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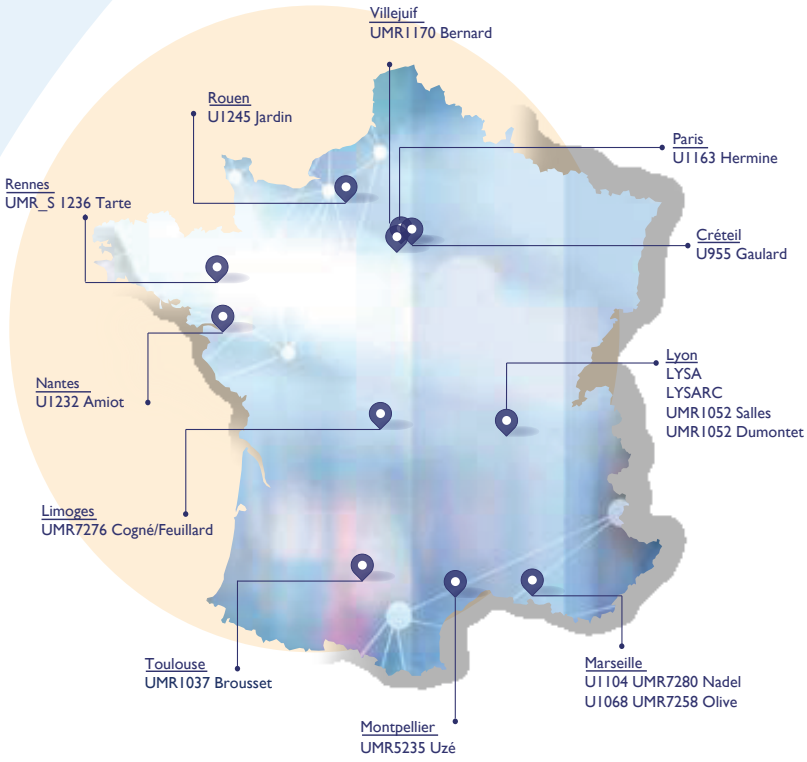
LIVRET DE PRÉSENTATION DES EQUIPES

TEAMS' PRESENTATION BOOKLET



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Sommaire / *Content*

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LYSA, the Lymphoma Study Association

PRESIDENT
Gilles Salles

TYPE OF COLLABORATION
Collaborative research
Expertise
Access to databases and collections
Training

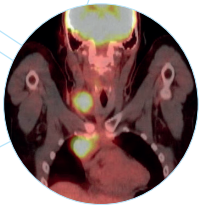
RESEARCH AREAS & OBJECTIVES

Research areas
- Clinical, biological, anatomo-pathological and epidemiological lymphomas studies
- Conception of research programs and clinical assays protocols in lymphoma field
- Imaging and bioinformatics

Objectives
LYSA aims at bringing together professionals specializing in the field of lymphoma in order to promote basic and clinical research, improve prevention, management, and treatment of lymphoma patients, and share their knowledge on lymphoma. LYSA focuses on world-leading clinical and translational research dedicated to lymphoma patients.

EXPERTISE

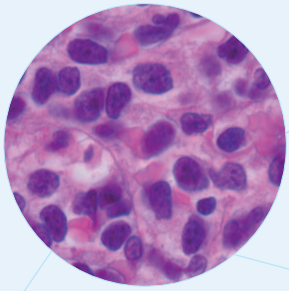
Tools, processes and platforms in connection with clinical research
To conduct clinical and biological studies, LYSA is supported by an operational organisation called the Lymphoma Academic Research Organisation (LYSARC), which develops all the resources that are needed for carrying out good clinical trials. LYSA and LYSARC were certified as an "international cooperative group in clinical cancer research" by the French National Cancer Institute (INCa) in November 2012.



PLATFORMS & TECHNICAL RESOURCES

LYSA is a network of 750 members, lymphoma experts physicians - hematologists, oncologists, anatomo-pathologists, biologists, nuclear imaging specialists, radiologists, statisticians, within 150 hospital centers in 5 countries (France, Belgium, Luxembourg, Switzerland, Portugal).

LYSA-LYSARC Platforms
- LYSA-P, centralized review of partient tissue sample: more than 16 000 reviewed cases up to date
- LYSA-IM, online review of imaging examinations (positron electron or computed tomography): 4 000 images per year
- LYSA-BIO, collecting, labeling, management of biological samples
- EARLY, early phase translational and clinical research: phase I/IIa, first-in-man, first-in-lymphoma or first combo studies: 12 phase I and 30 phase II trials



Databases
Clinical, biological, anatomo-pathological and imaging databases of more than 20 000 patients

Professional softwares and applications
- Clinsight Solutions (data management, e-CRF, e-randomization)
- SAS (biostatistics)
- Safety Easy (pharmacovigilance)
- Imagys (imaging central review)
- Sciforma (project portfolio management)
- GFi (CTMS)
- Android application ClinTrial Refer LYSA trials status and patient enrolment)

R&D OFFER

LYSA offers several types of collaborative research projects, all focused on lymphoma: clinical studies from Phase I to IV (in particular, evaluation of new active treatments, new imaging tools), biological and anatomical-pathological studies to gain a better understanding of lymphoma biology and treatment efficacy, cross-disciplinary and ancillary studies such as clinical-biological correlations, studies of subpopulations, meta-analyses, data extraction, and so on. Studies designed by LYSA generate rich clinical, biological, anatomical-pathological and imaging databases than can be made accessible to its potential partners.

KEY WORDS
Clinical research, Translational research, Prevention, Management and treatment of lymphoma, Knowledge dissemination, Hematology, Lymphocyte, Lymphoma

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LYSARC, the Lymphoma Academic Research Organisation

GENERAL MANAGER
Pascal Deschaseaux

TYPE OF COLLABORATION
Collaborative projects
Expertise
Access to databases

RESEARCH AREAS & OBJECTIVES

LYSARC is a scientifically independent non-profit organization focused on lymphoma clinical research. It is the operational structure associated to the research activities of LYSA, the Lymphoma Study Association, a cooperative group, international leader of lymphoma research with 750 members. LYSARC conducts its research on four continents in accordance with the Charter of relationship between Cooperative Groups in Oncology (GCO), coordination to which it belongs, and industry. It runs clinical trials from first-in-man to Phase IV and non-interventional studies. It provides operational support to biological, histopathological, imaging, statistical and bioinformatics studies with its 170 staff. LYSARC is the largest European academic organization devoted to lymphoma clinical research operations.

EXPERTISE

Clinical research operations in lymphoma

PLATFORMS & TECHNICAL RESOURCES

Platforms (co-operated with LYSA experts)
- LYSA-P: central pathology review
- LYSA-IM: central imaging review
- LYSA-BIO: management of biological samples
- EARLY: early phase clinical and translational research

Databases
- Clinical, biological, pathological and imaging proprietary databases for more than 20,000 patients

Professional softwares and applications
- Clinsight (data management, e-CRF, e-randomization)
- SAS (biostatistics)
- Safety Easy (pharmacovigilance)
- Imagys (imaging central review)
- Sciforma (project portfolio management)
- GFi (CTMS)
- Modul'Bio (biobanking), online document management
- Sharepoint
- Microsoft Dynamics (CRM)
- Android application ClinTrial Refer LYSA (trials status and patient enrolment)

Other
The Lymphoma Academy (training)

R&D OFFER

LYSARC puts its operational expertise and long-standing experience of collaborative clinical research in the lymphoma field at the service of LYSA and its academic and industry (pharma, biotech, *in vitro* diagnosis and imaging) partners to help them answering at the shortest, the unmet medical needs for this cancer.

KEY WORDS
Clinical research, Lymphoma, Clinical operations

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Anticancer Antibodies

TEAM LEADER
Charles Dumontet

LABORATORY
Inserm UMR1052 CNRS 5286 Centre Léon Bérard
Centre de Recherche en Cancérologie de Lyon

TYPE OF COLLABORATION
Collaboration to develop customized new preclinical resistant models. Partnering with animal facilities exploiting animal species other than mice (rat or other).

RESEARCH AREAS & OBJECTIVES

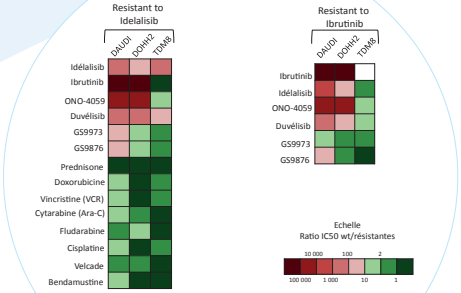
Research areas
Study of mechanisms of action of monoclonal antibodies that target cancer cells and study of mechanisms of resistance towards these biomolecules in order to increase the activity of therapies based on monoclonal antibodies in patients with hematological malignancies or with solid tumors.

Objectives
The laboratory aims at setting up *in vitro* and/or *in vivo* tumor models resistant to monoclonal antibodies and at characterizing obtained models in order to develop new therapeutic treatments (in combination or in monotherapy).

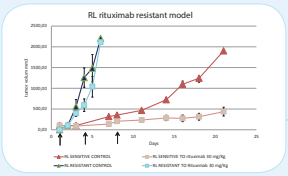
EXPERTISE

Biological targets and *in vitro* / *in vivo*/ *ex vivo* models
Targets:
- CD20
- Immune checkpoints

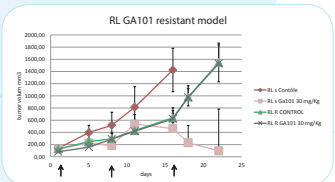
Models:
- *In vitro* models resistant to Idealisib and Ibrutinib
- Syngeneic *in vivo* models and xenografts
- Models of ADCC/ CDC
- Models of resistance to GA101 and Rituximab validated, resistance to R-CHOP in progress and resistance to immune checkpoint inhibitors (anti-PD1) in progress
- Samples of *ex vivo* ALL, AML, CML, myeloma and NHL



Heat map presenting cross resistance of different anticancer agents in various lymphoma cell lines.



In vivo resistance model generated in a NHL model (RL) exposed to the anti CD20 monoclonal antibody (Mab) rituximab.
(For the legend of the figure, please note that S mean "sensitive" and R mean "resistant" tumors)



In vivo resistance model generated in a NHL model (RL) exposed to the anti CD20 monoclonal antibody (Mab) obinutuzumab
(For the legend of the figure, please note that S mean "sensitive" and R mean "resistant" tumors)

PLATFORMS & TECHNICAL RESOURCES

Privileged access to Rockefeller animal facility, partnering with ProfilXpert platform (platform of microgenomics and genomics), Anipath (center of histology for rodents), Imthernat (center of laboratory small animal imaging), Antineo (CRO of innovative anticancer agents development).

R&D OFFER

Preclinical evaluation of biocompounds (efficacy / toxicity, in combination and/or in monotherapy) through the laboratory *in vivo* and *in vitro* resistance models.

KEY WORDS
Screening, Anticancer agent, Lymphoma, Preclinical models

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Clinical and Experimental Models of Lymphomagenesis

TEAM LEADERS
Gilles Salles
Laurent Genestier

LABORATORY
Inserm UMR1052 CNRS 5286 Centre Léon Bérard, Université C. Bernard Lyon-1
Centre de Recherche en Cancérologie de Lyon

TYPE OF COLLABORATION
Collaborative projects

RESEARCH AREAS & OBJECTIVES

Research areas

- T-cell lymphomas: functional genomics, new murine models, role of TCR signaling
- B-cell lmphomas: molecular and cellular characterization of marginal zone, follicular and CNS lymphomas
- Clinical impact of molecular alterations of B- and T-cell lymphomas

Objectives

1) We aim to analyze transformation mechanisms of T lymphocytes into T-cell lymphomas by using functional genomics approaches, evaluated on human cell lines and primary samples as well as dedicated murine models.
2) We aim to characterize genomic alterations of several sub-types of B-cell lymphomas to improve diagnostic and prognostic markers.
3) We aim to analyze the mechanisms of resistance to inhibitors of the BCR signaling pathway in B-cell lymphomas.
4) We study metabolic dysregulations in different lymphoma sub-types.

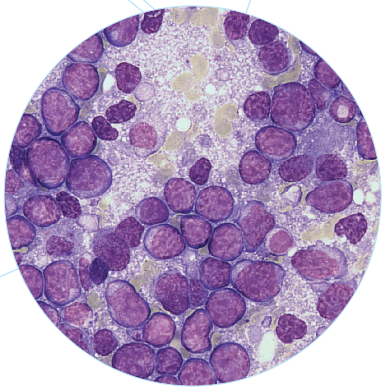
EXPERTISE

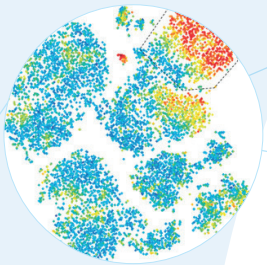
Biological targets and *in vitro* / *in vivo* / *ex vivo* models
Targets:
TCR and BCR signaling, cellular metabolism
Models:
B and T cell lines (modification by CRISPR/Cas9), T-cell lymphoma murine models; other murine models ; primary human tumors

Blood and tissue biomarkers
Transcriptomics, mutations, SNP

Early pharmacodynamic signs of activity
Cytof

Tools, processes and platforms in connection with clinical research
Closed links with LYSA clinical trials



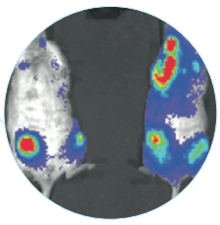


PLATFORMS & TECHNICAL RESOURCES

Cellular and molecular biology
Flow cytometry

R&D OFFER

The laboratory offers *in vitro* and *in vivo* research collaborative projects on TCR and BCR signaling pathways and on T-cell lymphomas models (drugs efficacy, mechanism of action) using human cell lines or primary samples as well as original murine models.



KEY WORDS
T- and B-cell lymphomas, TCR signaling pathway, BCR signaling pathway, Metabolomics

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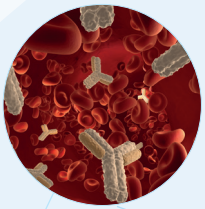
Control of the B-Cell Immune Response and Lymphoproliferations (CRIBL)

TEAM LEADER
Michel Cogné
Jean Feuillard

LABORATORY
CRNS UMR 7276
Centre de Biologie et Recherche en Santé

TYPE OF COLLABORATION
Scientific and technical expertise in the immunology field
Know-how and equipment: collaborative contracts or provision of services



RESEARCH AREAS & OBJECTIVES

Research areas
- Genetics, physiology and physiopathology of the B lymphocyte cell line
- Mechanisms of lymphomagenesis
- Antibodies engineering
- Ig deposition disease

Objectives
The CRIBL laboratory focuses on the study of the B lymphocyte cell line. Its research objectives are:
- **Fundamental:** mechanisms regulating antibodies production, study of genetic remodeling associated to differentiation and maturation of B lymphocyte, biology of B cell lymphomagenesis, physiology of normal B cells.
- **Applied to experimental medical issues**: setup of mouse models of immune and onco-hematologic pathologies and participation to clinical research activities (through the National Reference Center of Ig deposition disease), setup of new diagnostic tools for lymphomas.
- **Finalized:** with approaches aiming at improving diagnostic and treatment of tumor or dysimmune diseases and through developments in flow cytometry and imaging domains.

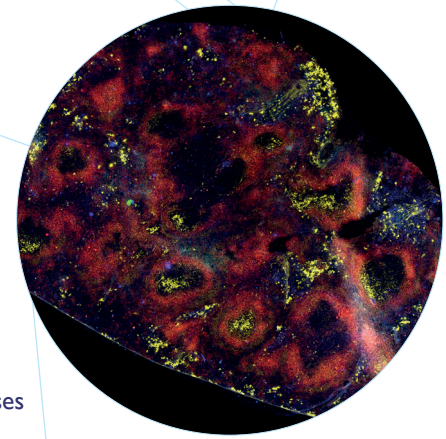
EXPERTISE

Biological targets and *in vitro* / *in vivo* / *ex vivo* models
- Targets: BCR, oncogenes (Myc, Bcl2,…), NF-kappaB
- *In vivo* models: murine model of lymphomagenesis and Ig deposition disease
- *In vitro* models: lymphoma cell lines

Blood and tissue biomarkers
- Multicolor FACS analysis of lymphocyte subpopulations
- Analysis of B-cell repertoire by NGS
- Immunohistochemistry (including confocal microscopy)

Early pharmacodynamic signs of activity
Development of biomarkers and companion assays in flow cytometry

Tools, processes and platforms in connection with clinical research
- National Reference Center for Amylose AL and other monoclonal Ig deposition diseases
- Center of Clinical Investigation (CIC Inserm), Limoges University Hospital
- Unité Fonctionnelle de Recherche en Hématologie Biologique, Limoges Univ. Hospital
- Unité de Recherche Clinique en Hématologie (URC-H), Limoges Univ. Hospital



Visualization by immunofluorescence of B follicles (red halos) from spleen section containing germinal centers. Within germinal centers, B lymphocytes proliferate (dark areas) and then differentiate into memory B cells or plasma cells (yellow marked areas) ®.
Works of L. Deply - Image of Claire Carrion, CRIBL, Limoges

PLATFORMS & TECHNICAL RESOURCES

The laboratory has a transgenesis platform and has access to the technological BISCEm platform of Limoges University including:
- Animal facility: SOPF and conventional
- Histology
- Fluorescent microscopy (confocal and macroconfocal)
- Flow cytometry (analyser and high-speed cell sorter) and flow imager
- Genomics (high and average throughput)
- Mass spectrometry, NMR
- Bioinformatics

R&D OFFER

The laboratory offers its renowned expertise in the immunology field of B cell and particularly in the generation of animal models for the study of expression of Ig and B lymphomagenesis: models mimicking human onco-hematologic pathologies and models of Ig deposition.
The laboratory is closely linked to the "Unité de Recherche Clinique du Service d'Hématologie Clinique" of Limoges University Hospital and the Center of Clinical Investigation (CIC Inserm).

KEY WORDS
Lymphoproliferations, Mouse models, B-cell genetics, Immunology, Onco-hematology, Transgenesis

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Cytokines Receptors and Signaling

TEAM LEADERS
Gilles Uzé
Guillaume Cartron

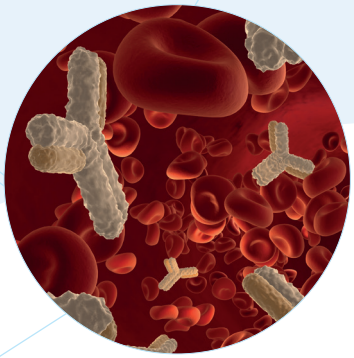
LABORATORY
CNRS UMR 5235
Dynamique des Interactions Membranaires Normales et Pathologiques (DIMNP)

TYPE OF COLLABORATION
Collaborative projects
Access to cohort/ collection of malign blood disease

RESEARCH AREAS & OBJECTIVES

Reasearch areas
Activation mechanisms of immune system in antibody therapies

Objectives
The laboratory aims at:
- identifying interferon cellular targets for its antitumor activity,
- better understanding mechanisms and variability of response to monoclonal antibodies including clinical, constitutive and pharmacological parameters.



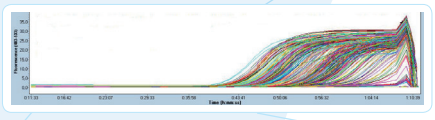
EXPERTISE

Biological targets and *in vitro* / *in vivo* / *ex vivo* models
Targets:
- Immune system (CD8α, PDL1, PDL2, CLEC9A, XCR1, FcγR, B10)
- Tumor target marker (CD20, microRNA)
Models:
Murine lymphoma models, functions and engineering of type I interferon

Blood and tissue biomarkers
- Biomarkers of long-term immunity activation after antibody treatment in preclinical models
- Biomarkers of response to monoclonal therapeutic antibodies
- Biomarkers of adverse effects to monoclonal therapeutic antibodies

Early pharmacodynamic signs of activity
PK-PD modeling of therapeutic and adverse effects activity of monoclonal antibodies

Tools, processes and platforms in connection with clinical research
- Center of clinical investigation of Montpellier's University Hospital
- Biological platform of the Institute for Regenerative Medicine & Biotherapy, particularly in genomics, proteomics and flow cytometry

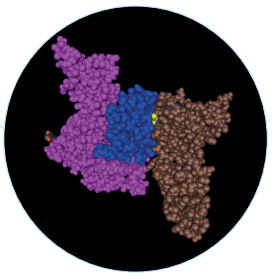


PLATFORMS & TECHNICAL RESOURCES

- Flow cytometry platform and high throughput quantitative PCR
- Antibodies engineering of mabimprove Laboratory of Excellence

R&D OFFER

The laboratory offers collaborative research on predictive factors of response to monoclonal antibodies and access to the HEMODIAG cohort / collection of malign blood diseases of the haematological department.



KEY WORDS
Antibody, Immune response, Interferon

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Early Steps of Haematopoietic Transformation

TEAM LEADER
Olivier Bernard

LABORATORY
Inserm UMR 1170 Institut Gustave Roussy

TYPE OF COLLABORATION
Collaborative projects

RESEARCH AREAS & OBJECTIVES

Research areas
TET2 and normal and pathological haematopoiesis

Objectives
The overall aim of the group is to identify the acquired mutations in the early step of haematopoietic transformation, understand the network of cooperating events underlying transformation and develop experimental models to allow functional investigations and serve as preclinical models.
In particular, the team is investigating the role of TET2/3 and of 5mC/5hmC epigenetic marks in normal and malignant of both T-lymphoid and myeloid differentiation and is studying the cooperation between TET2 and DNMT3A mutations in transformation.

EXPERTISE

Tissues (frozen/FFPE)
Blood / bone marrow, mononuclear cells, platelet, plasma
Cell lines

Molecular analysis
- Pre-analytical (DNA, mRNA)
- Genomic analysis, library/PGM/ Miseq
- Transcriptomic: qPCR

Biochemical studies
- Immunological: NPM-ALK antibody titer
- Proteomic: Western Blot

Cellular analysis
- Cell sorting/ transfection
- Viability and apoptosis: WST, Annexin V
- Cellular caracterisation using flow cytometer

PLATFORMS & TECHNICAL RESOURCES

The laboratory has access to the different platforms Gustave Roussy Institute:
- Department of Integrated Biology (PBI) integrating next-generation sequencing and the «omics» units: Genomics, Proteomics, Metabolomics
- Translational Research Laboratory (LRT)
- Biological Resources Centre (CRB)
- Imaging Flow Cytometry Platform
- Bioinformatics Platforms
- Immunomonitoring in Oncology Laboratory (LIO)
- Pre-clinical Evaluation Unit (PFEP)

R&D OFFER

- Preclinical evaluation of molecules (efficacy / toxicity, in combination and/ or in monotherapy) on *in vivo* and *in vitro* mantle cell lymphoma models
- Biomarker assays development in phase I trials
- Molecular screening in phase I trials

KEY WORDS
TET2, TET3, Hematopoiesis, Epigenetics, Differentiation

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Genomics and Biomarkers of Lymphoma and Solid Tumours

TEAM LEADER
Fabrice Jardin

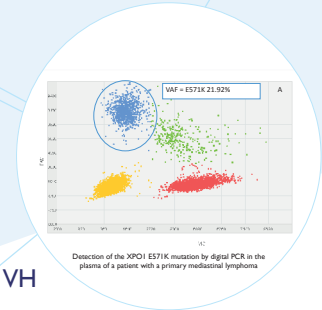
LABORATORY
Inserm U1245

TYPE OF COLLABORATION
Collaborative projects

RESEARCH AREAS & OBJECTIVES

Research areas
Genomic and transcriptomic of lymphomas

Objectives
The laboratory aims at establishing correlations between molecular data and phenotype / clinic of lymphomas: prognostic or theranostic value; setup of diagnostic assays; identification of the biological value of identified variants in tumor and plasma.



Detection of the XPO1 E571K mutation by digital PCR in the plasma of a patient with a primary mediastinal lymphoma

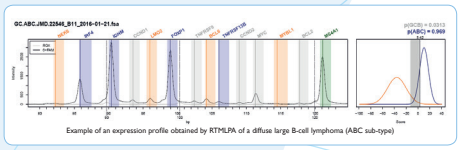
EXPERTISE

Biological targets and *in vitro* / *in vivo* / *ex vivo* models
Targets: molecular studies of genes coding for BCR component and particularly VH genes

Blood and tissue biomarkers
- Study of recurrent mutations and abnormal copy number of genes affecting prognostic
- Targeted transcriptomic studies and transfer in immunohistochemistry

Early pharmacodynamic signs of activity
Correlation between transcriptome/ genomics and PETScan imaging

Tools, processes and platforms in connection with clinical research
- Average throughput genotyping platform, multiplex PCR analysis, study of key gene methylation by pyrosequencing
- Tumor bank
- Conventional cytogenetics and FISH
- Clinical research unit including early phase trials


Example of an expression profile obtained by RTMLPA of a diffuse large B-cell lymphoma (ABC sub-type)

PLATFORMS & TECHNICAL RESOURCES

- Sequencing, (PGM) quantitative PCR (TaqMan) pyrosequencing
- Genotyping platform and transcriptomic analysis of average throughput (Illumina, BeadExpress)
- Flow cytometry
- Cell transfection (Amaxa), cloning, cell culture
- Tissue-microarray
- Conventional cytogenetics and FISH
- Bioinformatics

R&D OFFER

The laboratory offers collaborative projects on:
- targeted sequencing (tumor and plasmatic DNA) and molecular phenotyping (genetic expression profiles) in clinical assays
- quantification of recurrent mutations in plasmatic DNA
- correlation between anatomical-clinical / molecular and PET scan imaging
- bioinformatics tools for analysis of variants and their integration in routine diagnosis
- development of B and T-cell lymphomas phenotyping tools.

KEY WORDS
Genome, Genotyping, Transcriptome, Immunoglobulin genes, Transfer methylation

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Genomic Instability and Human Hemopathies

TEAM LEADER
Bertrand Nadel

LABORATORY
Inserm U1104 CNRS UMR7280
Centre d'Immunologie de Marseille-Luminy

TYPE OF COLLABORATION
Collaborative research
Screening and validation of targets / inhibitors

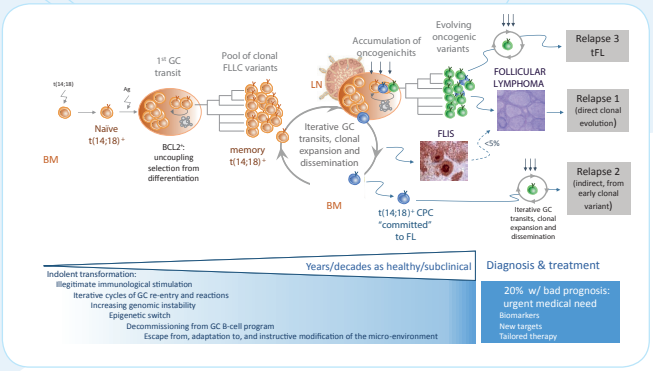
RESEARCH AREAS & OBJECTIVES

Research areas

Identification of biomarkers of progression and new therapeutic targets in Lymphoma and lymphoblastic leukemia

Objectives

The laboratory aims at identifying "addictive" molecular alterations present in lymphoïd neoplasia and in particular mutations founding the precursor cancer cells (CPC) that cause relapses.The research team tests inhibition of these targets in preclinical *in vitro*/*in vivo* customized models.



EXPERTISE

Biological targets and *in vitro* / *in vivo* / *ex vivo* models

Discovery and functional validation of therapeutic targets:

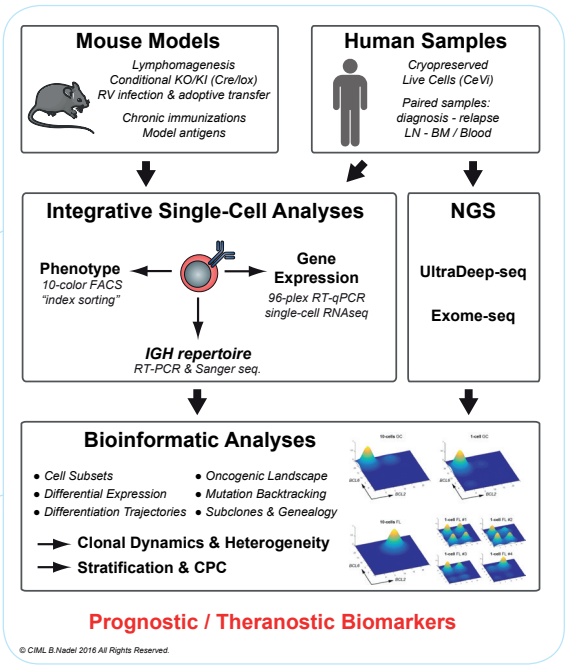
- Tumor genetics, including -omics (NGS, including single-cell)
- *Ex vivo* functional validation (CRISPR/CAS9, shRNA, 3D culture, chemograms)
- *In vivo* functional validation: production of murine preclinical customized models (KI/KO/Tg, conditional retrovirus, BMT, long-term chronic immunisation, tumor transplantation, PDX) and fine characterization of tumors (IHC, IF, CMF, molecular including NGS, single-cell)

Blood and tissue biomarkers

- Forward and reverse genetic / NGS screening of cohorts (clinical, epidemiological)

PLATFORMS & TECHNICAL RESOURCES

- L2/3 laboratory (CMF/cell sorting, technical platform of lentivirus production)
- Imaging (confocal/two-photon microscopy)
- Mouse engineering
- Single Cell (Biomark/C1)
- Collection of transplantable, biologically characterized and clinically annotated PDX from T-ALL patients



R&D OFFER

- Lymphoïd neoplasia expertise
- Single-cell technology expertise and bioinformatics analysis pipelines
- CRISPR/CAS9 expertise
- Concept, design and customization of preclinical models
- PDX collection (T-ALL)

KEY WORDS
Follicular lymphoma, LAL-T, Oncogenesis, Oncogenic addiction, CPC, Single-cell, OMICS, Preclinical models, Predictive and prognostic biomarkers

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Immunity and Cancer

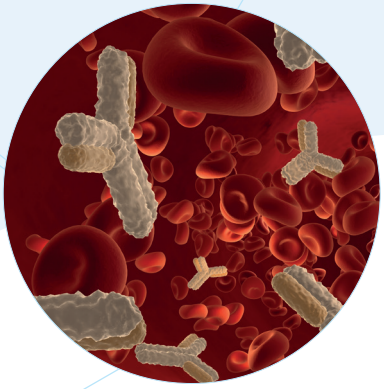
TEAM LEADER
Daniel Olive

LABORATORY
Inserm U1068 CNRS UMR7258
Centre de Recherche en cancérologie de Marseille

TYPE OF COLLABORATION
Collaborative projects
Expertise
Training for master and PhD
Immunological databases from lymphoma patients

RESEARCH AREAS & OBJECTIVES

- Alterations of innate immunity associated to cancers
- Molecules of immune co-signaling and co-stimulation
- Role of the immune system in the microenvironment of lymphoproliferations
- Acquired immunodeficiencies related to cancer
- PI-3K signaling pathway
- Immunomonitoring of biotherapies in cancerology



EXPERTISE

Biological targets and *in vitro* / *in vivo* / *ex vivo* models
Targets
- Co-signaling molecules and innate immunity
- Innate immunity and cancer

Models
- *Ex-vivo* cultures
- Immunodéficient mice
- KO and KI models

Blood and tissue biomarkers
Co-signaling molecules and lymphomas

Early pharmacodynamic signs of activity
Co-stimulation of T-cells and phosphatidyl-inositol 3'-kinase (PI-3K) signaling pathway

Tools, processes and platforms in connection with clinical research
- Immunohistochemistry
- Generation of monoclonal antibodies
- IBiSA platform of cancers immunomonitoring
- Advanced Flow cytometry
- Regional platform of somatic molecular oncogenetics

PLATFORMS & TECHNICAL RESOURCES

- Cancer immunomonitoring: Phase I studies
- Preclinical models
- Works on patients samples
- Polychromatic flow cytometry
- IHC

R&D OFFER

- Collaborative projects
- Expertise in immunology related to cancer
- Setup of immunomonitoring projects
- Training for master and PhD including "Master Pro" of flow cytometry
- Access to immunological databases from lymphoma patients
- ADCC NK assay in *in vitro* cell models of lymphoma patients
- Immune biomarkers analysis (flow cytometry)

KEY WORDS
Co-signaling molecules, Microenvironment, Innate immunity, Immunodeficiency related to cancer

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Immunology and Oncogenesis of Lymphoid Tumors

TEAM LEADER
Philippe Gaulard

LABORATORY
Inserm U955
Institut Mondor de Recherche Biomédicale

TYPE OF COLLABORATION
Collaborative research
Access to databases

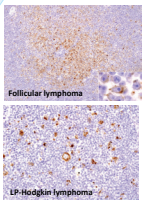
RESEARCH AREAS & OBJECTIVES

Research areas
- Oncogenesis of peripheral T-cell lymphomas
- Immunoregulation by the immunosuppressive enzyme IL4I1
- Identification of diagnostic, prognostic and predictive biomarkers in lymphomas

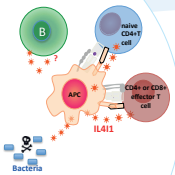
Objectives
The team's objectives are to:
- describe oncogenic events that transform normal lymphocytes to tumour cells to improve lymphoma diagnosis and treatment,
- understand the mechanisms responsible of the decreased anti-cancer immune responses mediated by IL4I1.

EXPERTISE

Biological targets and *in vitro* / *in vivo* / *ex vivo* models
Targets:
- Molecular alterations in lymphoma entities, especially in epigenetic regulators and in cell signalling (especially TCR and co stimulatory signalling) in T-cell lymphomas
- Immunomodulatory effect of IL4I1
Models:
- KO IL4I1 and double KO IL4I1/IDO mice
- Numerous lymphoma cell lines



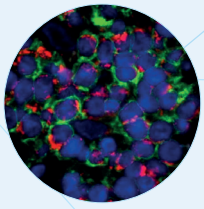
IL4I1 staining in brown



Multiple functions of IL4I1 in immune cells and expression in lymphomas

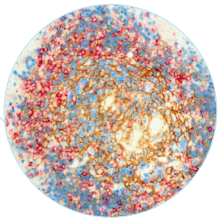
Blood and tissue biomarkers
- Mutations identification: allele specific PCR, High-Resolution DNA Melting (HRM), Next Generation Sequencing
- Gene expression: RT PCR, microarray , RT MLPA
- Cytogenetic studies: aCGH, FISH
- In situ protein expression: immunohistochemistry allowing the analysis of markers on the tumor cell and on the microenvironnement, in particular IL4I1 (monoclonal antibody developed by the group)

Tools, processes and platforms in connection with clinical research
- Biological ressources:
  - TENOMIC collection: more than 800 T-cell lymphoma with multiples annotations and molecular data
  - LYSA-P
  - Mondor Biobank
- Imaging platform (IHC, FISH, TMAs, scanning and image analysis related to LYSA-P platform)
- Clinical ressources:
  - LYSA
  - CLIP², allowing development of early phase clinical trial



PLATFORMS & TECHNICAL RESOURCES

Microscopy / FISH / Tissue chips / Virtual images / Genomic platform with NGS



R&D OFFER

- *In vitro* preclinical models
- Access to well annotated and characterized lymphoma collection (more than 800 PTCL in TENOMIC)
- Pathological review, immunochemistry, FISH, molecular diagnosis
- Early phase clinical trial

KEY WORDS
Peripheral T-cell lymphomas, Oncogenesis, Lymphoma biomarkers, IL4I1

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Laboratory of Molecular Mechanisms of Hematologic Disorders and Therapeutic Implications

TEAM LEADER
Olivier Hermine

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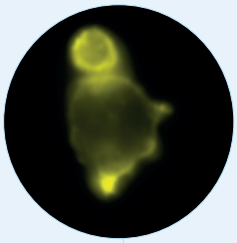
Institut des maladies génétiques
IMAGINE

TYPE OF COLLABORATION
Collaborative research
Partnering research
Expertise
Clinical databases
Collections



RESEARCH AREAS & OBJECTIVES

Research areas
- Virus-associated lymphoproliferations (HTLV1, HCV, EBV)
- Lymphoproliferations associated with immunodeficiencies
- Mantle cell lymphoma
- Enteropathy-associated T-cell lymphoma (EATL)
- Graft-versus-host disease
- Antitumoral immunotherapy

Objectives
The laboratory covers several aspects of the physiopathology and treatment of malignant and benign hematologic disorders. Major research objectives are: i) the characterization of mechanisms governing the physiopathology of hematological disorders; ii) the development of therapeutic strategies to treat these diseases; iii) the development of clinical research and iv) technology transfer.

EXPERTISE

Biological targets and *in vitro* / *in vivo* / *ex vivo* models
Targets:
- Immune checkpoints and immunological synapse
- Tyrosine kinases (ex: Ckit, PDGF-R, Lyn)
- NK receptors (ex: KIR), Neuropilin 1 (NRP1), Transferrin receptor (TFR)

Models:
- *In vitro*: cell lines of B and T-cell non-Hodgkin lymphoma and acute lymphoblastic leukemia, coculture of cell lines or primary cells with macrophages or NK cells
- *In vivo:* immunodeficient mice (xenografts of cell lines or primary cells), spontaneous animal models (dogs, cats)
- *Ex vivo*: *in vitro* expansion of primary iNKT cells, expansion of normal and pathologic CD34+ cells

Blood and tissue biomarkers
- Assessment of *in vitro* human iNKT cells expansion to predict GVH
- Expression of NRP1 and TFR as prognostic factors

Early pharmacodynamic signs of activity
- Kinases activation
- Telomeres and telomerase activity

Tools, processes and platforms in connection with clinical research
- Bioinformatics (sequencing data analysis) and biostatistics platforms
- Imaging technics (image stream, confocal microscopy)
- Patients cohorts: EATL, HTLV1-associated lymphomas, NK/T-cell lymphomas, subcutaneous panniculitis-like gamma/delta T-cell lymphomas

PLATFORMS & TECHNICAL RESOURCES

Available platforms
- Genomics (exome sequencing, targeted resequencing, SNP array), proteomics
- Flow cytometry and cell sorting, microscopy (confocal microscopy, image stream, videomicroscopy)
- Mice facility / Transgenesis
- Induced pluripotent stem cells

Other available tools
Study of ADCC, apoptosis, vaccine response in mouse models, activity of regulatory T cells, lymphocytotoxicity (mediated by CD8+ T lymphocytes or NK cells).

R&D OFFER

- Collaborative and partnering research: pharmacologic modulation of biological targets, prognostic biomarkers development
- Expertise: HTLV1-associated lymphomas, mantle cell lymphomas, EATL, immunodeficiency-related lymphomas, HCV-associated lymphomas
- Clinical databases: HTLV1-associated lymphomas, EATL, NK/T-cell lymphomas
- Tumor samples collections: EATL, HTLV1-associated lymphomas, NK/T lymphomas, subcutaneous panniculitis-like gamma/delta T-cell lymphomas
- Spontaneous tumor animal models

KEY WORDS
Molecular and cellular mechanisms of pathogenesis, Therapeutic innovation, Valorisation

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Microenvironment Cell differentiation, iMmunology And Cancer (MICMAC)

TEAM LEADER
Karin Tarte
Thierry Fest (*Rennes University Hospital*)

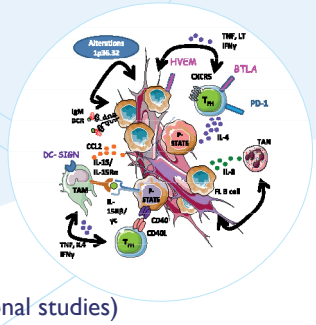
LABORATORY
Inserm UMR U917

TYPE OF COLLABORATION
Collaborative research
Expertise

RESEARCH AREAS & OBJECTIVES

Research areas
Germinal center B-cell Lymphomas:
- Study of normal and malignant germinal center B-cell differentiation
- Study of B-cell lymphoma tumor niches

Objectives
The laboratory aims at:
- identifying mechanisms of host/tumor interaction in B-cell lymphomas
- therefore finding therapeutic targets and potential biomarkers.



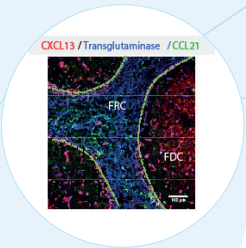
EXPERTISE

Biological targets and *in vitro* / *in vivo* / *ex vivo* models
Targets : anti-CD137 antibodies and lymphomas, CXCL12, cellular targets (TFH, tumor-supportive stromal cells)
Models:
- Models of *in vitro* differentiation of human normal naive B cells
- Models of *in vitro* study (flow cytometry, microscopy, transcriptomic, functional studies) of interactions between normal and tumor B lymphocytes and microenvironment actors (stromal cells, TFH, macrophages)

Blood and tissue biomarkers
Program of identification of diagnostic and prognostic blood biomarkers in DLBCL and FL by transcriptomic, proteomic, phenotypic and functional studies

Early pharmacodynamic signs of activity
Immunomonitoring platform allowing standardized monitoring (SOP) by multicolor flow cytometry and functional studies of patients treated with innovative therapeutic approaches (DC-NK dialogue, Treg activity, IDO activity, characterization by multicolor flow cytometry of T/B/myeloid/stromal cell sub-populations)

Tools, processes and platforms in connection with clinical research
- Lymphoma tumor collection including frozen samples of viable cells from lymphoid organs and bone marrow of patients and healthy individuals (Lymphoma Biological Resource Center of Rennes)
- Clinical-biological databases (Marguerite Program)
- Phase I trials platform (Clinical Investigation Center of Rennes)



PLATFORMS & TECHNICAL RESOURCES

- Immunomonitoring laboratory (SITI)
- Lymphoma tumor collection
- Access to platforms of BIOSIT SFR: microscopy (MRic IBISA platform http://microscopie.univ-rennes1.fr/), genomics (Biogenouest IBISA platform of Rennes), L3 laboratory (lentiviral vectors), animal facility

R&D OFFER

The laboratory offers collaborative projects on:
- cocultures of primary B cells/stroma from healthy individuals and patients (survival, proliferation, drug resistance…)
- cocultures of B cells/macrophages and PN (ADCP)
- antibody-dependent cell-mediated cytotoxicity (ADCC)
- multicolor standardized immunomonitoring of multicentric studies (assays validated at day+1).

KEY WORDS
Follicular lymphoma, DLBCL, Microenvironment, Stromal cells, TFH, Macrophages, Normal and tumoral B cell differentiation, Blood biomarkers

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Regulation of Bcl2 and p53 Networks in Multiple Myeloma and Mantle Cell Lymphoma

TEAM LEADER
Martine Amiot

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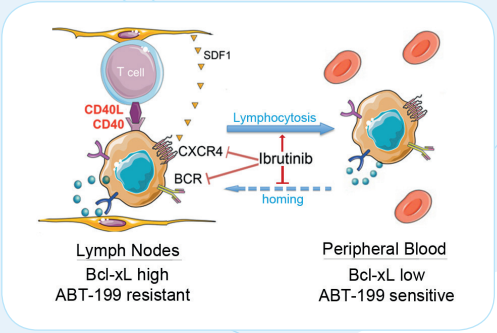
Centre de recherche en cancérologie
Nantes-Angers

TYPE OF COLLABORATION
Collaborative research
Access to collections and databases

RESEARCH AREAS & OBJECTIVES

The laboratory studies the role of the microenvironment in the reactivation of signaling pro-apoptotic pathways in B-cell lymphopathy: molecular and preclinical mechanisms.

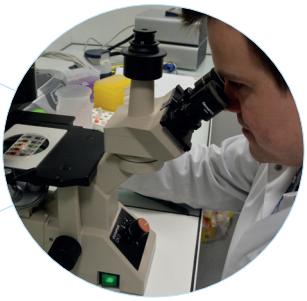


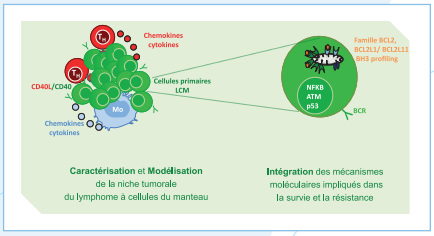
EXPERTISE

Biological targets and *in vitro* / *in vivo* / *ex vivo* models

Targets:
- Apoptosis intrinsic pathway (BCL2 family)
- TP53 pathway
- BCR pathway (BTK)

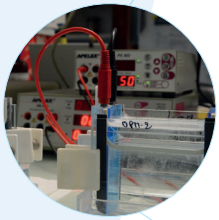
Models:
In vitro models: mantle lymphoma cell lines (n= 9)
Ex vivo models: coculture system of primary cells of LCM + L40 + cytokines





PLATFORMS & TECHNICAL RESOURCES

Platforms of the François Bonamy SFR (www.sfrsante.univ-nantes.fr):
- Cytocell platform: flow cytometry and cells sorting (Biogenouest)
- GenoBIRD platform: bioinformatics and genomics (IBISA/Biogenouest)



R&D OFFER

The laboratory offers to evaluate drugs that directly activate the intrinsic apoptosis pathway or that modulate actors implicated in that pathway mainly by inhibiting the protective role of microenvironment.
To do so, the laboratory has set up a coculture system in the medium run (15 days) of primary cells of Mantle Cell Lymphoma. This coculture system mimics the effect of microenvironment and reproduces molecular signatures of tumor cells observed in lymphoid tissue.
The laboratory offers access to collections and databases: REFRACT-LYMA (Hanf M, 7 authors, Le Gouill S. The REFRACT-LYMA Cohort Study: a French observational prospective cohort study of patients with Mantle Cell Lymphoma BMC Cancer in press).

KEY WORDS
Microenvironment, B-Cell lymphoma, Cellular cycle, Cellular death

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RNA Biology in Hematological Cancers

TEAM LEADER
Pierre Brousset

LABORATORY
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Centre de Recherche en Cancérologie de Toulouse

TYPE OF COLLABORATION
Collaborative research
PhD CIFRE fellowships

RESEARCH AREAS & OBJECTIVES

The laboratory has three lines of research focusing on:
i) the characterisation and modeling of molecular events responsible for hematopoietic tumors such as the role of non-coding RNA in hematopoietic tumors and the study of X-ALK fusion proteins and their impact on lymphomagenesis,
ii) the research and development of monoclonal antibodies production used in tumor pathology,
iii) the study of immune microenvironment in lymphomas and immunomonitoring.

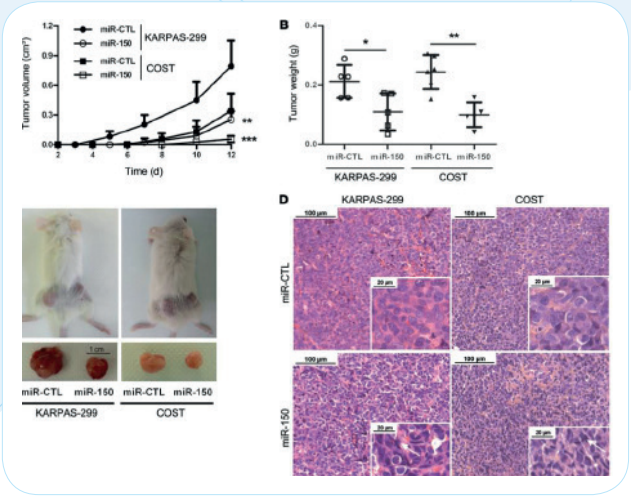
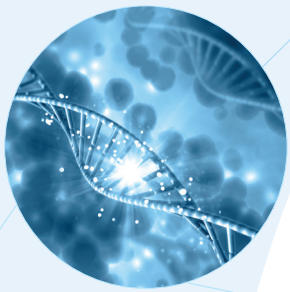


Figure: miR-150 overexpression inhibitis KARPAS-299 and COST xenograft growth in NOD/SCID mice (Hoareau-Aveilla C, et al. JCI 2016)
(A) NPM-ALK(+) KARPAS-299 and COST cells transfected either with miR-CTL or miR-150 were injected s.s. in the left or right flank of 5 NOD/SCID mice, respectively (n=5). Tumor volume was evaluated over time by caliper measurements and reported as mean ± SEM (bars). **P<0.001, ***P<0.0001, using unpaired 2-tailed Student's t test. (B) Tumor weight measurement, reported as mean ± SEM (bars). *P<0.05, **P<0.001, using unpaired 2-tailed Student's t test. (C) Representative tumors resected from mice xenografted with miR-CTL- or miR-150-transfected KARPASS-299 and COST cells. Scale 1 cm. (D) Micrographs of hematoxylin and eosin staining of excised miR-CTL or miR-150 tumors (scale bars: 100 µm, inset 20 µm; original magnification x20, inset x80). Arrows indicate cells with phenotypic hallmarks of cellular degeneration, i.e., uncommon chromatin condensation, nuclear piknosis, cellular volume decrease, or muclear envelope disruption.

EXPERTISE

Biological targets
- ALK
- NPM/ALK transgenic mice
- TPM3/ALK

Blood and tissue biomarkers
- NPM/ALK fusion transcripts
- MicroRNA
- Small nucleolar RNAs
- AU-binding proteins



PLATFORMS & TECHNICAL RESOURCES

- Cancer research center of Toulouse (CRCT)
- High throughput genomics: arrays, Fluidigm, Next Generation Sequencing
- Animal facility
- Transgenesis

R&D OFFER

Partnering with *in vitro* diagnostics industry to co-develop and/or out-licence a patent on molecular signature of snoRNA, predictive of the prognostic of peripheral T-cell lymphomas.

KEY WORDS
T-cell lymphoma, Anaplastic large cell lymphoma, ALK, Non-coding RNA, Post transcriptional regulation, Monoclonal antibodies production, Study of immune microenvironment

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