3 - to build on the excellent track record of Centre Léon Bérard in leading state-of-the art molecular triage programs, and 4-to train young clinicians interested in MD-PhD dual degree

CRCL
CENTRE DE RECHERCHE EN CANCÉROLOGIE DE LYON

UMR Inserm 1052 - CNRS 5286 - UCBL - CLB
CENTRE LEON BERARD
28, rue Laennec
69373 Lyon - Cedex 08

www.crcl.fr

Crédits photos : J CEA / R Etienne_item / Comm_CLB / Comm_CRCL