NATIONAL CLINICAL RESEARCH NETWORK FOR THE DESIGN, SPONSORING AND CONDUCT OF PHASE I-IV INTERVENTIONAL AND NON-INTERVENTIONAL CLINICAL TRIALS (AML)

Keywords

Clinical development | AML | Targeted therapy | Cell therapy | Immunotherapy | Hematopoietic stem cell transplant | Chemotherapy | Clinical research (TRL 3-8) |

OPALE entity

Acute Leukemia French Association (ALFA)

Head

Prof. Hervé Dombret

Responsable de l'Entité

Contact

Dr. Sandrine Palcy

Responsable du Business Development

Within the current regulatory framework, ALFA sponsors national multicenter clinical trials in the field of acute myeloid leukemia (AML) in adults. Comprising clinicians, biologists and clinical research assistants, the group has a network of centralized operational structures and interfaces with translational research laboratories.

Focused on improving care and its benefits, academically sponsored independent clinical trials (IIT, investigator initiated trial; IST, investigator sponsored trial) are of key importance in optimizing the efficacy, safety and cost/benefit ratio of healthcare. Conducted at the initiative of ALFA members, these studies aim to provide the best treatment option for a given patient (or group of patients).

Description

Scope

Clinical research on AML, with the aim of improving patient care and quality of life:

- Interventional research: clinical trials testing new therapeutic approaches, usually oligo- or multi-centric for ALFA, but could possibly be uni-centric
- Non-interventional research: studies based on real-life observatory data, to assess the efficacy and safety of approved treatments, but also to identify prognostic biomarkers; ALFA favors prospective observational studies

Role

- Clinical trial/study sponsor
- Operational coordination of clinical studies, including modern, centralized somatic genomics and residual detectable disease (MRD) monitoring

Investigation centers

33 investigative centers in mainland France and on Reunion Island

Organization

- Dr. Renaud Buffet, Medical coordination
- Prof. Raphaêl Itzykson, President of the Scientific Council

Infrastructure

- Centralized review of conventional cytogenetic results
- Centralized molecular biology laboratory (somatic genomics, molecular MRD)
- Network of laboratories monitoring residual disease by flow cytometry (FMC)
- Centralized biobank
- Data Center and independent Biostatistics unit
- Network of translational research laboratories linked to ALFA.

Quality assurance

- Standard Operating Procedures (SOPs)
- Coordination unit

Specifications

Type of platform: national multicenter network

Type of studies: prospective interventional or non-interventional clinical studies within the current European regulatory framework

Phases: I to IV

Examples of partnerships

Prospective non-interventional study documenting the management and outcome of adult patients with AML (ALFA-PPP observational cohort) - Prospective collection of all initial and follow-up clinico-biological data from adult patients with newly diagnosed or relapsed/refractory AML, treated according to options approved by the health authorities, including early access to new drugs.

Partners: Astellas, BMS-Celgene, Servier

Terms

- Clinical research project initiated and sponsored by ALFA
- Partnership agreement with the concerned manufacturers to support the study (supply of study drugs and financial support).

NATIONAL CLINICAL RESEARCH NETWORK TO SUPPORT SPONSORS OF PHASE I TO IV INTERVENTIONAL AND NON-INTERVENTIONAL CLINICAL TRIALS (AML)

Keywords

Clinical development | AML | Targeted therapy | Cell therapy | Immunotherapy | Hematopoietic stem cell transplant | Clinical research (TRL 6-8) |

OPALE entity

Acute Leukemia French Association (ALFA)

Head

Prof. Hervé Dombret

Responsable de l'Entité

Contact

Dr. Sandrine Palcy

Responsable du Business Development

ALFA brings its expertise and network of specialists and recruitment centers to bear on clinical trials and studies of innovative treatments for acute myeloid leukemia (AML) in adults.

The support of the ALFA national network optimizes access to centers for sponsors and contributes to improving the quality and safety of trials. Its internationally recognized laboratories (somatic genomics, MRD monitoring, translational platforms) can provide centralized assessment of certain key elements of the protocol. Finally, through its international collaborations, ALFA can facilitate contacts for extending trials or studies to other regions of the world.

Description

Scope

Clinical research in AML, with the aim of improving patient care and quality of life:

- Interventional research: clinical trials testing new therapeutic approaches
- Non-interventional research: studies based on real-life observation data, to assess the efficacy and safety of approved treatments

Role

- Support in designing a clinical trial/study protocol
- Recommendations on the choice and number of centers participating in the study
- Recommendations of experts (Key Opinion Leader) for the study's steering committee or independent data safety monitoring board
- Assumption of tasks delegated by the sponsor in the operational conduct of the study/trial, including characterization and centralized biological monitoring of the disease
- Conduct of correlative biological studies with translational laboratories linked to the ALFA group

Investigation centers

33 investigating centers in mainland France and Reunion Island

Organization

- Dr. Renaud Buffet, Medical Coordinator
- Prof. Raphaêl Itzykson, President of the Scientific Council

Infrastructure

- Centralized review of conventional cytogenetic results
- Centralized molecular biology laboratory (somatic genomics, molecular MRD)
- Network of laboratories monitoring residual disease by flow cytometry (FMC)
- Centralized biobank
- Data Center and independent Biostatistics Unit
- Network of translational research laboratories linked to the ALFA group

Quality assurance

- Standard Operating Procedures (SOPs)

- Coordination unit

Specifications

Type of platform: national multicenter network

Type of studies: prospective interventional or non-interventional clinical studies within the current European regulatory framework.

Phases: I to IV

Examples of partnerships

Efficacy of oral azacitidine plus best supportive care as maintenance therapy in subject with AML in complete remission (QUAZAR AML-001) - AH. Wei et al. N Engl J Med. 2020;383:2526-2537 - This study enrolled 472 participants, aged 55 or older, with a diagnosis of de novo acute myeloid leukemia (AML) or AML secondary to prior myelodysplastic disease or chronic myelomonocytic leukemia (CMML), and who have achieved first complete remission (CR)/ complete remission with incomplete blood count recovery (CRi) following induction with or without consolidation chemotherapy.

Partner: BMS-Celgene

Efficacy study of anti-KIR monoclonal antibody as maintenance treatment in AML (EFFIKIR) - N. Vey et al. Annual ASH Meeting, 2017 (abstract) - Double-Blind Placebo-Controlled Randomized Phase 2 Study evaluating the efficacy of lirilumab (IPH2102/BMS-986015) as Maintenance Treatment administered in elderly patients with Acute Myeloid Leukemia (AML) in first complete remission.

Partner: Innate-Pharma

Terms

- Clinical research project promoted by industry
- Partnership agreement with industrial partners to support study coordination

DATA AND SAMPLES FROM ADULT PATIENTS WITH ACUTE MYELOID LEUKEMIA (AML)

Keywords

Collections | Database | AML | Targeted therapy | Cell therapy | Immunotherapy | Hematopoietic stem cell transplant | Clinical research (TRL 6-8) |

OPALE entity

Acute Leukemia French Association (ALFA)

Head

Prof. Hervé Dombret

Responsable de l'Entité

Contact

Dr. Sandrine Palcy

Responsable du Business Development

Access to the ALFA group's databases and sample collections for clinical-biological studies of cohorts of adult patients with acute myeloid leukemia (AML) at all stages of the disease, at diagnosis and under treatment (response to treatment, relapse, follow-up).

Comprehensive clinico-biological data from patients included in clinical trials, combined with qualified blood and bone marrow samples. Benefit from homogeneously treated patient data/samples. Access to individual longitudinal follow-up (diagnosis/remission/relapse).

Description

Scope

Samples and sets of clinico-biological data monitored as part of therapeutic protocols, enabling projects to be carried out in the field of AML:

- Clinico-biological control cohorts (external control arms)
- Highly qualified and annotated biological samples
- Translational studies in collaboration with the network's translational platforms

Provision of anonymized data sets and/or samples

- Submission of application to ALFA
- Review by ALFA's Scientific Council
- Approval by ALFA Board of Directors
- Contractualization with OPALE's legal and partnerships manager

Organization

- Dr. Renaud Buffet, Medical Coordinator
- Prof. Raphaêl Itzykson, President of the Scientific Council

Infrastructure

- Database hosting on secure servers
- Project managers and clinical research assistants

Quality assurance

The quality assurance procedures used to build up collections and gather data around them comply with current legislation. In particular, they ensure:

- Patient information and consent to the use of biological samples for research purposes
- Compliance with data retention periods
- Data security and confidentiality throughout the chain, from consent to storage of the material and all associated data

Specifications

Collections

Annotated collections of nucleic acids (DNA and RNA, samples from several thousand patients), cells (leukemic blasts, non-leukemic

mononuclear cells), serum or plasma.

Samples collected at initial diagnosis, in remission phase and at diagnosis of refractory state or relapse.

Data sets:

- Relevant patient medical history
- Biological characteristics of the disease, including its somatic mutational landscape described according to the current best standards (ELN 2022)
- Documentation of first-line treatment (including, when performed, information on allogeneic transplantation). Documentation of refractory status and possible relapses, monitoring of residual disease by molecular biology, and, less systematically, residual disease by flow cytometry.
- Documentation of disease response, or refractory state, residual disease (MRD), remission, possible relapses (dates, lines of treatment), date and cause of possible death

Type of study: interventional and non-interventional clinical studies

Phases: I-IV

Examples of partnerships

An ALFA 2101 Multicenter Randomized Phase II Study: CPX-351 Versus Intensive Chemotherapy in Patients With de Novo Intermediate or Adverse Risk AML Stratified by Genomics (ALFA2101) -The trial is a randomized, open-label phase II study comparing CPX-351 vs conventional intensive chemotherapy in patients with newly diagnosed de novo AML and intermediate- or adverse-risk genetics (according to 2017 ELN criteria).

Partner: Jazz pharmaceutical

A Phase 2 Study of Gemtuzumab Ozogamicin (GO)-Gilteritinib Combination in Adults With FLT3-ITD Relapse/Refractory (R/R) AML (AGORA-1) - This is a national, open-label, single-arm, multicenter phase II trial evaluating the safety and efficacy of adding gilteritinib, a new FLT3 inhibitor to the AGORA platform, consisting of the combination of an intermediate dose of cytarabine and a divided dose of GO in adult patients with R / R AML with an FLT3-ITD mutation."

Partners: Astellas, Pfizer

Terms

- Research project approved by the ALFA Board of Directors
  - Provision of samples - Biological Material Transfer Agreement
  - Provision of data sets - Licensing agreement

NATIONAL CLINICAL RESEARCH NETWORK TO SUPPORT DRUG RESEARCH AND DEVELOPMENT (AML)

Keywords

Experts' advice | AML | Targeted therapy | Cell therapy | Immunotherapy | Hematopoietic stem cell transplant | Clinical research (TRL 3-8) |

OPALE entity

Acute Leukemia French Association (ALFA)

Head

Prof. Hervé Dombret

Responsable de l'Entité

Contact

Dr. Sandrine Palcy

Responsable du Business Development

With many years of expertise in conducting clinical and translational studies, ALFA Group's experts can help you establish a research and development strategy for innovative treatments in acute myeloid leukemia (AML).

In the context of regulatory, clinical, medico-economic and market access issues, ALFA guides you in the construction of your treatment development plan, including the evaluation of new therapeutic combinations.

Description

Scope

Our consulting services include:

- Personalized support, adapted to the development stage, from preclinical and correlative studies (in liaison with the network's translational laboratories) to registration trials, including early phase I/II trials.
- The provision of clinical, scientific and regulatory expertise, and market knowledge

Setting up support

- Multidisciplinary advisory boards
- Defining the elements of identified partnerships. These may take the form of expert reports, translational study projects, or even clinical trials
- Drafting of roadmaps, study projects and related reports

Organization

- Dr. Renaud Buffet, Medical Coordination
- Prof. Raphaêl Itzykson, President of the Scientific Council

Quality assurance

- Traceability of all stages of collaboration

Specifications

Therapeutic approach: Chemotherapy; Targeted therapy; Immunotherapy; Cell therapy-Hematopoietic stem cell transplantation

Development phases: I-IV

Support steps:

- Multidisciplinary advisory boards
- Definition of identified partnership elements. These may vary widely, and take the form of expert reports, translational study projects or even clinical trials
- Drafting of roadmaps, study projects and related reports

Examples of partnerships

Biomarkers study in relapsing/refractory AMLpatientsOrg - Expression of original markers of leukemic cells and potential targets of

immunotherapeutic agents from patients with AML refractory to or relapsing after a first-line therapy and enrolled in ALFA-PPP study.

Partner: Advesya

Terms

- Consulting contract

NATIONAL CLINICAL RESEARCH NETWORK FOR THE DESIGN, SPONSORING AND CONDUCT OF PHASE I-IV INTERVENTIONAL AND NON-INTERVENTIONAL CLINICAL TRIALS (CLL/WM/AML/MPS)

Keywords

Clinical development | CLL | Waldenström's macroglobulinemia | AML | MPS | Targeted therapy | Cell therapy | Immunotherapy | Chemotherapy | Clinical research (TRL 6-8) |

OPALE entity

French Innovative Leukemia Organization (FILO)

Head

Prof. Arnaud Pigneux

Responsable de l'Entité

Contact

Dr. Sandrine Palcy

Responsable du Business Development

FILO sponsors national multicenter clinical trials in hematology: acute myeloid leukemia (AML), myelofibrosis, essential thrombocythemia (in collaboration with the France Intergroupe des syndromes Myéloprolifératifs - FIM), chronic lymphocytic leukemia (CLL) and Waldenström macroglobulinemia (WM). FILO members represent all French and Belgian specialists involved in the study of these diseases (apart from members of the Acute Leukemia French Association - ALFA).

Focused on improving care and its benefits, independent (i.e. academically sponsored) clinical studies are of key importance in optimizing the efficacy, safety and cost/benefit ratio of healthcare. Conducted at the initiative of FILO members, these investigations aim to provide the best treatment option for a given patient (or group of patients).

Description

Scope

Clinical research in AML, CLL and WM pathologies, with the aim of improving patient care and quality of life:

- Interventional research: multicenter clinical trials for new therapeutic approaches
- Non-interventional research: retrospective or prospective studies based on real-life observatory data, to assess the efficacy and safety of treatments

Role

- Clinical trial sponsor
- Operational coordination of clinical trials

Investigation centers

80 investigator centers in France (80 specialized in CLL-MW and 35 specialized in AML)

Infrastructure

- Operational investigation platform: project coordination, trial monitoring, regulatory management
- Electronic case report forms (eCRF)
- FILOTHEQUE: ISO 20 387-certified biobank. Centralized sampling and preparation of plasma, serum, cells, DNA, RNA and cDNA samples, in compliance with clinical trial specifications, regulatory requirements and standards
- Centralized analysis laboratories (CLL): highly sensitive MRD, karyotyping, FISH reading

Quality assurance

- Standard Operating Procedures (SOPs)
- Coordination unit
- Network of regional clinical research associates (CRAs) for quality control and assistance to major recruitment centers

Specifications

Type of platform: national multicenter network

Type of studies: interventional and non-interventional clinical trials

Phases: I to IV

Examples of partnerships

ERADIC : Evaluation of Risk-Adapted and MRD-Driven Strategy for Untreated Fit Patients With Intermediate Risk Chronic Lymphocytic Leukemia - The aim of this study is to test the potential benefit of an innovative combination of targeted therapy over the standard the immunochemotherapy (FCR).

Partners: AbbVie, Janssen-Cilag

LAMSA2020-VENCOSA : A phase II randomized study to assess the efficacy on outcome of Venetoclax combined with Cytarabine versus Idarubicin combined with Cytarabine administered as post-remission therapy to elderly patients with acute myeloid leukemia in first remission - The primary objective of this trial is to compare the Relapse free survival (RFS) at 2 years after follow-up between the two arms: Venetoclax with Cytarabine versus Idarubicin with Cytarabine.

Partner: AbbVie

ELEGANCE : A non-interventional ambispective real-world cohort of rEfractory and reLapsed FLT3 mutated Acute MyEloid Leukemia patients treated with Gilteritinib in FrANCE – The aim of the study is to describe gilteritinib effectiveness in FLT3-mutated AML patients in R/R situation treated in the context of early access program to gilteritinib in France through Temporary Authorisation of Use, the so-called ATU program, and the post ATU period from marketing authorisation to launch when reimbursement and price are published..

Partner: Astellas

FOLLOW : French Observational study of patients with chronic Lymphocytic Leukemia Or small lymphocytic lymphoma in real-World settings – The aim of the study is to set a prospective cohort of real-world CLL/SLL patients with symptomatic disease in order to evaluate medical practices and their change and representativity over time.

Partners : Abbvie, AtsraZeneca, Beigene, Janssen-Cilag,

Terms

- Clinical research project initiated and sponsored by FILO
- Partnership agreement with the manufacturers concerned to support the trial or study

NATIONAL CLINICAL RESEARCH NETWORK FOR THE DESIGN, SPONSORING AND CONDUCT OF PHASE I-IV INTERVENTIONAL AND NON-INTERVENTIONAL CLINICAL TRIALS - COLLABORATION (CLL/WM/AML/MPS)

Keywords

Clinical development | CLL | Waldenström's macroglobulinemia | AML | MPS | Targeted therapy | Cell therapy | Immunotherapy | Chemotherapy | Clinical research (TRL 6-8) |

OPALE entity

French Innovative Leukemia Organization (FILO)

Head

Prof. Arnaud Pigneux

Responsable de l'Entité

Contact

Dr. Sandrine Palcy

Responsable du Business Development

FILO brings its expertise, technological platforms and network to the development of academically-sponsored hematology clinical trials on a national or international scale: acute myeloid leukemia (AML), myelofibrosis, essential thrombocythemia (in collaboration with FIM), chronic lymphocytic leukemia (CLL) and Waldenström's macroglobulinemia (WM). FILO members represent all French and Belgian specialists involved in the study of these diseases (apart from members of the Acute Leukemia French Association - ALFA).

Focused on improving care and its benefits, independent (i.e. academically sponsored) clinical trials are of key importance in optimizing the efficacy, safety and cost/benefit ratio of healthcare. Conducted at the initiative of academic organizations, these investigations aim to provide the best treatment option for a given patient (or group of patients).

Description

Scope

Clinical research for AML, myelofibrosis, essential thrombocythemia, CLL and WM pathologies, with the aim of improving patient care and quality of life:

- Interventional research: multicenter clinical trials for new therapeutic approaches
- Non-interventional research: retrospective or prospective studies based on real-life observatory data, to assess the efficacy and safety of treatments

Role

- Investigator-coordinator of clinical trials

And/or

- Operational coordination of trials

Investigation centers

80 investigator centers in France (80 specialized in CLL-MW and 35 specialized in AML).

Infrastructure

- Operational investigation platform: project coordination, trial monitoring, regulatory management
- Electronic case report forms (eCRF)
- FILOTHEQUE: ISO 20 387-certified biobank. Centralized sampling and preparation of plasma, serum, cells, DNA, RNA and cDNA samples, in compliance with clinical trial specifications, regulatory requirements and standards
- Centralized analysis laboratories (LLC): highly sensitive MRD, karyotyping, FISH reading

Quality assurance

- Standard Operating Procedures (SOPs)
- Coordination unit,
- Network of regional clinical research associates (CRAs) for quality control

Specifications

Type of platform: national multicenter network

Type of studies: interventional and non-interventional clinical trials

Phases: I to IV

Examples of partnerships

BIG-1 : Study to Improve OS in 18 to 60 Year-old Patients, Comparing Daunorubicin Versus High Dose Idarubicin Induction Regimens, High Dose Versus Intermediate Dose Cytarabine Consolidation Regimens, and Standard Versus MMF Prophylaxis of GvHD in Allografted Patients in First CR (BIG-1) - This open label, multicenter phase II/III study with multiple randomization phases at different stages of AML treatment (induction, consolidation and HSCT where applicable) is designed to improve OS in younger (18 to 60 year-old) patients, with AML risk-adapted patient strategies."

Sponsor: CHU Angers

LLC2007SA : Single-agent rituximab as maintenance treatment versus observation after combined induction immunochemotherapy with fludarabine, cyclophosphamide and rituximab (FCR) in patients older than 65 years with previously untreated B-cell chronic lymphocytic leukemia (B-CLL): a phase III intergroup trial of the GOELAMS1 and the FCGCLL/WM2 groups – The aim of the study was to demonstrate superiority in 3-year progression-free survival, (in the intent-to-treat, from randomization) of rituximab maintenance over observation in patients in Complete or Partial Response after induction by FCR.

Sponsor: CHU Tours

Partner : ROCHE

ECWM-1 : Efficacy of first line Dexamethasone, Rituximab and Cyclophosphamide (DRC) +/- Bortezomib for patients with Waldenström's Macroglobulinemia. A multicenter open label two-arm randomized european phase III study -The aim of the study is to test whether the efficacy of the well tolerated DRC regime can be further improved by adding Bortezomib.

Sponsor: University Hospital Ulm, Germany (represented in France by CH Lens)

CLL6-RESIDUUM : An Australasian and French, Phase III, Multicentre, Randomised Trial Comparing Lenalidomide Consolidation Vs No Consolidation in Patients With Chronic Lymphocytic Leukemia and Residual Disease Following Induction Chemotherapy - The primary objective is to investigate if lenalidomide consolidation is capable of extending progression free survival in previously untreated or minimally treated CLL patients with residual disease after chemotherapy

Sponsor: Australasian Leukaemia and Lymphoma Group (ALLG) (represented in France by FILO)

Terms

- Clinical research project with national or international academic promotion
- Partnership agreement with industrial partners to support the study.

PHASE I-IV INTERVENTIONAL AND NON-INTERVENTIONAL CLINICAL TRIAL DATABASES (MPN/CLL/WM/AML)

Keywords

Database | MPN | CLL | Waldenström's macroglobulinemia | AML | Targeted therapy | Cell therapy | Immunotherapy | Clinical research (TRL 6-8) |

OPALE entity

French Innovative Leukemia Organization (FILO)

Head

Prof. Arnaud Pigneux

Responsable de l'Entité

Contact

Dr. Sandrine Palcy

Responsable du Business Development

FILO's clinical study databases are a unique resource for retrospective studies in the field of acute myeloid leukemia (AML), myelofibrosis, essential thrombocythemia, chronic lymphocytic leukemia (CLL) and Waldenström's macroglobulinemia (WM).

Clinical protocols conducted under FILO's sponsoring include the use of an eCRF and monitoring procedures to ensure complete and highly annotated data sets.

Description

Scope

Clinical datasets in the field of AML, myelofibrosis, essential thrombocythemia, CLL and MW for retrospective research purposes, such as:

- Analysis of treatment efficacy and safety
- Identification of predictive or prognostic markers
- Identification of patient cohorts for clinical research

Provision of data

- Submission of retrospective study project to FILO
- Project review by FILO's Scientific Advisory Board (LLC-MW or LAM)

Infrastructure

- Data hosted in an eCRF (Quanticsoft webtrial®)
- Project and data managers

Quality assurance

- Data collected in compliance with good clinical practices and GDPR
- Data from clinical trials monitored against source data

Specifications

Data sets

- About 15 clinical studies in AML, representing more than 2,800 patients
- About 20 clinical trials in CLL and WM, representing more than 3,000 patients
- 5 clinical trials in SMP in collaboration with the FIM Group, representing close to 2,000 patients (including 1,700 in a COVID19 observatory)

Type of studies: interventional and non-interventional clinical trials

Phases: I to IV

Terms

- Research project approved by the FILO scientific committee

- License agreement

HEMATOLOGICAL MALIGNANCIES BIOBANK (CLL/AML)

Keywords

Collections | CLL | AML | Targeted therapy | Cell therapy | Immunotherapy | Chemotherapy | Clinical research (TRL 6-8) |

OPALE entity

French Innovative Leukemia Organization (FILO)

Head

Prof. Arnaud Pigneux

Responsable de l'Entité

Contact

Dr. Sandrine Palcy

Responsable du Business Development

FILOThèque is the FILO Group's biological resource center, specializing in the biobanking of hematological malignancies.

With 15 years' experience in pre-analytical work in onco-hematology, Filothèque uses quality-controlled operating procedures and method validation. The quality, level of annotation and scope of the collection (around 4500 patients) make it a strong scientific research tool.

Description

Scope

Multicentric, homogeneous and annotated collections of clinico-biological data monitored as part of clinical trials, enabling projects to be conducted in the field of AML and CLL, such as:

- New target discovery
- Biomarker research
- Patient stratification

Provision of samples

Samples stored in the Filothèque can be made available to researchers for academic or industrial projects. This is done in compliance with the laws in force and is stipulated in the informed consent given to patients when they are enrolled in a FILO clinical trial. Requests for access to samples and associated data may be made in response to Filothèque's calls for tenders, or spontaneously by filling in the Sample Access Request Form and sending it to the indicated contact.

The provision of samples is subject to a fee to cover the costs of receipt, processing, conservation and removal from storage.

All projects are submitted to the Scientific Advisory Board for review and approval. Each approved project is the subject of a Material Transfer Contract between FILO and the concerned parties.

Infrastructure

- Samples and derived products are stored in mirror. Plasma, cells in dry pellets, cells in trizol and nucleic acids are stored at -80°. Viable cells are stored in nitrogen. Cryo-preservers are under permanent surveillance in controlled-access premises.
- Our technical staff are qualified by initial and ongoing training. For each operational task, a personnel authorization process is implemented and monitored.

Quality management

- ISO 20 387 version 2018 certification

Specifications

Nature of samples:

From blood, bone marrow, hair bulb and saliva samples:

- Plasma and serum samples

- Viable cell samples
- Leukemic DNA and RNA samples
- Constitutional DNA samples

Type of study: interventional clinical studies

Phases: I to IV

Examples of partnerships

Prognostic impact of the DDX41 mutation in acute myeloid leukemia (AML) - Molecular analysis of the DDX41 mutation in a large series of AML patients involved in 5 clinical trials from the ALFA and FILO groups. Molecular analysis results were interpreted in conjunction with clinical data to identify the prognostic impact of the mutation. (Duployez N et al. Prognostic impact of DDX41 germline mutations in intensively treated acute myeloid leukemia patients: an ALFA-FILO study. Blood. 2022 Aug.)

Project leader: Nicolas Duployez (Hematology Laboratory, Unité 1277-Cancer Heterogeneity Plasticity and Resistance to Therapies (CANTHER), Centre Hospitalier Universitaire (CHU) de Lille, University of Lille, INSERM)

Interest of Lomustine in AML treatment - Analysis of the molecular profile and clinical data of elderly AML patients with intermediate karyotype and unfavorable prognosis (ELN 2017 classification), to study the therapeutic benefit of adding Lomustine to conventional chemotherapy. (Largeaud L et al. Lomustine is beneficial to older AML with ELN2017 adverse risk profile and intermediate karyotype: a FILO study. Leukemia. 2021 May.)

Project leader: Laetitia Largeaud (Hematology Biology, Centre Hospitalier Universitaire de Toulouse, Institut Universitaire du Cancer de Toulouse Oncopôle, Université Toulouse III Paul Sabatier)

Terms

- Research project approved by the FILO scientific committee
- Contract for the provision of samples within the framework (or not) of a partnership

NATIONAL CLINICAL RESEARCH NETWORK FOR THE DESIGN, SPONSORING AND CONDUCT OF PHASE II TO IV INTERVENTIONAL AND NON-INTERVENTIONAL CLINICAL TRIALS (ALL)

Keywords

Clinical development | ALL | Cell therapy | Immunotherapy | Clinical research (TRL 6-8) |

OPALE entity

GRAALL

Head

Prof. Nicolas Boissel

Responsable de l'Entité

Contact

Dr. Sandrine Palcy

Responsable du Business Development

The GRAALL intergroup initiates multicenter clinical trials in Belgium, Switzerland and France in the field of acute lymphoblastic leukemia (ALL) in adults. It is a multidisciplinary clinical and translational research network, operating through shared operational centers. GRAALL members represent 79 clinical centers, including 60 in France, 9 in Belgium and 10 in Switzerland.

Focused on improving care and its benefits, independent (i.e. academically sponsored) clinical trials are of key importance in optimizing the efficacy, safety and cost/benefit of healthcare. Conducted by GRAALL members, these investigations aim to provide the best treatment option for a given patient (or group of patients).

Description

Scope

Clinical research in adult ALL pathology, with the aim of improving patient care and quality of life:

- Interventional research: multicenter clinical trials for new therapeutic approaches
- Non-interventional research: retrospective or prospective studies based on real-life observatory data, to assess the efficacy and safety of treatments

Role

- Clinical trial promoter
- Operational coordination of clinical trials

Investigation centers

79 investigator centers: 60 in France, 9 in Belgium and 10 in Switzerland.

Infrastructure

- Central coordination office (Lyon)
- Centralized molecular biology laboratory
  - B-ALL (Paris Saint-Louis)
  - T-ALL (Paris Necker)
- Centralized IG/TR MRD network
  - Brussels
  - Lille
  - Paris, Necker & Saint-Louis
  - Rennes
  - Toulouse
  - Zurich
- Independent data center & biostatistical unit (Paris Saint-Louis)

Quality assurance

- Standard Operating Procedures (SOPs)
- Coordination unit

Specifications

Type of platform: transnational multicenter network

Type of studies: interventional and non-interventional clinical trials

Phases: II to IV

Examples of partnerships

Efficacy and toxicity of Blinatumomab in the French ATU for adult BCP-ALL R/R, or with MRD+ (FRENCH-CYTO) (FRENCH-CYTO) – This study aimed at discovering the determinantes of the response to Blinatumomab based on a real-word data analysis of the compassionate use program in France.

Partner: Amgen

Multicenter protocol for the treatment of Acute Lymphoblastic Leukemia (ALL) in young adults (18-59 years old) PROTOCOL GRAALL-2014 - The purpose of this protocol is to improve the outcome of Adult frontline ALL through the incorporation of new chemotherapy (Nelarabine), immunotherapy (Blinatumomab) and targeted therapy (Nilotinib).

Partners: Amgen, Novartis, Sandoz

Terms

- Clinical research project initiated by GRAALL, under academic sponsoring
- Partnership agreement with industrial partners to support the clinical study

NATIONAL CLINICAL RESEARCH NETWORK FOR THE DESIGN, SPONSORING AND CONDUCT OF PHASE I TO III INTERVENTIONAL AND NON-INTERVENTIONAL CLINICAL TRIALS (MDS)

Keywords

Clinical development | MDS | Targeted therapy | Cell therapy | Immunotherapy | Chemotherapy | Clinical research (TRL 6-8) |

OPALE entity

Groupe Francophone des Myélodysplasies (GFM)

Head

Prof. Pierre Fenaux

Responsable de l'Entité

Contact

Dr. Sandrine Palcy

Responsable du Business Development

The GFM sponsors multicenter clinical trials in hematology: myelodysplastic syndromes (MDS). The GFM brings together specialists from France, Europe and other French-speaking countries involved in the study of MDS.

Focused on improving care and its benefits, independent (i.e. academically sponsored) clinical studies are of key importance in optimizing the efficacy, safety and cost/benefit ratio of healthcare. Conducted at the initiative of GFM members, these investigations aim to provide the best treatment option for a given patient (or group of patients).

Description

Scope

Clinical research into myelodysplastic syndromes, with the aim of improving patient care and quality of life:

- Interventional research: multicenter clinical trials for new therapeutic approaches
- Non-interventional research: retrospective or prospective studies based on real-life observatory data, to assess the efficacy and safety of treatments

Role

- Clinical trial promoter
- Operational coordination of clinical trials

Investigation centers

65 investigator centers in France.

Infrastructure

Project coordination, regulatory management, trial monitoring, administrative management.

- Operational team
- Promotional team
- Coordinators
- Monitors

Quality assurance

Quality assurance procedures developed by GFM for the promotion of clinical studies.

Specifications

Type of platform: national and European multicenter network

Type of studies: interventional and non-interventional clinical trials

Phase: I to III

Examples of partnerships

COMBOLA Trial - A randomized phase I/ II multicenter study evaluating combination of luspatercept in LR-MDS without RS having failed or being ineligible to ESA.

Partner: BMS

AVENHIR trial - Phase II study with safety run-in of Azacitidine (AZA) combined with Venetoclax (VEN) in patients with higher-risk Chronic Myelomonocytic Leukemia (CMML).

Partner: ABBVIE

GFM-ONUVEN-MDS - A phase I/II, open-label, single arm, multicenter dose-finding study to assess the safety and preliminary efficacy of Oral Azacitidine CC-486 (ONUREG®) in combination with Venetoclax (VENCLYXTO®) in previously untreated higher-risk myelodysplastic syndromes ineligible for allogenic transplantation.

Partners: ABBVIE, Bristol-Myers Squibb (BMS)

GFM-DACORAL-DLI - A phase II prospective study: ASTX727 and donor lymphocyte infusions (DLI) after allogeneic stem cell transplantation (ALLO SCT) in very high-risk MDS or AML patients.

Partners: ASTEX, SANOFI

Terms

- Clinical research project initiated and sponsored by GFM
- Partnership agreement with the manufacturers concerned to support the trial or study

NATIONAL CLINICAL RESEARCH NETWORK FOR THE DESIGN AND CONDUCT OF PHASE I-IV INTERVENTIONAL AND NON-INTERVENTIONAL CLINICAL TRIALS IN CHILDHOOD AND ADOLESCENT LEUKEMIA (AML/ALL/MPS/MDS)

Keywords

Clinical development | AML | MPS | MDS | ALL | Targeted therapy | Cell therapy | Immunotherapy | Hematopoietic stem cell transplant | Chemotherapy | Clinical research (TRL 6-8) |

OPALE entity

SFCE

Head

Prof. Arnaud Petit

Responsable de l'Entité

Contact

Dr. Sandrine Palcy

Responsable du Business Development

The Société Française de lutte contre les cancers et les leucémies de l'Enfant et de l'adolescent (SFCE) is the leading partner for coordinating care and research into childhood cancers at national level. Together with the various players in pediatric oncology and hematology, it contributes to improving France's attractiveness in terms of clinical and translational research. SFCE centers are involved in the design and conduct of international clinical trials, helping to increase enrolment and bring new treatments to young patients. The SFCE Leukemia Committee coordinates the 28 clinical centers that treat acute leukemia, in liaison with biologists and researchers. It encourages the emergence of clinical and translational research projects, which are approved by the SFCE Scientific Advisory Board.

The SFCE is an association of healthcare professionals (surgeons, pediatric oncologists and hematologists, radiotherapists, radiologists, pathologists, biologists, nurses, researchers, psychologists). It has over 500 members (clinicians, researchers, engineers and clinical research technicians), spread across 30 clinical centers accredited by the French Cancer Institute (INCa) to care for children and adolescents with cancer and leukemia.

Description

Scope

The SFCE Leukemia Committee is divided into five subgroups:

- 1st-line ALL: divided into 3 subsections: ALL, Ph1 ALL and ALL < 1 year
- 2nd-line ALL
- AML
- Myeloproliferative syndromes (MPS)
- JMML and MDS

Role

A large number of clinical trials (www.u-link.eu) have been designed and conducted by SFCE members. Expert centers play an active role in enrolling patients in phase 1 to 4 trials. For leukemia and related diseases, clinical research protocols are discussed by the Leukemia Committee. The committee works closely with national, European and international research structures, in particular by actively participating in discussions on protocols for the care of children with leukemia.

One or more representatives for international relations is/are appointed within the sub-committees and/or at the suggestion of the Board to facilitate this collaboration. Among the objectives of the SFCE Leukemia Committee:

- To design and activate therapeutic trials in all areas of comprehensive management of the various leukemias at national and international level, and to participate in international clinical research efforts.
- To design and coordinate phase I-II studies to evaluate innovative treatments, in close collaboration with the SFCE's "new drugs" group, the pediatric INCa-certified early-phase centers (CLIPP) and the European "Innovative Therapies in Childhood Cancer" (ITCC) group.
- To develop biological studies in various pathologies.
- To interact with other national and international groups involved in the management of these pathologies.

Investigation centers

- 30 expert centers
- Operational clinical research teams from the 30 centers meet annually, coordinated by the SFCE, to discuss the conduct of protocols in

the centers

Infrastructure

National pediatric AML database (DOREMy), in conjunction with the CONECT-AML consortium (www.conect-aml.fr) : harmonized clinical and biological databases for integrated research into the management of pediatric acute myeloid leukemia.

Specifications

Type of platform: national multicenter network

Type of studies: interventional and non-interventional clinical studies

Phases: I to IV

Examples of partnerships

ALARM project - The ALARM3 project comprises 3 work packages (WP). WP2 aims to compare the sensitivity of leukemia cells to a panel of drugs at initial diagnosis and relapse, using ex vivo drug testing. A specific study is being carried out on Vyxeos.

Partner: Jazz Pharmaceutical

Terms

- Clinical research project initiated and sponsored by an SFCE member
- Partnership agreement between the SFCE member and the industry concerned to support the trial or study

COHORT GENOMIC ANNOTATION PLATFORM FOR PHASE I TO III CLINICAL TRIALS (AML/MDS/LEUKEMIA PREDISPOSITION SYNDROMES)

Keywords

Clinical development | AML | MDS | Leukemia predisposition syndromes | Targeted therapy | Immunotherapy | Clinical research (TRL 6-8) |

OPALE entity

CANTHER (UMR-9020/1277)

Head

Dr. Nicolas Duployez

Responsable Opale

Contact

Dr. Sandrine Palcy

Responsable du Business Development

The Lille University Hospital Hematology Laboratory provides molecular biology expertise for systematic annotation of patient samples in clinical trials.

The laboratory has expertise in annotating the cohorts of academic cooperative groups.

Description

Scope of research activities

Clinical research into AML, MDS and ARCH (age-related clonal hematopoiesis) pathologies, with the aim of improving patient care and quality of life:

- Interventional clinical research

Role

- Participation in establishing clinical protocol
- Analysis design
- Organization, implementation and conduct of analyses
- Interpretation and communication of results

Infrastructure

Experimental and analysis platforms:

- Genomics (Novaseq sequencer)

Models:

- Primary cells from clinical study patients

Technical personnel:

- Qualified personnel: engineers, laboratory technicians, molecular biologists
- Bioinformatics support: Bioinformatics team at the common molecular biology platform of the Centre de Biologie Pathologie at Lille University Hospital (in partnership)

Specifications

The platform

Standardized genomic analysis platform for annotating patient samples in Phase I to III clinical trials:

- Complete myeloid NGS panel (100 genes)

The studies

Genomic analysis:

- Identification of nucleotide variations and DNA insertions/deletions
- Sensitivity threshold 2% mutated cells

Measurement of residual disease:

- Monitoring of a previously identified genetic marker
- Threshold varies according to technique used (10^{-4} to 10^{-6})

Examples of partnerships

Genomic annotation of the ALFA-0702 cohort (young adult AML) - The aim of this study was to identify molecular abnormalities in young adult AML and to monitor residual disease during treatment in order to establish a prognostic stratification model based on a "knowledge bank" approach.

Partner: ALFA Group

Genomic annotation of the AZA-PLUS cohort (high-risk MDS) - This study aimed to identify molecular abnormalities in high-risk MDS and define the impact of the various therapies proposed in the molecular subgroups.

Partner: GFM

Terms

- Clinical research project with industrial sponsoring
- Partnership agreement with study sponsor

PLATFORM FOR GENOMIC ANNOTATION AND RETROSPECTIVE ANALYSIS OF AML COHORTS

Keywords

Clinical development | AML | Targeted therapy | Immunotherapy | Clinical research (TRL 6-8) |

OPALE entity

CANTHER (UMR-9020/1277)

Head

Dr. Nicolas Duployez

Responsable Opale

Contact

Dr. Sandrine Palcy

Responsable du Business Development

Retrospective analyses of patient data from the Hauts de France AML Observatory.

The Hauts-de-France Observatory gathers initial and follow-up clinical and biological data on adult patients with AML diagnosed in clinical hematology centers in the Hauts-de-France region. In 2022, this observatory included data on around 2,500 patients.

Description

Scope of research activities

Clinical research into AML pathology, with the aim of improving patient care and quality of life:

- Non-interventional clinical research

Role

- Provision of clinical and biological data
- Participation in the analysis of extracted data

Infrastructure

Analysis platforms:

- Database / eCRF

Models:

- Primary cells from clinical study patients

Technical personnel:

- 2 clinical research associates

Specifications

The platform

Platform for retrospective analysis of AML observatory data:

Studies

Data study

- Frequency of a clinical or biological parameter
- Study of a population defined according to clinical, biological or demographic criteria

Examples of partnerships

Establishment of a validation cohort for AML in elderly adult - The study aimed to establish a cohort of patients with the same

characteristics as those included in the ALFA-1200 protocol in order to validate a prognostic score based on genetic alterations.

Partner: ALFA Group

Terms

- Clinical research project with industrial sponsoring
- Partnership agreement with study sponsor

CLINICAL INVESTIGATION CENTER FOR THE SPONSORING AND CONDUCT OF PHASE I TO III INTERVENTIONAL CLINICAL TRIALS (ALL/AML/MPS/MDS)

Keywords

Clinical development | ALL | AML | MPS | MDS | Targeted therapy | Immunotherapy | Clinical research (TRL 6-8) |

OPALE entity

CRCM / IPC (UMR-1068)

Head

Dr. Sylvain Garciaz

Responsable Opale

Contact

Dr. Sandrine Palcy

Responsable du Business Development

The Clinical Investigation Center conducts studies ranging from first-in-man administration to multicenter phase III trials, in collaboration with the FILO, GRAALL, GFM and FIM cooperative groups. Studies are sponsored by the Clinical Research and Innovation Department (DRCI).

Focused on improving care and its benefits, independent (i.e. academically sponsored) clinical studies are of key importance in optimizing the efficacy, safety and cost/benefit ratio of healthcare. Conducted at the initiative of cooperative groups' members, these investigations aim to provide the best treatment option for a given patient (or group of patients).

Description

Scope

Clinical research in AML, SMP, MDS and ALL diseases, with the aim of improving patient care and quality of life:

- Interventional research: early (phase I) and multi-center (phases II-III) clinical trials for new therapeutic approaches

Role

- Operational coordination of clinical trials

Infrastructure

- Operational investigation platform: project coordination, trial monitoring, regulatory management
- Electronic case report forms (e-CRF)
- Biobank: blood and bone marrow samples containing viable cells, nucleic acids and serum, from patients with AML, SMP, MDS, ALL
- Analysis laboratories: cytology, cytogenetics, immunophenotyping, molecular biology, immunomonitoring

Quality assurance

DRCI has been ISO 9001 certified since 2013 (2008 and 2015 versions). The scope of this certification includes sponsoring and clinical investigation.

Specifications

Type of platform: Clinical investigation center with a CLIP^2-certified early trial unit (PHOCEA)

Type of study: interventional clinical trials

Phases: I to III

Examples of partnerships

INA-03 - Open-label, first-in-man, dose-escalation study of intravenous INA03 in adult patients with relapsed/refractory acute leukemia.

Partner: INATHERYS

Terms

- Clinical research project initiated and sponsored by the clinical investigation center
- Partnership agreement with the manufacturers concerned to support the conduct of the study

CLINICAL INVESTIGATION CENTER FOR THE COORDINATION AND CONDUCT OF PHASE I TO III CLINICAL TRIALS IN LEUKEMIA AND RELATED DISEASES (AML, MPS, MDS, ALL)

Keywords

Clinical development | ALL | AML | MPS | MDS | Targeted therapy | Immunotherapy | Clinical research (TRL 6-8) |

OPALE entity

CRCM / IPC (UMR-1068)

Head

Dr. Sylvain Garciaz

Responsable Opale

Contact

Dr. Sandrine Palcy

Responsable du Business Development

The Clinical Investigation Center brings its expertise, technological platforms and network to the development of industrially sponsored trials, from first-in-man administration to multi-center phase III studies.

The support provided by the Clinical Investigation Center helps to improve the quality and safety of trials for patients and optimize access for sponsors. Through its national collaborations, the center fosters contacts for the expansion of studies across the country.

Description

Scope

Clinical research into AML, MPS, MDS and ALL diseases, with the aim of improving patient care and quality of life:

- Interventional research: early (phase I) and multi-center (phases II-III) clinical trials for new therapeutic approaches.

Role

- Operational coordination of clinical trials

Infrastructure

- Operational investigation platform: project coordination, trial monitoring, regulatory management
- Electronic case report forms (e-CRF)
- Biobank: blood and bone marrow samples containing viable cells, nucleic acids and serum, from patients with AML, MPS, MDS, ALL
- Analysis laboratories: cytology, cytogenetics, immunophenotyping, molecular biology, immunomonitoring

Quality assurance

The Clinical Research and Innovation Department (DRCI) has been ISO 9001 certified since 2013 (2008 and 2015 versions). The scope of this certification includes sponsoring and clinical investigation.

Specifications

Type of platform: Clinical investigation center with a CLIP^2-certified early trial unit (PHOCEA)

Type of study: interventional clinical trials

Phases: I to III

Examples of partnerships

ICT01-101 – EVICTION - A two-part, open-label, first-in-man clinical trial to evaluate the safety, tolerability and activity of intravenous doses of ICT01 as a single agent and in combination with a checkpoint inhibitor (ICI), in relapsed/refractory patients with advanced cancer, including leukemia.

Sponsor: Imcheck Therapeutics

CPX-351 TA-SMP - Phase II trial of CPX-351 monotherapy in acute leukemia secondary to myeloproliferative syndrome.

Sponsor: FILO

Partner: Jazz Pharmaceuticals

Terms

- Clinical research project sponsored by industry
- Partnership agreement with industrial partners to support study implementation

PLATFORM FOR DEVELOPING AND IMPLEMENTING TESTS FOR PRECLINICAL VALIDATION IN VITRO, EX VIVO, AND IN VIVO (ACUTE LEUKEMIA)

Keywords

Preclinical development | ALL | AML | Toutes thérapies | Preclinical research (TRL 4-5) |

OPALE entity

CRCM / IPC (UMR-1068)

Head

Dr. Rémy Castellano

Responsable d'équipe

Contact

Dr. Sandrine Palcy

Responsable du Business Development

TrGET is a preclinical testing platform specializing in the implementation and development of in vitro and in vivo tests to assess the involvement of a target gene in tumorigenesis or the biological activity of innovative single or combined therapeutic solutions.

The platform is the result of significant technological development (development of tests, tools and cellular and animal models proposed). It offers a variety of flexible and adaptable tests, based mainly but not exclusively on bioluminescence technology. Models are developed in close collaboration with the hematology department and the early-phase clinical investigation center of the Institut Paoli-Calmettes (cancer comprehensive center - CLCC).

Description

Scope of research activities

Preclinical research using in vivo and in vitro models to discover new therapeutic avenues:

- Target validation
- Evaluation of drug candidates
- Evaluation of combination effects

Conduct of studies

Steps :

- Study design in co-construction with the partner
- Definition of means/resources and proposed schedule (steps, GO/NO-GO, etc)
- Carrying out of the experimentation in constant contact with the partner (with any necessary adjustments)
- Data analysis and study report with recommendations

Organization

- Dr. Yves Collette, Scientific Director
- Dr. Rémy Castellano, Operational Manager

Research infrastructure

Experimental and analysis platforms:

- Access to ECHO550 (nL) high-throughput acoustic distribution system integrated into ACCESS robotic station (Beckman Coulter) and Pherastar reading system (BMG Labtech)
- RS2000 X-ray generator (RadSource)
- Small animal imaging system (Optima Photon Imager, BioSpace Lab) equipped with X-ray module, MiniHub gas anesthesia station (TEM-SEGA)
- L2 cell culture laboratory
- SOPF animal facility

Models :

- CDX acute leukemia models (>20 including bioluminescence)
- PDX acute leukemia models (>30)
- Cell lines derived from murine AML tumors

- Xenobank annotated and characterized (in vivo and ex vivo)
- Primary sample collection (acute leukemia)

Technical staff :

- 1 scientific manager and 1 operational engineer manager
- 2 engineers and 2 highly qualified technicians
- 2 engineers

Quality assurance

- Level 3 Quality approach (GIS IBiSA standards)
- IBiSA certification
- Aix Marseille University Technology Platform certification

Specifications

The platform

A set of technologies for the development of specialized in vitro and in vivo tests, for the validation of therapeutic targets or drug candidates for the treatment of acute leukemia.

The studies

In vitro tests:

- Multiplex tests (96/384-well format): proliferation/cytotoxicity; cell death pathways (apoptosis, ferroptosis, necroptosis, etc.); clonogenicity; migration
- -Sensitivity/resistance profiles to drug collections (possible design)
- Evaluation of combination effects (synergy, additivity, antagonism)

In vivo tests:

- Graft uptake (syngeneic models, immunocompromised mice, orthotopic, etc)
- Monitoring by flow cytometry and/or non-invasive intravital imaging in small animals: measurements (number of leukemia cells/µL blood, photons); progression or doubling time / dissemination (blood, marrow, spleen, etc.) / survival, etc
- Limit dilution (LSC)
- Modalities and timing of therapeutic solution administration, efficacy, combination

Examples of partnerships

Preclinical evaluation of BTN3A antibodies in combination with LTgd in AML xenograft models – Contract studies to develop a proof-of-concept model and evaluate the activity of antibodies targeting a new innate immune checkpoint in preclinical models of AML. This programme has also resulted in a publication co-authored with the partners (De Gassart A et al, Science Translational Medicine 2021, PMID: 34669444) and is part of an early phase trial involving the Institut Paoli-Calmettes (clinicaltrials.gov : NCT04243499).

Partner: Imcheck Therapeutics

DIAC2010 preclinical evaluation in AML – Contract studies to evaluate the preclinical anti-leukemic efficacy of a selective KIF20A inhibitor: DIAC2010. In this study, we have characterized anti-tumoral activity against acute myeloid leukemia models (AML), both in vitro (cytotoxic activity, cell cycle blockade, apoptosis induction) and in vivo, in mice models (both in bioluminescent CDX and PDX-models). This programme has also resulted in publications co-authored with the partners (Blood, ASH 2022 abstract DOI: 10.1182/BLOOD-2022-166820. And Cancer Research, AACR 2017, abstract DOI: 10.1158/1538-7445.AM2017-4140).

Partner: Diaccurate

Terms

- **Research partnership**
- **Public aid to companies**
- **Collaborative project (multi-beneficiary partnership)**

PLATFORM FOR ACCELERATING THE DISCOVERY AND OPTIMIZATION OF NEW BIOACTIVE MOLECULES (ACUTE LEUKEMIA)

Keywords

Drug design | ALL | MPAL | AML | Targeted therapy | Basic research (TRL 1-3) |

OPALE entity

CRCM / IPC (UMR-1068)

Head

Dr. Xavier Morelli

Responsable d'équipe

Contact

Dr. Sandrine Palcy

Responsable du Business Development

Set of skills and technologies to accelerate the identification and optimization of small chemical molecules for therapeutic purposes.

Our objectives are to identify, understand, validate and target signaling pathways involving key targets in tumor development (enzymes, protein/protein interaction surfaces …), with the specific aim of facilitating the transfer of identified therapeutic / pharmacological targets to preclinical and clinical development programs in oncology. The aim is to shorten the time "from discovery to patent filing".

Description

Scope of research activities

Studies for the identification, validation and optimization of new drug candidates:

- Miniaturized and automated experimental screening in vitro or in cellulo
- Biophysical characterization and orthogonal validation
- Optimization of drug candidates (hit-to-lead) using a semi-automated (Chemo)DOTS approach

Conducting studies

Steps :

- Study design
- Define means/resources and propose schedule (steps, GO/NO-GO, cost estimate)
- Study organization, implementation and conduct
- Data analysis and delivery of a study report with recommendations

Research infrastructure

Experimental and analysis platforms:

- ACCESS integrated robotic platform (Beckman) with in-line Echo 650 acoustic transfer system (2.5nl drop), centrifuge, plate sealer, multimodal dispenser (Certus gyger) and microplate reader (Pherastar FS BMG Labtech)
- 384-well RT-PCR for TSA (CFX384 Biorad)
- FPLC (Akta Pure Cytivia)
- Microcalorimeter ITC200 (Malvern)
- Incubators (cell culture & crystallography)
- Database and calculation servers

Technologies :

- Fluorescence
- Luminescence
- Absorbance
- TR-FRET (HTRF®)
- Protein thermostability (Thermal Shift Assay)
- Isothermal calorimetric titration
- Cytotoxicity (adherent and non-adherent cells)
- Chemoinformatics (ChemoDOTS, CovaDOTS, Chemaxon, SeeSar, MOE)

Staff :

- 1 scientific manager and 1 operational engineer manager
- 1 researcher and 2 engineers - cell screening and HTS
- 1 researcher and 1 assistant engineer - molecular modeling & chemoinformatics

Quality assurance

- IBiSA certification
- Aix Marseille-Université Technology Platforms certification

Specifications

The studies

Target identification and characterization:

- Expression in various prokaryotic systems
- Biochemical production, purification and characterization

Experimental screening:

- Development of miniaturized, automated assays in 384- or 1536-well plates (enzymatic assays, protein-protein interaction, cytotoxicity)
- High-throughput screening on purified proteins or different cell types (adherent or suspension cell lines, primary cells). Use of acoustic Echo technology to transfer liquid nanodroplets to prepare screening plates.
- Validation of 'touch molecules' in combination or dose-response.
- Provision of commercial or in-house chemical libraries

Optimization:

- Crystallization & co-crystallization. Resolution and analysis of the crystallographic structure of the "target/ligand" complex (if no 3D structure of the complex, modeling service available)
- Integrated 'DOTS' approach: Chemoinformatics (ChemoDOTS), virtual screening
- Search for adjacent 'pockets
- Proposal of new molecules based on starting molecule - Study plan
- List of new molecules to be prioritized for synthesis - Validation request
- Custom synthesis / medicinal chemistry (possible service)

Examples of partnerships

Optimization of compounds for an epigenetic target - Based on a chemical starting structure (hit), proposal of optimizations by cycle (fragment-based drug design) to accelerate hit-to-lead.

Partner: EISAI

Custom synthesis of chemical compounds - Custom synthesis of compounds for a feasibility study.

Partner: CISBIO

Terms

- **Research partnership**
- **Public aid to companies**
- **Collaborative project (multi-beneficiary partnership)**

ROLE OF PPAR-Y IN HEMATOPOIESIS AND THE BONE MARROW ENVIRONMENT: PRECLINICAL MODELS AND TESTS (MPN)

Keywords

Functional studies | MPN | Targeted therapy | Alternative therapy | Basic research (TRL 1-3) |

OPALE entity

IDMIT (UMR-1184)

Head

Dr. Stéphane Prost

Responsable de l'Entité

Contact

Dr. Sandrine Palcy

Responsable du Business Development

Study of the mechanisms of PPAR-Y nuclear receptor activity in hematopoietic stem cells and their microenvironment.

A joint research team of CEA researchers and university hospital staff, addressing both fundamental and clinical aspects of the theme.

Description

Scope of research activities

Basic research to study the function of PPAR-Y in hematopoiesis and bone marrow stroma.

Conduct of studies

Steps :

- Definition of hypothesis and study design
- Drafting of study plans
- Creation and validation of "in vitro" and " in vivo" models required to address the hypotheses.
- Conducting the study
- Analysis and results communication

Research infrastructure

Experimental and analytical platforms:

- Flow cytometry
- Molecular biology
- Biological safety levels 2 and 3 laboratories
- Small animal imaging
- Animal facility

Models:

- Culture of hematopoietic or bone marrow stromal cell lines
- Patient primary cell cultures (hematopoietic or bone marrow stromal)
- In vitro (CRISPR/Cas9) or ex-vivo (shRNA) PPARy invalidation models on cell lines.
- Mouse model of PPARy invalidation in medullary stromal cells expressing the leptin receptor (C57BL/6 (B6.129(Cg)-Leprtm2(cre)Rck/J (008320) _ B6.129-Ppargtm2Rev/J (004584)).

Technical personnel:

- Animaliance company staff for animal facility management
- Anatomopathology platform

Specifications

The approach

Development of "in vitro" and "in vivo" models and assays for the evaluation of drug candidates for the management of myeloproliferative neoplasia (MPN) and acute myeloid leukemia (AML). Study of the therapeutic potential of PPAR-y receptor activation in these hematological

disorders.

The studies

Study of drug candidates on myeloproliferation and leukemia cell persistence in MPNs and AML.:

- Evaluation of the use of PPAR-y agonists as therapeutic candidates in the management of MPNs. In vitro approach in cell lines, ex vivo approach in patient cells and in preclinical mouse models of MPNs (JAK2 V617F, CALRdel52, TPOhigh). In vitro and ex-vivo viability, proliferation and clonogenicity tests (CFC; LTC-IC). Analysis of proliferating or quiescent populations (CFSE), screening of therapeutic candidates. In vivo monitoring of the hematological compartment (normal and/or pathological, treated or untreated) by blood count and flow cytometry. End-point anatomopathological analyses.

Study of the impact of medullary stromal pre-fibrosis/fibrosis in the natural history of myeloid hemopathies:

- Analysis and characterization of the role of PPARy in bone marrow mesenchymal stromal cells. Effect on 1) hematopoietic support, 2) homing of hematopoietic cells, 3) susceptibility to the development of bone marrow fibrosis, 4) establishment/non-resorption of an inflammatory syndrome.

Examples of partnerships

ACTIM study (NCT02888964) - A phase II study to evaluate the efficacy and safety of pioglitazone (ACTOS®) as add-on therapy to imatinib mesylate (GLEEVEC®) in chronic phase, chronic myelogenous leukemia patients (CP-CML) in major molecular response (MMR).

Partner: Partnership with CHV de Versailles (PI: Prof. Philippe Rousselot), associated biological study (UMR-1184) (clonogenic tests and STAT5 factor expression).

Study of the therapeutic potential of PPARgamma nuclear receptor activation in myelofibrosis - Evaluation of a treatment using PPARg agonists in the management of myelofibrosis (in vitro, ex vivo and in preclinical mouse models of the disease).

Partners: UMR 1287; CIC 1427

Terms

- **Research partnership**

MODELS FOR PRECLINICAL STUDIES OF THE IMPACT OF BONE MARROW FIBROSIS ON THE NATURAL HISTORY OF HEMOPATHIES (MPN)

Keywords

Preclinical development | MPN | Targeted therapy | Alternative therapy | Preclinical research (TRL 4-5) |

OPALE entity

IDMIT (UMR-1184)

Head

Dr. Stéphane Prost

Responsable de l'Entité

Contact

Dr. Sandrine Palcy

Responsable du Business Development

In vivo study models to assess the role of PPAR-Y in the development of bone marrow fibrosis and the progression of hematological malignancies.

Description

Scope of research activities

In myeloid hemopathies, the presence of bone marrow fibrosis is associated with a poor prognosis. The objectives are:

1. To determine whether the presence of fibrosis is a simple indicator, or whether bone marrow remodeling is a pathological player with a direct impact on the natural history of hematological disorders
2. To characterize the parameters affected by bone marrow fibrosis
3. To determine whether treatment of bone marrow fibrosis with a PPARy agonist offers a therapeutic advantage over conventional therapies targeting hematopoietic cells alone
4. To evaluate combination treatments (PPARy agonists +/- conventional therapy)

Conduct of studies

Steps:

- Definition of hypotheses and study design.
- Drafting study plans, calculating headcounts, validating drugs and obtaining regulatory approvals.
- Conducting the study
- Analysis and results communication

Research infrastructure

Experimental and analytical platforms:

- Flow cytometry
- Molecular biology
- Biological safety levels 2 and 3 laboratories
- Small animal imaging
- Animal facility

Models :

- Mouse models of myeloproliferative neoplasia (donor mice)
- Mouse models of haploinsufficiency or depletion of the Ppar-y gene in marrow mesenchymal stromal cells (recipient mice)

Technical personnel:

- Animaliance company staff for animal facility management
- Anatomopathology platform

Specifications

The approach

Mouse models predisposed to bone marrow fibrosis to assess 1) the impact of bone marrow fibrosis on the natural history of hematological diseases, 2) the pro- or anti-fibrosis potential of new molecules.

The studies

Study of the impact of medullary stromal pre-fibrosis/fibrosis on the natural history of myeloid hemopathies:

- Analysis and characterization of the role of PPARy in bone marrow mesenchymal stromal cells. Effect on 1) hematopoietic support, 2) homing of hematopoietic cells, 3) susceptibility to the development of bone marrow fibrosis, 4) establishment/non-resorption of an inflammatory syndrome.

Examples of partnerships

Study of the therapeutic potential of PPARgamma nuclear receptor activation in myelofibrosis - Evaluation of a treatment using PPARg agonists in the management of myelofibrosis (in vitro, ex vivo and in preclinical mouse models of the disease).

Partners: UMR 1287; CIC 1427

Terms

- **Research partnership**

CLINICAL TRIALS CENTER FOR THE DESIGN, SPONSORING AND CONDUCT OF PHASE I TO IV INTERVENTIONAL AND NON-INTERVENTIONAL CLINICAL TRIALS IN LEUKEMIA (CML, AML, ALL)

Keywords

Clinical development | ALL | Targeted therapy | Alternative therapy | Precision medicine | Clinical research (TRL 6-8) |

OPALE entity

IDMIT (UMR-1184)

Head

Prof. Philippe Rousselot

Responsable d'équipe

Contact

Dr. Sandrine Palcy

Responsable du Business Development

The Centre Hospitalier de Versailles sponsors multicenter clinical trials in hematology for Chronic Myeloid Leukemia (CML), Acute Myeloblastic Leukemia (AML) and Lymphoblastic Leukemia.

Focused on improving care and its benefits, independent clinical trials (i.e. academically sponsored) are of key importance in optimizing the efficacy, safety and cost/benefit ratio of healthcare. Conducted at the initiative of the Centre Hospitalier de Versailles and in collaboration with industrial and academic partners, these investigations aim to provide the best treatment option for a given patient (or group of patients). The structure's responsiveness is an asset in reducing administrative processing times. Our experience enables us to conduct national and international studies. DRCI department (Direction de la Recherche Clinique et de l'Innovation) also works closely with patient associations.

Description

Scope of research activities

Clinical research in pathologies with the aim of improving patient care and quality of life:

- Interventional research: multicenter clinical trials for new therapeutic approaches
- Precision medicine with pragmatic trials and observatories

Role

- Clinical trial sponsor
- Operational coordination of clinical trials

Investigation centers

The number of investigator centers involved in sponsored studies ranges from 5 to over 60, depending on the scope of the study. Most studies are based on existing collaborative structures (ALFA, GRAALL, EWALL, FiLMC).

Infrastructure

- Sponsoring unit
- Investigation unit
- Quality unit
- Pharmacovigilance unit
- Data and data protection units
- Electronic Case Report Forms (eCRF)
- Analysis laboratories
- ALL TARGET OBS observatory databases (Centre Hospitalier de Versailles) - An observatory of patients treated for relapsed/refractory T-cell acute lymphoblastic leukemia with oncogenetic characterization. The first observatory to implement precision medicine in hematology

Quality assurance

- Standard Operating Procedures (SOP)
- Sponsoring unit
- Investigation unit

Specifications

The platform

The Clinical Research Center (Centre Hospitalier de Versailles) includes a Sponsoring Unit, which manages trials initiated by the Versailles Hospital teams. An Investigation Unit oversees the setting up and monitoring of the studies.

Type of study: interventional clinical trials, Research Involving the Human Person (RIPH) 1 to 5

Phases: II to III

Examples of partnerships

A combination of ponatinib and 5-azacitidine in chronic myelogenous leukaemia in accelerated phase or in myeloid blast crisis (PONAZA) – This project is aiming to improve the survival of patients with chronic myelogenous leukemia in advanced phase and myeloid blast crisis. The basis of this strategy is to add the demethylating agent 5-Azacitidine to the tyrosine kinase inhibitor ponatinib and evaluate its activity in 2 cohorts of patients with either chronic myelogenous leukemia in advanced phase or myeloid blast crisis.

Partner: Incyte

Therapies in combination or sequentially with tyrosine kinase inhibitors (TKIS) in chronic phase chronic myelogenous leukemia patients in ccr (ACTIW) – This study aims to select, according to an adaptive plan, molecules of interest capable of inducing the deep molecular response of patients with CML (MR4.5) by targeting quiescent stem cells .

Partner: Pfizer

Philadelphia positive B-cell ALL. EWALLPH-03-study – European study. An open label, 3-arm, Randomised phase II study to Compare the Safety and Efficacy of Ponatinib in combination with either Chemotherapy or Blinatumomab with Imatinib plus Chemotherapy as front-line therapy for patients aged 55 years and over with Philadelphia chromosome positive (Ph+ or BCR-ABL+) acute lymphoblastic leukemia (ALL).

Partner: Incyte

B-cell ALL in the elderly. EWALL-INO study – European study. A Phase 2 Study of Inotuzumab Ozogamicin (INO) Combined to Chemotherapy in Older Patients with Philadelphia Chromosome-negative CD22+ B-cell Precursor Acute Lymphoblastic Leukemia - EWALL INO.

Partner: Pfizer

Terms

- Clinical research project initiated and sponsored by the Centre Hospitalier de Versailles
- Partnership agreement with the manufacturers involved to support the study

IN VITRO EVALUATION OF THE EFFECTS OF ANTILEUKEMIC DRUGS IN A MODELED LEUKEMIC NICHE WITH OPTIMIZED BONE MARROW MICROENVIRONMENT (MSCS, HYPOXIA, PRESSURE) (MPN/ALL/AML/MDS)

Keywords

Preclinical development | MPN | ALL | AML | MDS | Targeted therapy | Precision medicine | Chemotherapy | Preclinical research (TRL 4-5) |

OPALE entity

U1069-N2COx

Head

Prof. Olivier Hérault

Responsable de l'Entité

Contact

Dr. Sandrine Palcy

Responsable du Business Development

In vitro models for assessing the functional impact of antileukemic drugs in a modeled leukemic niche with optimized bone marrow microenvironment (mesenchymal stromal cells, hypoxia, intramedullary pressure).

These models enable us to assess the impact of drug candidates on leukemia cells within the bone marrow, particularly with regard to oxidative and energetic niche metabolism in relation to chemoresistance and pharmaco-modulation.

Description

Scope of research activities

Preclinical research using various in vitro models to test the action of metabolic drugs on the medullary niche:

- Assessment of toxicity

Conduct of studies

Steps:

- Analysis of innovative product development strategy
- Study design based on scientific data and mechanistic hypotheses
- Drafting of study plans
- Analysis and communication of results

Research infrastructure

Experimental and analysis platforms:

- Hypoxia and intramedullary pressure modeling stations (Avatar®)
- Flow cytometry: FACS (BD Melody®)
- Real-time metabolic analysis (Seahorse®, Omnilog®)
- Small animal irradiator (Faxitron®)
- Single cell analysis systems (including Chromium Controller 10X Genomics)
- Genomic, transcriptomic, metabolomic and lipidomic analyses

Models:

- Tumor niche models with primary MSCs and cell lines (MS5, HS27a, HS5)
- Primary patient cells
- Leukemia cell lines (over 20 available)
- Murine leukemias (FLA2, FLB1)

Technical personnel:

- 4 PhD engineers
- 3 technicians

Specifications

The platform

Set of preclinical studies using in vitro leukemia models for functional evaluation of the impact of metabolic drugs on the tumor environment.

The studies

Assessment of drug candidate toxicity:

- Analysis of cell cycle, apoptosis and DNA breaks
- Oxidative (ROS quantification by CMF, antioxidograms, NRF2 pathway, MAPK signaling) and energetic (glycolysis, oxidative phosphorylation) metabolism analyses
- Transcriptomic (RNAseq, scRNAseq, RT-qPCR), genomic (NGS mutational profiles) and epigenomic (DNA methylation) analyses
- Functional analyses (hematopoietic progenitor cultures, LTC-IC in limiting dilution, MSC differentiation).
- Mouse models of stem cell leukemias (FLA2 & FLB1 leukemias / Cf. Herault O et al, J Exp Med 2012, 209:895-901)

Terms

- **Research partnership**
- **Public aid to companies**
- **Collaborative project (multi-beneficiary partnership)**

METABOLIC, GENOMIC, TRANSCRIPTOMIC AND FUNCTIONAL ANALYSES OF THE LEUKEMIC NICHE FOR PHASE 1 TRIALS (MPN/ALL/AML/MDS)

Keywords

Clinical development | MPN | ALL | AML | MDS | Targeted therapy | Precision medicine | Chemotherapy | Clinical research (TRL 6-8) |

OPALE entity

U1069-N2COx

Head

Prof. Olivier Hérault

Responsable de l'Entité

Contact

Dr. Sandrine Palcy

Responsable du Business Development

The Biological Hematology Department of the CHRU de Tours (Prof. Olivier HERAULT) brings its expertise in chemoresistance mechanisms and its metabolic, genomic, transcriptomic and functional analysis platforms for Phase I clinical trials in leukemia.

The Biological Hematology Department develops, performs, interprets and monitors specialized cellular hematology examinations for the whole of the Tours University Hospital, and more widely for the Centre region in the fields of hematological malignancies and hematopoietic stem cell transplants.

Description

Scope of research activities

Clinical research in AML, MNP, MDS and ALL pathologies, with the aim of improving patient care and quality of life:

- Interventional research: early clinical trials for new therapeutic approaches

Role

- Participation in drafting the clinical protocol for biological analyses
- Analysis design
- Organization, implementation and conduct of analyses
- Interpretation and communication of results

Infrastructure

Experimental and analysis platforms:

- Hypoxia and intramedullary pressure modeling stations (Avatar®)
- Flow cytometry: FACS (BD Melody®)
- Real-time metabolic analysis (Seahorse®, Omnilog®)
- Single cell analysis systems (including Chromium Controller 10X Genomics)
- Genomic, transcriptomic, metabolomic, lipidomic analyses

Models:

- Primary cells from clinical study patients, with FACS sorting possibilities within the entity to study subpopulations of interest

Technical personnel:

- 4 PhD engineers
- 3 technicians

Quality assurance

Analyses performed in a COFRAQ-accredited hospital laboratory; clinical-grade analyses with exclusive intra-CHU circuit (clinical departments, Clinical Investigation Centre, biological haematology department).

Specifications

The platform

Metabolic analyses (energetic/oxidative) coupled with genomic, transcriptomic and functional analyses of leukemic niche players (hematopoietic cells, mesenchymal stromal cells) for Phase I trials, using patients' primary cells (marrow, blood).

The studies

Evaluation of drug candidate toxicity:

- Analyses of cell cycle, apoptosis, DNA breaks
- Analyses of oxidative metabolism (ROS quantification by CMF, antioxidograms, NRF2 pathway, MAPK signalling) and energy metabolism (glycolysis, oxidative phosphorylation)
- Transcriptomic (RNAseq, scRNAseq, RT-qPCR), genomic (NGS mutational profiles) and epigenomic (DNA methylation) analyses
- Functional analyses (hematopoietic progenitor cultures, LTC-IC in limiting dilution, MSC differentiation)

Terms

- Clinical research project with industrial promotion
- Partnership agreement with study sponsor

PLATFORM FOR SCREENING MOLECULES ABLE OF REPROGRAMMING PRIMARY HUMAN MACROPHAGES (AML/Myelofibrosis/MDS/CMML)

Keywords

Preclinical development | AML | Myelofibrosis | MDS | CMML | Targeted therapy | Immunotherapy | Alternative therapy | Preclinical research (TRL 4-5) |

OPALE entity

C3M (UMR-1065)

Head

Dr. Arnaud Jacquel

Responsable d'équipe

Contact

Dr. Sandrine Palcy

Responsable du Business Development

Analytical platform (MACROTOOLS) for the identification of compounds with the ability to modulate or reprogram macrophage phenotype and function.

The immunomodulatory effect of compounds is evaluated in ex vivo human macrophage models from healthy subjects or patients, using an integrative analysis approach. The platform can test some thirty different compounds every day.

Description

Scope of research activities

Preclinical research using ex vivo models to select macrophage immunomodulating compounds:

- Screening
- Evaluation of toxicity, reprogramming

Conduct of studies

Steps:

- Study strategy analysis
- Study design
- Drafting of study plans
- Organization, implementation and conduct of studies
- Analysis and communication of results

Research infrastructure

Experimental and analysis platforms:

- Flow cytometry
- RT-qPCR
- ELISA (Simple PlexTM assays)
- Metabolomics: Seahorse, Ysi, Omnilog
- T-cell polarization
- Phagocytosis tests

Cellular models:

- Ex vivo macrophage models: immature macrophages (M0-type macrophages), pro-inflammatory macrophages (M1-type macrophages) and anti-inflammatory macrophages (M2-type macrophages),

Technical personnel:

- 2 engineers

Specifications

The platform

Ex vivo analysis platform for assessing the effect of compounds on the reprogramming of human macrophages.

The studies

Screening:

- Flow cytometry: analysis of the expression of pro- or anti-inflammatory membrane markers (CD80, CD86, HLA-DR, CD163, CD206, CD209, CD200R)
- RT-qPCR: analysis of mRNA expression coding for pro- or anti-inflammatory cytokines
- ELISA (Simple PlexTM assays): Analysis of the expression of pro- or anti-inflammatory cytokines secreted into the cytokine culture medium
- Metabolomics (Seahorse, Ysi, Omnilog): detect and quantify oxidative and glycolytic metabolic processes at the cellular level to assess the metabolic effects of molecules of interest
- T-cell polarization: the immunosuppressive capacity of macrophages treated or untreated with molecules of interest is assessed by co-culturing macrophages with naive T cells. The impact of co-culture on T lymphocytes is analyzed by flow cytometry, focusing on the expression of membrane or intracytoplasmic markers specific to Treg, Th1 or Th2 lymphocytes
- Phagocytosis tests: the aim of this test is to determine the ability of the molecules of interest to modulate the capacity of macrophages to phagocytose leukemia cells

Toxicity assessment:

- The toxicity of molecules of interest is assessed by DAPI labeling, enabling us to evaluate the non-toxic dose to be used on macrophages

Terms

- Research services contract

PLATFORM FOR THE ISOLATION OF ORGANELLES IN LEUKEMIA CELLS TO ASSESS FUNCTIONAL MODULATIONS LINKED TO PATHOLOGY OR CHEMOTHERAPEUTIC TREATMENT (AML/MDS/CMML)

Keywords

Preclinical development | AML | MDS | CMML | Targeted therapy | Immunotherapy | Chemotherapy | Preclinical research (TRL 4-5) |

OPALE entity

C3M (UMR-1065)

Head

Dr. Guillaume Robert

Responsable d'équipe

Contact

Dr. Sandrine Palcy

Responsable du Business Development

Isolation of cellular organelles to assess functional modulations linked to pathology or chemotherapeutic treatment.

The lysosomes and mitochondria that we purify retain their integrity and functionality intact.

Description

Scope of research activities

Preclinical research using subcellular fractions of myeloid leukemia cells:

- Subcellular localization
- Functional studies

Conduct of studies

Steps:

- Analysis of study strategy
- Study design
- Drafting of study plans
- Organization, implementation and conduct of studies
- Analysis and communication of results

Research infrastructure

Experimental and analytical platforms:

- Nitrogen cavitation
- Gradient ultracentrifugation
- Flow cytometry
- Western blot

Cell models: (human and murine)

- Primary cells
- Tumor cells
- Cell lines

Technical personnel:

- 1 engineer

Specifications

The platform

Isolation of cellular organelles for the evaluation of functional modulations linked to a pathology or chemotherapeutic treatment.

The studies

Subcellular localization:

- Nucleus/Cytoplasm/Membrane
- Lysosome
- Mitochondria
- Autophagosomes

Functional studies:

- Mitochondria (Permeabilization; Loss of potential)
- Lysosomes (Intra-lysosomal pH analysis)

Terms

- **Research partnership**

CHARACTERIZATION OF CELL DEATH IN LEUKEMIA CELLS TO ASSESS THE EFFICACY OF THERAPEUTIC SOLUTIONS IN THE TREATMENT OF MYELOID LEUKEMIA (AML/MDS/CMML)

Keywords

Preclinical development | AML | MDS | CMML | Targeted therapy | Immunotherapy | Alternative therapy | Chemotherapy | Preclinical research (TRL 4-5) |

OPALE entity

C3M (UMR-1065)

Head

Dr. Guillaume Robert

Responsable d'équipe

Contact

Dr. Sandrine Palcy

Responsable du Business Development

Study of the characterization of cell death for the evaluation of the efficacy of therapeutic solutions in the treatment of myeloid leukemias.

Demonstration of direct anti-tumor action or overcome resistance to conventional treatment.

Description

Scope of research activities

Preclinical research to demonstrate the efficacy of drug candidates in inducing leukemia cell death.

- Demonstration of efficacy

Conduct of studies

Steps:

- Study strategy analysis
- Study design
- Drafting of study plans
- Organization, implementation and conduct of studies
- Analysis and communication of results

Research infrastructure

Experimental and analysis platforms:

- Apoptosis
- Autophagy
- Ferroptosis
- BH3 profiling

Models:

- Cell models (cell lines), primary cells (blood bone marrow), mouse models

Technical personnel:

- 1 engineer

Specifications

The platform

Analysis of the efficacy of drug candidates on the induction (direct or indirect) of cell death in leukemia models.

The studies

Demonstration of cell death induction:

- Apoptosis: BH3 profiling, Caspase assay, SiRNA, AV/Dapi, loss of mitochondrial potential
- Autophagy: LC3 conversion, Cathepsin assay, MET
- Ferroptosis: Lipid peroxidation, reversion by specific inhibitors, GPX4 activity assay, evaluation of intracellular ROS.

Terms

- **Research partnership**

IN CELLULO IDENTIFICATION OR VALIDATION OF THERAPEUTIC TARGETS IN MYELOID LEUKEMIA USING CLICK CHEMISTRY TECHNOLOGY TO DEVELOP NEW DIAGNOSTIC METHODS OR TARGETED THERAPIES

Keywords

Preclinical development | AML | MDS | CMML | Targeted therapy | Immunotherapy | Chemotherapy | Preclinical research (TRL 4-5) |

OPALE entity

C3M (UMR-1065)

Head

Dr. Guillaume Robert

Responsable d'équipe

Contact

Dr. Sandrine Palcy

Responsable du Business Development

Identification or validation of therapeutic targets in cellulo using click chemistry technology, to develop new diagnostic methods or targeted therapies.

The Click chemistry technology, which consists in precipitating a molecule with its target after their interaction in cellulo, offers numerous opportunities in biological and medical research. Applied in the field of hematological malignancies, it is used to identify protein targets in their cellular environment.

Description

Scope of research activities

Preclinical research to study protein targets in leukemia cells.

- Demonstration of mechanism of action

Conduct of studies

Steps:

- Analysis of study strategy
- Study design and feasibility
- Drafting of study plans
- Organization, implementation and conduct of studies
- Analysis and communication of results

Research infrastructure

Experimental and analytical platforms:

- Click-chemistry in cellulo
- Western blot (1D, 2D)
- Mass spectrometry

Models: (human or murine)

- Primary cells
- Tumor cells
- Cell lines

Technical personnel:

- 1 engineer

Specifications

The platform

Identification of therapeutic targets in cellulo using click chemistry technology.

The studies

Study steps:

- In cellulo click chemistry
- Western blot (1D, 2D)
- Mass spectrometry

Identification and validation of therapeutic targets:

- Identification of targets of a compound under therapeutic development
- Validation of targets of a compound already clinically validated

Terms

- **Research partnership**

PHARMACODYNAMIC STUDIES FOR THE DEVELOPMENT OF NEW TREATMENTS FOR ACUTE MYELOID LEUKEMIA

Keywords

Preclinical development | AML | Targeted therapy | Chemotherapy | Preclinical research (TRL 4-5) |

OPALE entity

CRCT (UMR-1037)

Head

Dr. Jean-Emmanuel Sarry

Responsable de l'Entité (METAML)

Contact

Dr. Sandrine Palcy

Responsable du Business Development

In vivo models of acute myeloblastic leukemia to validate the proof of concept of the therapeutic action of new molecules.

PDX models of different AML subtypes enable us to mimic the heterogeneity of the disease in the patient, and to study the behavior of tumor cells and their microenvironment to understand their various degrees of sensitivity to different treatments.

Description

Scope of research activities

Preclinical research using various AML-specific models to test drug candidates:

- Study of mechanism of action
- Evaluation of efficacy
- Evaluation of toxicity

Conduct of studies

Steps:

- Literature review of target and drug candidate
- Design of preliminary in vitro studies
- Design of in vivo studies
- Setting up study cohorts
- Cellular, molecular and multi-omics analysis of ex vivo samples

Research infrastructure

Experimental and analytical platforms:

- Cytometry and cell sorting
- Single-cell sequencing
- Metabolomics
- Experimental zootechnics

Models:

- Patient-derived xenograft (PDX) mouse models AML
- AML cell line xenograft mouse models

Technical personnel:

- In vivo engineer

Quality assurance

SOPF (Specific and Opportunistic Pathogen Free) sanitary status of animal experimentation area.

Specifications

The platform

A set of preclinical studies using specific in vivo models of AML.

The studies

Study of the mechanism of action of the anti-leukemic effect of drug candidates:

- Cell sorting of resistant leukemic populations
- Molecular studies of gene expression in these populations

Evaluation of anti-leukemic activity of drug candidates:

- Measurement of tumor reduction in leukemic tissues by flow cytometry

Evaluation of drug candidate toxicity:

- Terminal autopsy of treated animals to verify absence of macroscopic organ dysfunction
- Weight monitoring of animals to verify for weight loss following treatment

Examples of partnerships

Development of anti-CALCRL monoclonal antibodies - Selection and validation of a lead candidate blocking the target. Measurement of specificity, anti-leukemic efficacy and signaling in vitro and in vivo. Objective of preclinical development of lead candidate.

Partners: METATherapeutix, Biocluster MIB (Prof. Daniel Olive), Montpellier Mabs platform (GenAc)

Development of anti-CD39 monoclonal antibodies - Anti-leukemic effect in vivo by blocking the stress response after treatment.

Partners: Innate Pharma, Evitria

Development of CAR-T cells - Development of an anti-CALCRL CAR-T cell based on an anti-CALCRL monoclonal antibody developed and produced. In vitro efficacy demonstrated. Objective to demonstrate efficacy and low toxicity in vivo.

Partner: University of Geneva (Dr. Jérôme Tamburini, Dr. Federico Simonetta)

Terms

- **Research partnership**
- **Public aid to companies**
- **Collaborative project (multi-beneficiary partnership)**

PRECLINICAL MOUSE MODELS FOR NEW MOLECULES SCREENING IN THE TREATMENT OF ACUTE LYMPHOBLASTIC LEUKEMIA B

Keywords

Preclinical development | ALL | Targeted therapy | Chemotherapy | Preclinical research (TRL 4-5) |

OPALE entity

CRCT (UMR-1037)

Head

Dr. Bastien Gerby

Équipe IGAALD

Contact

Dr. Sandrine Palcy

Responsable du Business Development

Use of transgenic mouse models to develop pharmacological approaches by screening chemical compounds on B-ALL initiating and/or propagating cells.

The originality and competitive advantages of the offer are based on:

- The use of a chemical screening model on primary murine cells enriched with pre-leukemic ALL-B stem cells
- Evaluation of chemical compounds on cells carrying only a primary oncogene (initiator cells)
- Multiparametric FACS reading taking into account phenotypic heterogeneity of normal and pre-leukemic B-systems
- Simultaneous evaluation of the impact of each molecule on pre-leukemic cells and on all subpopulations of the normal B compartment (from pre-pro-B to mature B)
- Consideration of the dependence of normal and pre-leukemic B cells on their microenvironment (miniaturized co-culture on stromal cells)
- Chemical screening also possible on transformed leukemia cells (propagating cells carrying the primary oncogene and secondary genetic alterations)

Description

Scope of research activities

Preclinical research using a transgenic mouse model to screen drug candidates on pre-leukemic B-ALL stem cells.

- Murine model expressing the primary oncogene PAX5-ELN and recapitulating the multi-step development of B-ALL by acquisition of secondary events (Jamrog et al., 2018)
- Initiating pre-leukemic cells (PAX5-ELN oncogene) mimicking the molecular mechanisms of disease relapse in patients (Fregona et al., 2024)
- Transformed leukemia cells carrying secondary mutations
- Screening of drug candidates

Conducting studies

Steps :

- Analysis/definition of study strategy
- Identification of relevant compound libraries to be screened according to the question posed, including commercial libraries, custom libraries and academic libraries (Chimiothèque Nationale)
- Screening of candidate compounds on murine pre-leukemic (initiator) or leukemic (propagator) cells
- Selection of candidate compounds capable of inhibiting the viability of (pre-)leukemic cells and/or restoring their differentiation
- Dose-response counter-screening to determine IC50s of candidate molecules
- Collaboration with chemists to generate pharmacological analogues
- Synthesis and evaluation of biological activity of analogues
- Development and detailed investigation (in vitro and in vivo) of the selected analog
- Molecule testing on other mouse models of ALL-B (PAX5-P80R, TCF3-PBX1) and on PDXs (read more)
- Analysis and communication of results

Research infrastructure

Experimental and analysis platforms:

- Animal house
- Cell sorting platform
- Analytical cytometer
- Commercialized or contract chemical libraries
- CNRS French national chemical library (Mahuteau-Betzer, 2015)

Models :

- Murine models of ALL-B

Technical personnel:

- Engineer for screening and analysis

Specifications

The platform

Set of in vitro and in vivo preclinical models specific to B-ALL for the identification of drug candidates.

The studies

Primary screening of drug candidates:

- Day 0: Inoculation of MS5 stromal cells in 96-well plates
- Day 1: Enrichment and seeding of (pre-)leukemia cells from mice transgenic on stromal cells
- Day 1: Treatment (dose to be determined) of (pre-)leukemic cells (1 compound per well)
- Day 3: Multiparametric FACS analysis (12 antibodies) covering all B differentiation steps (from pre-pro-B to mature-B) and discriminating (pre-)leukemic cells (Fregona et al., 2024)
- Read out: Calculation of the percentage and absolute number of each normal and (pre-)leukemic B subpopulation
- Impact of each compound on normal and (pre-)leukemic B subpopulation cells.

Counter-screening of drug candidates:

- Dose-response counter-screening of selected hits (96-well plate, triplicate/dose)
- Calculation of IC50 for each selected hit
- Read out: Same as primary screening for each dose

Functional validation of drug candidate:

- In vitro treatment and transplantation to determine whether the drug affects the self-renewal function of ALL-B initiator cells
- In vivo treatment of transgenic mice
- In vivo treatment of B-ALL PDXs (read more)

Terms

- **Research partnership**

PRECLINICAL XENOGRAFT MODELS FOR THE EVALUATION OF NEW COMPOUNDS IN THE TREATMENT OF ACUTE LYMPHOBLASTIC LEUKEMIA B

Keywords

Preclinical development | ALL | Targeted therapy | Chemotherapy | Preclinical research (TRL 4-5) |

OPALE entity

CRCT (UMR-1037)

Head

Dr. Bastien Gerby

Équipe IGAALD

Contact

Dr. Sandrine Palcy

Responsable du Business Development

Utilization of preclinical models using human B-ALL xenografts.

The originality and competitive advantages of this offer are based on:

- Privileged access to the Toulouse Cancer University Institute's biological resource center (CRB-IUC), and in particular to the HIMIP tumor library (Inserm Hematological Malignancies in the Midi-Pyrénées region), bringing together collections of frozen biological samples (blood, bone marrow) and associated information (clinical data)
- Access to samples of ALL-B cells from patients at diagnosis and relapse
- Generation of patient-derived xenograft (PDX) models of ALL-B from patients leukemia cells at diagnosis and relapse
- Stocking of frozen cells from PDXs transplantable into NOD-SCID $gc^{-/-}$ immunodeficient mice for expansion of patient leukemia cells in vivo
- Evaluation of the kinetics of in vivo leukemic reconstitution by bone marrow puncture in live animals
- Evaluation of drug candidate efficacy in vivo by bone marrow puncture on live animals

Description

Scope of research activities

Preclinical research using a PDXs model for the evaluation of drug candidates on human ALL-B leukemia cells.

- Transplantation of human ALL-B cells (from diagnosis and/or relapse) into NOD-SCID $gc^{-/-}$ (NSG) immunodeficient mic
- Kinetics of leukemic reconstitution in live animals
- In vivo treatment by intraperitoneal, intravenous or osmotic pump routes
- Evaluation of the efficacy of the drug candidate on leukemic development

Conducting studies

Steps:

- Analysis/definition of study strategy
- Clinico-biological characterization (oncogenic subtype, secondary mutations, phenotypic classification) of the cells of the patient(s) with whom the study will be conducted
- Purchase of primary cell ampoules stored in DMSO and available at the HIMIP CRB
- Transplantation, expansion and follow-up of engraftment of patient cells into NSG immunodeficient mice
- Testing the molecule on the in vivo development of leukemia cells in xenografts
- Molecule testing in mouse models of ALL-B (read more)
- Analysis and communication of results.

Research infrastructure

Experimental and analysis platforms:

- Animal facility
- Cell sorting platform
- Analysis cytometer

Models:

- Human ALL-B and NSG immunodeficient mice

Technical personnel:

- Design engineer for screening and analysis

Specifications

The platform

A set of preclinical in vivo models of human B-ALL for the evaluation of drug candidates.

The studies

- Thawing of patient or PDX samples and transplantation into NSG immunodeficient mice
- Kinetics of human ALL-B development (% hCD45+hCD19+) will be analyzed by regular bone marrow aspiration
- Transplanted mice will be treated (n=5) or not (Vehicle, n=5) with the drug candidate intraperitoneally, intravenously or with osmotic pumps (Alzet Model 2001, 1 mL/h) implanted in the animal for one week
- The efficacy of the treatment on leukemic development will be assessed by the presence of human blasts in the peripheral blood, BM and spleen of the mice (percentage and absolute number)
- The effects of the drug candidate on the propagation and self-renewal of human leukemia cells can be assessed by serial transplantation followed by survival curves for the mice

Terms

- **Research partnership**

DEVELOPMENT OF MOLECULAR DIAGNOSTICS KITS FOR GENOMIC ALTERATION IN LEUKEMIA AND OTHER MALIGNANT HEMOPATHIES

Keywords

Medical diagnostics | MPN | ALL | CLL | AML | Targeted therapy | Chemotherapy | Clinical research (TRL 6-8) | Real-world research (TRL 9) |

OPALE entity

CRCT (UMR-1037)

Head

Prof. Eric Delabesse

Responsable de l'Entité (IGAALD)

Contact

Dr. Sandrine Palcy

Responsable du Business Development

Development of medical diagnostic kits using NGS technology, for the detection of mutations in acute leukemia, at the hematology laboratory of Toulouse University Hospital.

The clinical management of leukemia is based on the results of cytology, flow cytometry, cytogenetics and molecular biology in a time frame increasingly constrained by the arrival of new targeted therapies used in induction of treatments. To respond to this challenge, we have developed rapid (3 days) and sensitive (0.5%) diagnostic methods based on restricted panels adapted to specific clinical requests tested for 7 years in the hematology laboratory of the Toulouse University Hospital. These techniques are Cofrac and EFI accredited (chimerism).

Description

Scope of the offer

Molecular medical diagnosis of leukemias.

Our original offer (design, production, validation of methods, Cofrac accreditation) of molecular diagnostics combined to extensive analyzes of leukemia makes it possible to respond to 2 clinical requests:

- A quick response in 3 days
- A very specific analysis of leukemia mutations, answering very precise clinical questions, critical for either patients monitoring, their diagnosis, or the use of a targeted treatment without the necessary need for an extensive analysis, allowing cost savings (reagent cost of around €15 per sample)

The analyzes carried out by a similar procedure allowing their combination concern:

- Acute myeloid leukemia (392 carried out in 2022)
- Myelodysplastic syndromes and myelodysplastic syndromes/myeloproliferative syndromes (622 carried out in 2022)
- Myeloproliferative neoplasia (essential thrombocythemia, polycythemia vera, myelofibrosis, mastocytosis, atypical CML; 2,083 carried out in 2022)
- Lymphoproliferative syndromes (641 carried out in 2022)
- Resistance to innovative therapies (364 carried out in 2022)
- Post-allograft chimerism (1149 performed in 2022)

Conduct of studies

Steps :

- Analysis of the diagnostic need
- Design
- Realization
- Method validation
- Cofrac accreditation

Research infrastructure

The molecular biology department of the hematology laboratory of the Toulouse University Hospital analyzes 5,000 patients suspected of hematologic malignancies and 10,000 samples per year. More than half of the molecular analyzes are carried out by next generation sequencing (NGS), either by restricted panel (proposed offer) or by expanded panel (bringing together 80 to 100 genes depending on the panels).

Experimental and analysis platforms:

- Genomics: analyzes are carried out on Illumina sequencers (MiSeq, NextSeq500, NovaSeq6000). The platform has 3 Hamilton robots and a Magnis robot in a circuit secured by the use of 2D tubes allowing the traceability of analytical monitoring

Technical personnel:

- 5 technicians
- 2 engineers
- 3 medical biologists

Quality assurance

The molecular biology department of the hematology laboratory of Toulouse University Hospital is Cofrac, EFI, ERICLL accredited and relies on external quality assessments from GBMHM and UKNeqas.

Specifications

- **The platform**

Development of NGS analyses for medical diagnosis of hematological malignancies.

- **The studies**

NGS analysis :

- Acute myeloid leukemias (AML restricted panel: ASXL1 (exon 12), DDX41 (exon 15), DNMT3A (exon 23), FLT3 (exons 16 and 20), IDH1 (exon 4), IDH2 (exon 4), NPM1 (exon 12))
- Myelodysplastic syndromes and myelodysplastic/myeloproliferative syndromes (restricted panel AML + restricted panel MDS: SF3B1 (exons 14 and 15), SRSF2 (exon 1, U2AF1 (exons 2 and 6), UBA1 (exon 3) +/- restricted panel RAS: KRAS (exons 2 and 3), NRAS (exons 2 and 3))
- Myeloproliferative neoplasia (essential thrombocythemia, Vaquez polyglobulia, myelofibrosis: SMP restricted panel: CALR (exon 9, JAK2 (exons 12 and 14), MPL (exon 10); mastocytosis : Mastocytosis restricted panel: KIT (exons 8, 9, 11, 13 and 17); Atypical CML: Atypical CML restricted panel: CSF3R (exons 14, 15, 16 and 17), ETNK1 (exon 3), SETBP1 (exon 4))
- Lymphoproliferative disorders (restricted panel SLP-B: BRAF (exon 15), CXCR4 (exon 2), MYD88 (exon 5), SPI1 (exon 5); restricted panel SLP-T: STAT3 (exons 20 and 21), STAT5B (exon 16))
- Resistance to innovative therapies (Resistance restricted panel: BCL2 (exon 2), BTK (exons 15 and 16), PLCG2 (exons 19, 20, 24, 27 and 30); TP53 restricted panel: TP53 (exons 2, 3, 4, 5, 6, 7, 8, 9,10 and 11))
- Post-allograft chimerism (44 markers assessed at diagnosis, 2 per chromosome; 6 markers distinguishing recipient and donor during follow-up)

Examples of partnerships

COVENIDAC, randomization R4, NCT02416388 - Rapid molecular typing of patients included in the BIG1 protocol, randomization R4-COVENIDAC using the AML restricted panel (454 patients tested)

Partner: FILO-AML

PHRC INTER REGIONAL EVATRYMS, NCT02441166 - Rapid molecular typing of patients included in the Evatryms PHRC using the KIT restricted panel for validation of mastocytosis status (219 patients tested)

Partner: Dermatology Department, Toulouse University Hospital.

Terms

- **Research partnership**

STUDIES OF THE MECHANISM OF HEMATOPOIETIC STEM CELL TRANSFORMATION IN ACUTE MYELOID LEUKEMIA AND CLONAL SELECTION MODELS

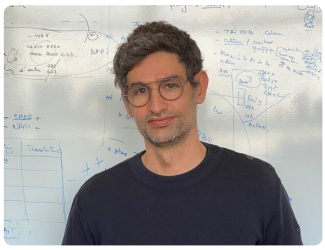
Keywords

Target discovery | AML | Targeted therapy | Alternative therapy | Basic research (TRL 1-3) |

OPALE entity

CRSA (UMR-938)

Head



Prof. François Delhommeau

Responsable de l'Entité

Contact

Dr. Sandrine Palcy

Responsable du Business Development

Study of the microenvironment's role (i.e. stromal cells, marrow plasma composition) in the transformation of hematopoietic stem cells in acute myeloid leukemia (AML) to understand the action of anti-leukemic drugs on clonal selection in AML. Comparative study with somatic genetic rescue phenomena in constitutional hematopoietic pathologies.

Expertise in the dialogue between hematopoietic cells and stromal cells, identification of microenvironment targets. Perspectives for combined action on leukemia cells and the pathological bone marrow microenvironment.

Description

Scope of research activities

Mechanistic studies of hematopoietic stem cells transformation in AML.

Conduct of studies

Steps:

- Evaluation of questions and objectives
- Design of studies and experimental plans
- Experimental and analytical implementation
- Valorization of results

Research infrastructure

Experimental and analytical platforms:

- Cell culture, co-culture
- Cytometry
- Microscopy/imaging
- Genomics, transcriptomics, single cell RNAseq
- Cytokine assays, protein analysis

Models:

- Primary hematopoietic and mesenchymal cells from healthy individuals
- Primary hematopoietic and mesenchymal cells from AML patients
- Stromal and leukemic cell lines

Technical personnel:

- Technicians / Engineers

Specifications

Our approach

Strategy based on our knowledge of the clonal architecture of AML and our tools for understanding the initiation and evolution of leukemic and pre-leukemic clones, integrating parameters of the bone marrow microenvironment as well as parameters dependent on predisposing situations. Study of the dialogue between hematopoietic cells and the microenvironment depending on pathology.

Studies

- Genomic analysis (bulk and single cell)
- Transcriptomic analysis (bulk and single cell)
- Hematopoietic functional analysis

Terms

- **Research partnership**
- **Public aid to companies**
- **Collaborative project (multi-beneficiary partnership)**

ARTIFICIAL INTELLIGENCE-AUGMENTED CELLULAR IMAGING IN ACUTE MYELOID LEUKEMIA (DIAGNOSIS, PROGNOSIS, STRATIFICATION)

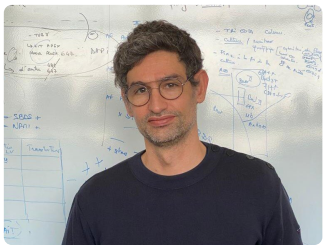
Keywords

Preclinical development | AML | Targeted therapy | Immunotherapy | Chemotherapy | Preclinical research (TRL 4-5) |

OPALE entity

CRSA (UMR-938)

Head



Prof. François Delhommeau

Responsable de l'Entité

Contact

Dr. Sandrine Palcy

Responsable du Business Development

Artificial intelligence (AI) platform for integrating next-generation cell imaging data with biological data (cytogenetics, flow cytometry, molecular, genomics)

A new cell microscopy technology for diagnosis, prognosis and preclinical drug evaluation or patient population stratification.

Description

Scope of research activities

Preclinical research using new AI-augmented cell microscopy technology with biological data.

- Evaluation of drug candidates
- Stratification of patient populations

Conduct of studies

Steps:

- Evaluation of questions and objectives
- Study and experimental design
- Experimental and analytical implementation
- Valorization of results

Research infrastructure

Experimental and analytical platforms:

- Cellular microscopy integrating biological data using AI technology

Models:

- Primary patient samples

Technical personnel:

- Technicians / Engineers

Specifications

The platform

New cell microscopy technology for correlating imaging data with biological data.

The studies

Production of an optical twin using synthetic holography: 3D representation of figurative elements in blood and bone marrow.

Integration of imaging data with :

- Cytomorphological examination of bone marrow
- Blood and/or bone marrow analysis: flow cytometry, cytogenetics, molecular biology or genomics
- Deep learning

Examples of partnerships

LABCOM Optical Twin For Diagnosis OT4D - Development of new approaches to next-generation optical microscopy to feed artificial intelligence tools for diagnosis, prognostic stratification and monitoring of blood diseases.

Partners: TRIBVN ; Sorbonne Center for Artificial Intelligence ; Telecom Sud Paris ; APHP

Terms

- **Research partnership**
- **Public aid to companies**
- **Collaborative project (multi-beneficiary partnership)**

DEVELOPMENT OF IMMUNOTHERAPIES TARGETING THE CYTOTOXIC ACTIVITY OF NK CELLS (ALL/MDS)

CLyMi

Keywords

Preclinical development | AML | MDS | Immunotherapy | Preclinical research (TRL 4-5) |

OPALE entity

EMiLy (INSERM U1160)

Head

Dr. Karl Balabanian

Responsable de l'Entité

Contact

Dr. Sandrine Palcy

Responsable du Business Development

3D model to study the cytotoxic activity of human NK cells for in vitro evaluation of new immunotherapies under conditions that mimic the complexity of the tumor environment.

By setting up three-dimensional interactions between the different cell types, the 3D model makes it possible to take into account the respective roles of immune and stromal cells in the development of an effective anti-leukemia response.

Description

Scope of research activities

Preclinical research using 3D in vitro models of MDS and AML:

- Screening
- Demonstration of mechanism of action
- Efficacy evaluation

Conduct of studies

Steps :

- Study design for innovative products designed to modulate anti-leukemic immune responses
- Organization, implementation and conduct of studies
- Drafting of study plans.
- Statistical analysis and interpretation of results

Research infrastructure

Experimental and analysis platforms:

- Cell cultures (lymphocyte or stromal populations)
- Spectral flow cytometry (40 simultaneous markers)
- Multiplex soluble molecule assay platform (Luminex)
- Fluorescence microscopy.
- Bioinformatics data analysis pipelines (flow cytometry, RNA-seq, etc.)

Biological resources:

- 3D medullary organoid model.

Specifications

The platform

Screening platform using 3D in vitro models (co-culture of stromal cells/mesenchymal strains, blast cells, NK cells from patients, healthy donors or lines depending on the question asked) to mimic the complexity of the tumor environment.

Studies

Screening of drug candidates targeting the anti-leukemic activity of NK cells:

- Cytokine assays (IFN-g, TNF-a)
- Cytotoxic activity

Evaluation of the activity of drug candidates on the anti-leukemic action of NK cells:

- Cytokine assays (IFN-g, TNF-a)
- Cytotoxic activity

Mechanism of action of drug candidates on the anti-leukemic activity of NK cells:

- Cytokine assays (IFN-g, TNF-a)
- Cytotoxic activity
- Molecular analyses (multiplex qRT-PCR, RNA-seq)

Terms

- **Research partnership**

IN VIVO MODEL OF WALDENSTRÖM DISEASE

CLyMi

Keywords

Preclinical development | Waldenström's macroglobulinemia | Targeted therapy | Preclinical research (TRL 4-5) |

OPALE entity

EMiLy (INSERM U1160)

Head

Dr. Karl Balabanian

Responsable de l'Entité

Contact

Dr. Sandrine Palcy

Responsable du Business Development

Unique WM mouse model, mutated for CXCR4 and MyD88, to assess the impact of treatments on immune cell biology and the bone marrow microenvironment.

First murine model, accurately reproducing key features of Waldenström disease biology, for drug candidate validation.

Description

Scope of research activities

Preclinical research using a WM mouse model, mutated for CXCR4 and MyD88:

- Pre- and post-treatment phenotypic and functional analyses
- Evaluation of treatments
- Mechanism of action

Conduct of studies

Steps :

- Study design for innovative products designed to modulate malignant cells and/or their environment
- Organization, implementation and conduct of studies
- Drafting of study plans.
- Statistical analysis and interpretation of results

Research infrastructure

Experimental and analytical platforms:

- Spectral flow cytometry (40 simultaneous markers)
- Cell culture
- Animal facility
- Confocal microscopy

Biological resources:

- Cxcr4+/1013 x Myd88B-L252P mouse model reproducing certain features of Waldenstrom's disease

Specifications

The platform

Preclinical mouse model with gain-of-function mutations for the Cxcr4 and MyD88 proteins and some Waldenström disease features (hyper IgM, bone marrow involvement, reduced survival).

The studies

Screening of drug candidates targeting the Btk and CXCR4 signaling axes:

- IgM production
- Clinical signs
- Phenotyping of B cells, immune and stromal compartments

Evaluation of treatment activity (or combination of treatments):

- IgM production
- Clinical signs
- Phenotyping of B cells, immune and stromal compartments

Mechanism of action of drug candidate:

- B-cell survival and migration
- B cell differentiation, signaling and activation
- Bone marrow hematopoiesis
- Bone marrow microenvironment

Examples of partnerships

CXCR4 antagonism in mouse models for hematological disorders associated with gain-of-CXCR4 function - Impact on how B cells adapt to and shape the bone marrow ecosystem.

Partner : X4 Pharmaceuticals

Terms

- **Research partnership**

STUDY OF IMMUNE CELL BIOLOGY IN RESPONSE TO TREATMENT IN AML/MDS/WM PATIENTS

CLyMi

Keywords

Preclinical development | Waldenström's macroglobulinemia | Immunotherapy | Preclinical research (TRL 4-5) |

OPALE entity

EMiLy (INSERM U1160)

Head

Dr. Karl Balabanian

Responsable de l'Entité

Contact

Dr. Sandrine Palcy

Responsable du Business Development

Analysis of lymphoid cells of the innate (NK) and adaptive (T) response in normal and in patients (AML, MDS, WM). Longitudinal studies before and after treatment of patients with immunotherapy or immunomodulating agents.

Measurement of the phenotypic and functional impact of the molecules used, alone or in combination, and over time, on the anti-leukemic potential of innate NK and adaptive T lymphocytes. Our experimental and analytical approaches combine the various parameters measured to provide an integrated picture of immune function following treatment.

Description

Scope of research activities

Preclinical/translational research using primary cells from healthy donors and patients (clinical trials, cohorts and observatories):

- Studies of the phenotypic and functional profiles of Natural Killer cells
- Checkpoint inhibitor studies
- Phenotypic and functional analyses at different stages of the disease
- Pre- and post-treatment phenotypic and functional analyses

Conducting the studies

Steps :

- Study design for innovative products to modulate anti-leukemic immune responses
- Organization, implementation and conduct of studies
- Drafting of study plans
- Statistical analysis and interpretation of results

Research infrastructure

Experimental and analysis platforms:

- Cell cultures (lymphocyte or stromal populations)
- Spectral flow cytometry (40 simultaneous markers)
- Multiplex soluble molecule assay platform (Luminex)
- Fluorescence microscopy
- Bioinformatics data analysis pipelines (flow cytometry, RNA-seq, etc.)

Biological resources:

- Access to primary cells from healthy donors via collaborations with clinical departments and Établissement français du sang (EFS)
- Access to primary cells from AML, MDS and WM patients via collaborations with clinical departments in Paris

Specifications

The platform

Characterization of innate (NK) and adaptive (T) lymphoid cells from primary cell cultures.

Studies

Phenotyping of innate (NK) and adaptive (T) lymphoid cells in healthy donors and patients during disease progression.

- Phenotypic characterization by flow cytometry
- Cytokine assays (IFN-g, TNF-a)
- Cytotoxic activity
- Molecular analysis (multiplex qRT-PCR, RNA-seq)

Phenotyping of innate (NK) and adaptive (T) lymphoid cells in response to treatment.

- Phenotypic characterization by flow cytometry
- Cytokine assays (IFN-g, TNF-a)
- Cytotoxic activity
- Molecular analyses (multiplex qRT-PCR, RNA-seq)

Studies of drug cytotoxicity on immune cells (NK and T cells).

- Cytokine assays
- Cytotoxic activity
- Molecular analyses (multiplex qRT-PCR, RNA-seq)
- Metabolic analysis

Checkpoint inhibitor studies using primary human normal and leukemia cells.

- Cytokine assays
- Cytotoxic activity
- Molecular analyses (multiplex qRT-PCR, RNA-seq)

Examples of partnerships

Biology of NK and T cells in response to treatment - Analysis of disease progression on NK and T cell phenotype in AML and MDS patients: pre- and post-treatment follow-up.

Partner: Sanofi R&D

Terms

- **Research partnership**

RAINBOW PLATFORM: PHARMACODYNAMIC MONITORING BY SINGLE-CELL OMICS

Keywords

Biomarkers | AML | Precision medicine | Translational research (TRL 4-5) |

OPALE entity

GenCellDis (UMR-944)

Head

Prof. Raphaël Itzykson

Responsable Opale

Contact

Dr. Sandrine Palcy

Responsable du Business Development

Single-cell omics analysis platform to study longitudinal changes during the course of therapy (including during aplasia) in patients treated for acute myeloid leukemia (AML).

AML is characterized by its heterogeneity, and rare cell populations within the leukemic bulk can significantly impact treatment outcomes. Our single-cell omics analysis platform allows for a comprehensive profiling of individual leukemic cells, providing unparalleled precision and specificity. This level of detail helps in identifying unique biomarkers that may not be detectable with bulk analysis, thus offering a more accurate reflection of the disease state and treatment response.

Description

Scope of research activities

Translational research to analyze longitudinal changes in genotype or phenotype of leukemic and immune cells at single-cell resolution in AML patients undergoing therapy and discover predictive biomarkers through:

- Single-cell omics (DNA, RNA, surface protein, methylation)
- Functional flow cytometry assays (e.g. BH3 profiling, PgP efflux, SCENITH) coupled with analysis of surface protein expression
- Including in rare subpopulations (LSCs) or non-leukemic cells (infiltrating T cells)
- Analysis of fresh or viably frozen samples
- Longitudinal monitoring including in hypocellular samples (e.g. drug-induced aplasia)

Conduct of studies

Steps:

- Study design
- Define means/resources and propose schedule (steps, GO/NO-GO, cost estimate)
- Study organization, implementation and conduct
- Data analysis and delivery of a study report with recommendations

Research infrastructure

Experimental and analysis platforms :

- Tapestri, Mission Bio
- Chromium X, 10X Genomics
- Automated liquid dispensing (Biomek i5, Beckmann Coulter)
- Magnetic cell enrichment (MACS, Miltenyi)
- Spectral cell sorting (BigFoot, ThermoFisher)
- High-Throughput Screening flow cytometer (3 lasers, 13 parameters, iQUE3, Sartorius)
- Conventional flow cytometer (2 lasers, 8 parameters, Cytoflex, Beckmann Coulter)

Models:

- Primary cells from AML patients (including R/R AMLs; fully annotated – demographics, prior therapies & genetics)
- Human AML cell lines (assay calibration)

Assays:

- Single-cell DNA ± Surface Protein ± Targeted methylation
- Single-cell DNA ± Surface Protein ± Chromatin Accessibility
- Flow cytometry
- BH3 profiling
- PgP efflux
- SCENITH
- Apoptosis / Ferroptosis

Technical personel :

- 1 physician-scientist (scientific supervision, bioinformatics) and 1 operational engineer manager
- 1 engineer and 1 assistant engineer – flow cytometry & single-cell assays

Quality assurance

Université Paris Cité Technology Platforms certification (ongoing)

Specifications

The platform

Translational studies using primary cells from AML patients, for the analysis of dynamic changes in genetic or functional biomarker at single-cell resolution.

The studies

Single-cell omics:

- Clonal dynamics under therapy
- Differentiation under therapy (with or without genetic information)
- Changes in biomarker gene expression at single-cell resolution under therapy (leukemic cells or immune cells, including in the context of drug-induced aplastic bone marrow)
- LSC dynamics under therapy

Functional flow cytometry:

- Protein expression (surface or intracellular) at single-cell resolution and changes under therapy
- BCL-2/BCL-xL/MCL-1 dependency and changes under therapy
- OXPHOS/glycolysis dependency and changes under therapy
- MDR phenotype (PgP activity) at single-cell resolution and changes under therapy
- Apoptotic (Annexin V) or Ferroptotic (C11-BODIPY) cell death and changes under therapy

Examples of partnerships

Surface expression of an immunotherapy target on leukemic and residual leukemic cells – Surface expression of a biomarker in primary samples from R/R AML samples with clinical annotations, including differential expression in leukemic compartments (e.g. LSCs)

Partner: ADVESYA

Dynamics of resistance to venetoclax azacitidine – Longitudinal monitoring of changes in gene expression, BCL-2 dependency and metabolic changes during the first courses of venetoclax-based regimens in newly diagnosed AML.

Partner: INCa / DGOS (PRT-K)

Terms

- **Research partnership**
- **Public aid to companies**
- **Collaborative project (multi-beneficiary partnership)**

NEXT PLATFORM: DRUG COMBINATION SCREENING OF PRIMARY SAMPLES FOR ACUTE MYELOID LEUKEMIA

Keywords

Biomarkers | Leads optimization | Drug combination identification | AML | Precision medicine | Translational research (TRL 4-5) |

OPALE entity

GenCellDis (UMR-944)

Head

Prof. Raphaël Itzykson

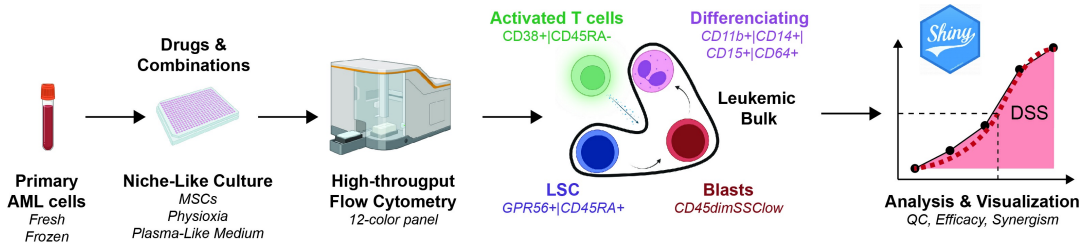
Responsable Opale

Contact

Dr. Sandrine Palcy

Responsable du Business Development

Functional precision medicine platform based on high-throughput flow cytometry for drug sensitivity testing and biomarker discovery in acute myeloid leukemia (AML).



Our cutting-edge ex vivo drug sensitivity testing platform offers a unique approach by combining custom ex vivo culture of primary patient samples, to better mimic the leukemia niche with multiparameter flow cytometry. This allows us to measure multiple readouts, including differentiation and T cell activation, in addition to cell viability.

We utilize primary AML samples, including relapsed/refractory (R/R) AMLs, from the ALFA multicenter prospective registry. These samples are enriched with extensive clinical and genetic annotations.

Furthermore, our platform employs high-throughput screening (HTS) and predictive modeling techniques to facilitate lead prioritization. Our Bayesian methods are adept at identifying and optimizing synergistic drug combinations, ensuring a targeted and efficient therapeutic strategy.

Description

Scope of research activities

Preclinical and translational research in AML:

- Lead optimization by testing their activity on primary AML samples
- Drug combination prioritization by testing their activity and synergism on primary AML samples
- Discovery of biomarkers by correlating ex vivo activity with clinical and genetic annotations
- In vivo validation of single agent or combination activity in PDX models

Conduct of studies

Steps :

- Study design
- Define means/resources and propose schedule (steps, GO/NO-GO, cost estimate)
- Study organization, implementation and conduct
- Data analysis and delivery of a study report with recommendations

Research infrastructure

Experimental and analysis platforms:

- Automated liquid dispensing (Biomek i5, Beckmann Coulter)
- Magnetic cell enrichment (MACS, Miltenyi)
- Spectral cell sorting (BigFoot, ThermoFisher)
- High-Throughput Screening flow cytometer (3 lasers, 13 parameters, iQUE3, Sartorius)
- Conventional flow cytometer (2 lasers, 8 parameters, Cytoflex, Beckmann Coulter)
- NSGS and NOG-EXL recipients for PDXs.

Models:

- Primary cells from annotated AML patients (including R/R AMLs) from the ALFA prospective registry, demographics, previous therapies, genetics data
- Human AML cell lines (assay calibration)
- PDX models

Technical personel:

- 1 physician-scientist (scientific supervision, data analysis) and 1 operational engineer manager
- 1 engineer (PDX models)
- 1 engineer and 1 assistant engineer – ex vivo drug testing

Quality assurance

- Université Paris Cité Technology Platforms certification (ongoing)
- Animal Facility at IRSL compliant with European and French Regulation (Directive 2010/63; Décret 2013-118)

Specifications

The platform

Preclinical and translational studies using primary cells from AML patients (or from PDXs), for the investigation of single agent or combination activity and further in vivo validation.

The studies

- Activity of single agent or drug combination on leukemic viability
- Activity of single agent or drug combination on differentiation of leukemic cells
- Differential activity of single agent or drug combination between phenotypically-defined leukemic stem and non-stem cells
- Differential activity of single agent or drug combination between leukemic cells and circulating T cells
- Differential activity of single agent or drug combination between clinically or genetically defined AML patient populations

Examples of partnerships

Preclinical investigation of a first-in-class kinase inhibitor in AML – Ex vivo exploration of single agent activity of a first-in-class kinase inhibitor in AML, prioritization of combinations, in vivo validation in PDX models.

Partner: SERVIER

Preclinical investigation of a first-in-class BET inhibitor in AML – Ex vivo exploration of single agent activity of a first-in-class BET inhibitor in AML, prioritization of combinations, dedicated long term cultures to explore impact on LSCs.

Partner: ONCOETHIX

Terms

- **Research partnership**
- **Public aid to companies**
- **Collaborative project (multi-beneficiary partnership)**

IN VITRO TRANSLATIONAL STUDIES FOR THE DEVELOPMENT OF DIFFERENTIATING TARGETED THERAPIES FOR ACUTE MYELOID LEUKEMIA

Keywords

Preclinical development | AML | Targeted therapy | Preclinical research (TRL 4-5) |

OPALE entity

Gustave Roussy (UMR-1170)

Head

Dr. Virginie Penard-Lacronique

Responsable de l'Entité

Contact

Dr. Sandrine Palcy

Responsable du Business Development

In vitro translational studies to evaluate new differentiating targeted therapies for the treatment of acute myeloid leukemia (AML).

UMR-1170 works closely with Gustave Roussy's Department of Therapeutic Innovation and Early Trials (DITEP), which has expertise in hematology and whose missions are to offer patients in therapeutic failure access to innovative molecules and to accelerate the development of new cancer treatments.

Description

Scope of research activities

Preclinical research using primary cells from AML patients to test drug candidates:

- Evaluation of the efficacy of targeted small molecules
- Demonstration of mechanism of action

Conduct of studies

Steps:

- Organize study set-up, technique development and quality control
- Organize cytometry data management
- Assist the bioinformatics engineer of the imaging and cytometry platform in analyzing the data set and interpreting results

Research infrastructure

Experimental and analysis platforms:

- Preclinical research platform (hosting of preclinical cancer models; preclinical evaluation of models and therapies, phenotyping, experimental pathology)
- Integrated biology platform (genomics, proteomics and metabolomics)
- Imaging and cytometry platform

Models:

- Primary cells from AML patients

Technical personnel:

- Technician

Specifications

The platform

In vitro studies on primary cells from AML patients to evaluate and understand the mechanism of action of new molecules targeting mutations involved in the early stages of hematopoietic cell transformation.

The studies

Evaluation of anti-leukemic activity:

- Morphology (cytology)
- Expression of cell surface markers studied by flow cytometry and spectral cytometry to analyze the process of breaking the blockade of differentiation

Examples of partnerships

Inhibitor FHD-286 Induces Differentiation in Preclinical Models of AML - The aim of the study was to evaluate the cytotoxic activity of a pharmacological inhibitor of the BRD9 catalytic subunit (SWI/SNIF complexes) on primary samples from AML patients by various assays, including spectral cytometry analysis.

Partner: Foghorn Therapeutics

Efficacy of FT-2102 (olutasidenib) on IDH1 Acute Myeloid Leukemia - The aim of the study was to investigate by RNA sequencing the cellular/molecular pathways associated with the first steps in the lifting of the differentiation blockade induced by FT-2102 alone or in combination with 5AZAdC.

Partner: Forma Therapeutics

Study of Orally Administered AG-120 in Subjects With Advanced Hematologic Malignancies With an IDH1 Mutation - The aim of the study was to evaluate the pro-differentiation activity of AG-120 in samples from patients with AML with an IDH1 mutation (IDH1m).

Partner: Agios Pharmaceuticals

Terms

- **Research partnership**

IN VITRO AND IN VIVO MODELS FOR STUDYING THE FUNCTIONAL GENETICS OF ACUTE MYELOID LEUKEMIA IN CHILDREN

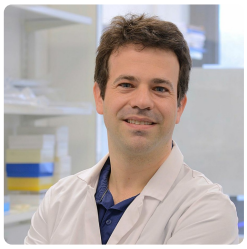
Keywords

Preclinical development | AML | Targeted therapy | Preclinical research (TRL 4-5) |

OPALE entity

Gustave Roussy (UMR-1170)

Head



Dr. Thomas Mercher

Responsable d'équipe

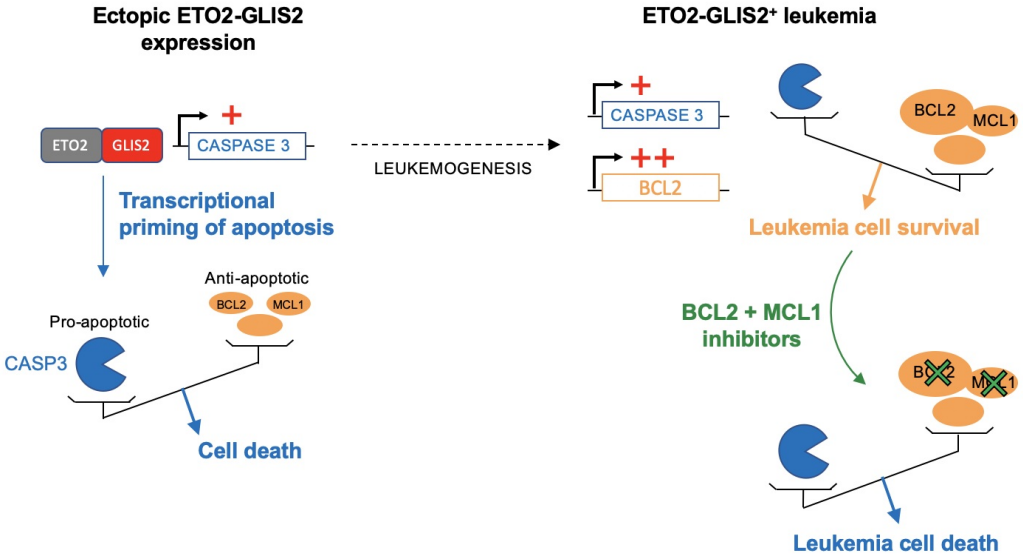
Contact

Dr. Sandrine Palcy

Responsable du Business Development

In vitro and in vivo studies of the molecular mechanisms involved in pediatric acute myeloid leukemia (AML).

We are developing in vitro and in vivo functional study models to address the molecular basis of pediatric acute myeloid leukemia. Our genetic and epigenetic analyses aim to better understand the activity of transcription factors and the influence of extrinsic factors on tumor development, leading to new therapeutic strategies.



Description

Scope of research activities

Preclinical research using in vitro and in vivo models for the development of new targeted therapies for pediatric AML:

- Molecular target validation
- Evaluation of drug candidate efficacy

Conduct of studies

Steps :

- Analysis of innovative product development strategy
- Study design
- Drafting of study plans
- Organization, implementation and conduct of studies
- Analysis and communication of results

Research infrastructure

Experimental and analytical platforms:

- Preclinical research platform (hosting preclinical cancer models; preclinical evaluation of models and therapies, phenotyping, experimental pathology)
- Integrated biology platform (genomics, proteomics and metabolomics)
- Imaging and cytometry platform
- Individual CRISPR/Cas9 screening or screens
- Bioinformatics (transcriptome, single cell transcriptome, chromatin accessibility, activity inference)

Models:

- AML PDX models
- Transgenic mouse models: doxycycline-inducible model of ETO2-GLIS2 fusion expression in a C57BL/6 background
- Leukemia cell lines: MO7e, CMS, CMK, HEL, lines with oncogenes expressing a fluorescent tag (GFP or Scarlet) or a degron
- Human induced pluripotent stem (iPSC) cell lines expressing oncogenes

Technical personnel:

- Pre-clinical experimentation technician/engineer

Specifications

The platform

Preclinical analysis of the efficacy of new molecules on leukemic development. Genetic analysis and functional characterization of molecular abnormalities in childhood AML.

Studies

Transcriptomic/epigenetic studies:

- Gene expression at population or single-cell level
- Access to chromatin (ATAC-seq)

Protein-protein interaction studies:

- Co-immunoprecipitation

Molecular engineering (CRISPR/Cas9 approach):

- Gene inactivation
- Screening using inactivation libraries of different sizes

Visualization of leukemic progression in preclinical models:

- Latency
- Phenotype (flow cytometry)

Examples of partnerships

Targeting aggressive AML - Testing the formulation of liposomes loaded with apoptosis inhibitors.

Partner: Université Paris-Saclay

Terms

- **Research partnership**
- **Public aid to companies**
- **Collaborative project (multi-beneficiary partnership)**

STUDY OF MOLECULAR MECHANISMS REGULATING NORMAL AND MALIGNANT HEMATOPOIESIS (AML)

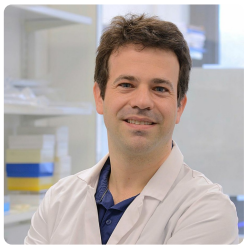
Keywords

Target discovery | AML | Targeted therapy | Basic research (TRL 1-3) |

OPALE entity

Gustave Roussy (UMR-1170)

Head



Dr. Thomas Mercher

Responsable d'équipe

Contact

Dr. Sandrine Palcy

Responsable du Business Development

Studies of transcription regulation in normal and tumor hematopoietic cells.

Knowledge of the transcription factors involved in the regulation of gene expression and epigenetics in normal and tumor hematopoietic cells. The perspectives are to identify specific markers of leukemia cells that could be targeted with minimal consequences on normal hematopoietic cells.

Description

Scope of research activities

Basic research in normal and tumor hematopoietic cells.

Conducting studies

Steps:

- Analysis of innovative product development strategy
- Study design
- Drafting of study plans
- Organization, implementation and conduct of studies
- Analysis and communication of results

Research infrastructure

Experimental and analytical platforms:

- Preclinical research platform (hosting preclinical cancer models; preclinical evaluation of models and therapies phenotyping, experimental pathology)
- Integrated biology platform (genomics, proteomics and metabolomics)
- Imaging and cytometry platform
- Individual CRISPR/Cas9 screening or screens
- Bioinformatics (transcriptome, single cell transcriptome, chromatin accessibility, activity inference)

Models:

- AML PDX models
- Transgenic mouse models: doxycycline-inducible model of ETO2-GLIS2 fusion expression in a C57BL/6 background
- Leukemia cell lines: MO7e, CMS, CMK, HEL, lines with oncogenes expressing a fluorescent tag (GFP or Scarlet) or a degron
- Human induced pluripotent stem (iPSC) cell lines expressing oncogenes

Technical personnel:

- Pre-clinical experimentation technician/engineer

Specifications

Studies

Analysis of epigenetic regulators:

- Transcriptome, single cell transcriptome
- ATAC-seq
- ChIP-seq (Transcription factors, Histone marks)

Terms

- **Research partnership**
- **Public aid to companies**
- **Collaborative project (multi-beneficiary partnership)**

INVESTIGATING THE MECHANISM OF ACTION OF DRUG CANDIDATES FOR THE TREATMENT OF MYELODYSPLASTIC SYNDROMES AND ACUTE MYELOID LEUKEMIA

Keywords

Preclinical development | Functional studies | AML | MDS | Targeted therapy | Immunotherapy | Chemotherapy | Preclinical research (TRL 4-5) |

OPALE entity

Cochin Institute (UMR-1016)

Head

Prof. Didier Bouscary

Responsable de l'Entité

Contact

Dr. Sandrine Palcy

Responsable du Business Development

Translational studies to identify the mechanism of action of drug candidates for the treatment of myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML).

Discovery of mechanisms of action in cell line models.

Validation in primary human AML and MDS cells.

Description

Scope of research activities

Preclinical research for the proof of concept of the mechanism of action of new molecules in in vitro models of MDS and AML:

- Biomarker research
- Research into synthetic lethality pathways

Conducting studies

Steps:

- Establishment of cell line models by target invalidation
- Analysis of intracellular modifications
- Search for synthetic lethal pathways
- Validation in primary human leukemia cells in vitro and in vivo in PDX
- Analysis and communication of results

Research infrastructure

Experimental and analytical platforms:

- CYBIO cytometry platform
- IMAG'IC confocal imaging platform
- GENOM'IC transcriptomic analysis platform
- PROTEOM'IC proteomic analysis platform
- EOPS animal facilities (human cell xenograft models in immunocompetent mice)

Models:

- Hematopoietic cell lines
- Primary cells from AML patients
- Primary cells from MDS patients

Technical personnel:

- 1 assistant engineer
- 1 research technician

Quality assurance

Institut Cochin Genomics (DNA-seq, RNA-seq, methylation) platform - GENOM'IC : ISO 9001 - IBISA certifications .

Institut Cochin Proteomics platform - PROTEOM'IC: ISO 9001/NF X 50-900 - IBISA certifications.

Specifications

The platform

Translational research platform for in vitro studies of the mechanism of action of drug candidates on primary cells from MDS and AML patients.

The studies

Mechanism of action of the drug candidate's anti-leukemic activity:

- Analysis of mitochondrial metabolic pathways and cell death pathways

Examples of partnerships

Biological studies of phase 2 clinical trial IMerge - Evaluation of gene expression profile of bone marrow mononuclear cells and of peripheral blood immune cell populations upon treatment. In vitro effect of MDS erythropoiesis.

Partner: GERON

Terms

- **Research partnership**
- **Public aid to companies**
- **Collaborative project (multi-beneficiary partnership)**

PRECLINICAL MODELS FOR THE DEVELOPMENT OF NEW TREATMENTS FOR MYELOPROLIFERATIVE NEOPLASIA

Keywords

Preclinical development | MPN | MDS | LMMJ | Targeted therapy | Chemotherapy | Preclinical research (TRL 4-5) |

OPALE entity

INSERM UMR-S 1131 (UMR-1131)

Head

Prof. Stéphane Giraudier

Responsable de l'Entité

Contact

Dr. Sandrine Palcy

Responsable du Business Development

In vitro and in vivo models of myeloproliferative neoplasia for preclinical testing to select and validate drug candidates.

Our team uses in vitro models such as cell lines carrying isogenic MPN initiator mutations. This enables us to test the impact of a mutation with the advantages and disadvantages of the cell lines.

We also use samples from patients, usually blood samples, as diseased cells are circulating in MPN. These cells are studied in liquid culture or clonogenic assays, with or without CD34 sorting. The advantage is that we can compare the fate of cells directly derived from patients, carrying the relevant abnormalities. In the various tests, we can compare the fate and drug sensitivity of diseased cells and residual normal cells from the same patient.

Description

Scope of research activities

Preclinical research using different specific models of myeloid leukemia or MPN to test drug candidates:

- Demonstration of mechanism of action
- Evaluation of efficacy
- Evaluation of toxicity

Conduct of studies

Steps:

- Design and drafting of study plan
- Organization, implementation and conduct of studies
- Analysis and communication of results

Research infrastructure

Experimental and analytical platforms:

- Flow cytometry
- Genomics
- Cell culture

Models:

- Murine leukemia models
- Primary cells from MPN patients: blood or bone marrow hematopoietic cells, stromal cells.
- Leukemia cell lines secondary to MPN

Specifications

The platform

Preclinical studies using in vitro and in vivo MPN models.

The studies

In vitro studies are carried out either in liquid medium or in semi-solid medium (clonogenic culture) on total mononuclear cells or cells sorted on CD34. A mouse model carrying the MPN-initiating JAK2 mutation is also used in this study.

Evaluation of anti-leukemic activity of drug candidates:

- Cell survival or apoptosis rate
- Number of colonies and ratio to untreated
- % of colonies remaining after treatment and carrying the initiating mutation
- Allelic load of the initiating mutation and additional mutations after culture with the drug candidate
- Mouse model: monitoring of blood parameters and survival of mice

Mechanism of action of the drug candidate's anti-leukemic activity:

- Study of signaling pathways activated by initiating mutations

Assessment of drug candidate toxicity:

- Same items as for anti-leukemic activity, but on the non-mutated population of patient samples
- Survival, apoptosis, clonogenicity on samples from healthy subjects obtained from EFS

Examples of partnerships

Study of the efficacy of Ropeg Interferon alpha on JAK2-mutated MPN cells - Test of antiproliferative action on JAK2-mutated cell lines and inhibition of clonogenic sprouting of JAK2-mutated hematopoietic progenitors. Comparison with the reference form of pegylated interferon alpha.

Partner: AOP Orphan

Testing the efficacy of an MDM2 inhibitor in MPN - In vitro and in vivo tests in JAK2-mutated MPN models of the efficacy of the MDM2 inhibitor.

Partner: KARTOS

Terms

- **Research partnership**

LEUKEMIC NICHE MODELING (AML)

Keywords

Preclinical development | AML | Targeted therapy | Chemotherapy | Preclinical research (TRL 4-5) |

OPALE entity

U1312 BRIC

Head

Dr. Jean-max Pasquet

Responsable de l'Entité

Contact

Dr. Sandrine Palcy

Responsable du Business Development

Tissue niche model by co-culture in physioxia (physiological oxygen concentration) for the selection and validation of drug candidates for the treatment of acute myeloid leukemia (AML).

The CellOxia cell culture platform offers equipment (XVivo Biosphérix) enabling studies to be carried out under controlled atmospheric conditions, to reproduce in vitro and ex vivo the physiological or pathophysiological parameters existing within the tissue niche, as in the case of leukemic bone marrow.

Description

Scope of research activities

Preclinical research using an in vitro and ex vivo leukemia niche model for the selection and validation of new molecules for the treatment of AML:

- Screening
- Demonstration of mechanism of action
- Efficacy evaluation
- In vivo validation in PDX AML

Conduct of studies

Steps:

- Study design after definition of the question raised and the services required
- Proposal of specifications according to the service required (service or simple use of equipment)
- Implementation of services and experiments
- Conducts of experiments and analyses of results
- Study report for services or experimenters' support

Research infrastructure

Experimental and analysis platforms:

- XVivo model X1 (Biosphérix)
- P2 culture laboratory
- PAULA intelligent cell imaging system (Leica)
- Nikon Ti inverted microscope with phase-contrast and fluorescence imaging

Cell models :

- Primary cells from AML patients (leukemic blasts)
- Mesenchymal or adipocytic cells
- Human AML cell lines and human and murine stromal cells

Technical personnel:

- Specialized engineer for design and implementation of hypoxia studies

Quality assurance

The CellOxia platform is part of the research support unit (UAR) CNRS 3427/US005 Inserm comprising 11 platforms. Created in 2016 and

accredited by Siric Brio, it joined the UAR in 2021. To date, it has 12 academic laboratories and two companies that have or are still using its services and equipment.

Specifications

The platform

A set of in vitro tests, reproducing the pathophysiological conditions of the leukemic niche, for selection and validation of drug candidates for the treatment of AML.

The studies

Screening of drug candidates:

- Proliferation and apoptosis assays +/- drugs in hypoxia
- Dose-response of agents to different oxygen concentrations
- Molecule screening

Evaluation of anti-leukemic activity of drug candidates:

- Test in vitro (cell lines), ex vivo (primary cells) or in vivo (xenograft with response and survival monitoring)

Mechanism of action of candidate's anti-leukemic activity:

- Analysis of signaling and key points using appropriate techniques (Western-blot, cytometry, PCR-Q, RNASeq)
- Modeling by generation of modified cell lines

Examples of partnerships

Search for genes involved in Giltritinib resistance in AML - To identify genes involved in Giltritinib resistance, a pan-genomic CrispR screen was performed under niche conditions (coculture and 3% oxygen).

Partner: Astellas Pharmaceutical

Search for resistance genes to therapeutic combinations in AML - In order to identify the genes involved in resistance to the various combinations used to date in AML (Ara-C, (-aza, Giltéritinib, vénétoclax), a CrispR pan-genomic screening was performed under niche conditions (coculture and 3% oxygen) with these agents alone or in combination.

Partner: Bristol Meyrs Squibb

Terms

- **Research partnership**

DEVELOPMENT OF NEW TARGETED THERAPIES FOR ACUTE MYELOID LEUKEMIA

Keywords

Target discovery | AML | Targeted therapy | Basic research (TRL 1-3) |

OPALE entity

U1312 BRIC

Head

Dr. Jean-max Pasquet

Responsable de l'Entité

Contact

Dr. Sandrine Palcy

Responsable du Business Development

Studies for the development of targeted therapies in Acute Myeloid Leukemia (AML) based on the identification of new molecular abnormalities in tumors.

The identification and characterization of molecular anomalies, combined with the search for biomarkers, enable us to propose new therapeutic targets for the treatment of AML. In collaboration with the Clinical Hematology Department of Bordeaux University Hospital, the new variants identified can be evaluated, within the framework of translational projects, as molecular markers for the prognosis and follow-up of residual disease.

Description

Scope of research activities

Studies to identify new therapeutic targets for the treatment of AML:

- Target identification and characterization
- Signaling studies
- Biomarker research
- Functional analysis

Conduct of studies

Steps :

- Study design after defining the question to be answered
- Proposal of a timetable based on the stages involved
- Implementation of schedule and experiments
- Conducts of experiments and analyses of results
- Study report by experimenters

Research infrastructure

Experimental and analysis platforms:

- Flow cytometry, vectorology and imaging platforms
- Tissue physioxia culture platform
- A2 animal facility

Models:

- AML mouse models
- Patient-derived xenograft (PDX) murine models AML
- Primary cells from AML patients

Technical personnel:

- 2 engineers
- 1 technician

Quality assurance

All platform members have undergone quality assurance training, and several platforms are certified.

Specifications

The studies

Target identification and characterization:

- Genome-wide CrispR screening to identify genes involved in treatment response or resistance
- Target validation and modeling

Signaling studies:

- Western-blot analysis and characterization, flow cytometry and functional testing of signaling pathways
- In vitro modeling of signaling pathways

Biomarker research:

- Cohort analysis (PCR-Q, NGS, flow cytometry)

Functional analysis:

- In vitro and ex vivo validation of response and/or resistance in physioxic systems
- In vivo validation in an immunodeficient mouse model (PDX LAM)

Examples of partnerships

In vitro and in vivo functional validation of Giltéritinib in FLT3-ITD AML - Recent development of dual inhibitor against FLT3 and AXL allow to treat ederly patients, to get deeper response but no change in overall survival. We identify a new cell subpopulation persistent in the hematopoietic niche.

Partner: Astellas Pharma

Search for a novel FLT3 isoform in AML patients - Identification of new oncogenic isoform of FLT3 in resistant AML lead to characterize the response to FLT3 inhibitors of this isoform and to identify it as a prognostic marker.

Partner: Bristol Meyrs Squibb

Terms

- **Research partnership**

PLATFORM FOR MULTIOMIC ANALYSIS OF HEMATOPOIESIS OR THE IMMUNE SYSTEM IN PATIENTS WITH HEMATOLOGICAL MALIGNANCIES OR AFTER CSH ALLOGRAFT (ALL/AML/MPS/MDS)

Keywords

Preclinical development | ALL | AML | MPS | MDS | Cell therapy | Immunotherapy | Preclinical research (TRL 4-5) |

OPALE entity

U976 - HIPI

Head

Prof. David Michonneau

Responsable Opale

Contact

Dr. Sandrine Palcy

Responsable du Business Development

Multiomic analysis of allograft patient samples to study new therapeutic targets aimed at limiting relapse (GvL) or preventing allogeneic reactions (GvHD).

Integrative approaches adapted to rare or limited patient samples. These approaches enable us to explore a wide range of biological dimensions in order to characterize circulating immune cells, their functional profile and their environment.

Description

Scope of research activities

Multiomic analysis of samples from allograft patients:

- Ancillary studies for clinical trials
- Retrospective studies
- Biomarker research
- Identification of therapeutic targets

Conduct of studies

Steps:

- Identification of the scientific question to be addressed, and the available samples.
- Definition of exploration modalities according to project needs (mass cytometry, metabolomics, single-cell transcriptomics, single-cell TCR/BCR sequence, microbiota exploration by 16S sequencing or shotgun metagenomics).
- Identification of associated clinical data
- Preparation of a data analysis plan, including raw data cleaning and normalization, dimensional reduction steps, cluster/signature/pathway identification, and statistical analyses (uni/multivariate, multinomial logistic regression, predictive model, etc.)
- Preparation of regulatory applications adapted to the research methodology, preparation of a data management plan
- Implementation of experiments following study planning, organization of interim meetings to monitor project progress and results
- Final analysis and communication of results and conclusions

Research infrastructure

Experimental and analytical platforms:

- Mass (CyPS) or spectral (Aurora) cytometry
- Metabolomics (MetaboHUB)
- Single-cell sequencing (10X genomics, Chromium controller): scRNAseq, scATAC-seq, scTCR-seq, CITE-seq
- scDNA-seq (Tapestri)

Biological resources:

- Biological collection in support of a trial (ancillary study)
- Collection of blood mononuclear cells (PBMC), plasma or dry pellet (CRYOSTEM multicenter collection)
- Retrospective stool collection (monocentric)

Quality assurance

Sharing of original biological data on public repositories and source code on GitHub in compliance with the FAIR (Findable, Accessible, Interoperable, Reusable) principle.

Specifications

The platform

Multiomic analysis of hematopoiesis or the immune system in patients with hematological malignancies or after HSC allogeneic transplantation.

The studies

Analysis of immune phenotype by mass cytometry:

- Unsupervised identification of immune subpopulations (FlowSOM algorithm)
- Characterization of functional profile (activated, depleted, cytotoxic)

Single-cell transcriptomic analysis:

- Unsupervised identification of immune populations by surface phenotype (CITE-seq) or transcriptome (scRNAseq)
- Analysis of cell cycle, differentially expressed genes (Seurat) or enriched biological pathways (GSEA)
- Analysis of ligand-receptor interactions and target genes (NicheNET)
- Pseudo-time trajectory analysis (Slingshot, Monocle3)

Metabolomics analysis:

- Relative or absolute quantification of targeted or non-targeted metabolites
- Analysis of enriched metabolic pathways
- Identification of metabolic signatures by PCA, PLSDA

Examples of partnerships

Operational tolerance after hematopoietic stem cell transplantation – Characterization of the transcriptional, immunological, and metabolomic features of operational tolerance in two cohorts of individuals who received HSCT from an HLA-matched sibling donor.

Partner: Ghent University (Dr Yvan Saeys, Data mining and modeling for biomedicine, VIB)

Role of Donor Clonal Hematopoiesis in Allogeneic Hematopoietic Stem-Cell Transplantation - Clonal hematopoiesis of indeterminate potential (CHIP) occurs in the blood of approximately 20% of older persons. CHIP is linked to an increased risk of hematologic malignancies and of all-cause mortality; thus, the eligibility of stem-cell donors with CHIP is questionable. We comprehensively investigated how donor CHIP affects outcome of allogeneic hematopoietic stem-cell transplantation (HSCT).

Partner: Charité, University Medical Center, Berlin (Pr Frederic Damm)

Terms

- **Research partnership**

MOUSE MODELS FOR THE STUDY OF GRAFT-VERSUS-HOST DISEASE (GVHD) OR GRAFT-VERSUS LEUKEMIA (GVL) (ALL/AML)

Keywords

Preclinical development | ALL | AML | Cell therapy | Immunotherapy | Preclinical research (TRL 4-5) |

OPALE entity

U976 - HIPI

Head

Prof. David Michonneau

Responsable Opale

Contact

Dr. Sandrine Palcy

Responsable du Business Development

Mouse models of allogenic transplantation for the study of new treatments to prevent or treat graft-versus-host disease (GvHD) or stimulate the antitumor response induced by the donor's T-cells (Graft-versus-leukemia (GVL) effect).

The model can be used to study new therapeutic solutions, from target identification to the validation of drug candidates.

Description

Scope of research activities

In vivo preclinical research using a mouse model mimicking patients with leukemia (AML and ALL) or lymphoma, treated by allogeneic transplantation, in the case of graft-versus-host disease or relapse:

- Action mechanisms
- Targets identification and validation
- Drug screening
- Evaluation of therapeutic potential (i.e. efficacy)
- Toxicity assessment (pre-regulatory)

Conduct of studies

Steps:

- Identification of relevant animal models according to the question raised, including models of acute or chronic GVH induced by major or minor antigenic incompatibilities, choice of the most relevant model of hematologic malignancies.
- Definition of experimental conditions to test the hypothesis or scientific question, including the use of syngeneic controls or allogeneic T-cell-free transplants, and definition of response assessment modalities (small animal imaging, bioluminescence, conventional, confocal or biphotonic microscopy, flow or mass cytometry, global or single-cell transcriptomics) and relevant response markers.
- Preparation of regulatory applications for the implementation of animal experimentation after detailed writing of the experimental plan.
- Implementation of experiments following study planning, organization of interim meetings to monitor project progress and results.
- Final analysis and communication of results and conclusions

Research infrastructure

Experimental and analytical platforms:

- Animal facility
- Cytometry, imaging and sequencing platform
- Cytometer and cell sorter available in the team
- Single-cell RNA sequencing using 10X genomics technology (CITE-seq, scRNA-seq, scATAC-seq, TCR-seq)
- A bioinformatics engineer to analyze results

Specifications

The platform

Preclinical mouse models of allogeneic transplantation.

Studies

Model of acute GVH due to major incompatibility (Balb/c in C57Bl/6 or C3H in C57Bl/6):

- Clinical GVH score
- Histological score of damaged tissue
- Blood or tissue immunophenotyping (cytometry)
- Confocal or immunofluorescence microscopy

Model of acute GVH due to multiple (C3H/SW in C57Bl/6) or single (Matahari in C57Bl/6) minor incompatibility:

- Clinical GVH score
- Histological score of damaged tissue
- Blood or tissue immunophenotyping (cytometry)
- Confocal or immunofluorescence microscopy

Model of anti-tumor response by injection of leukemic cells µMyc (ALL B) in the above allograft models:

- Evaluation of tumor infiltration by cytometry (bone marrow, lymph node, spleen)
- Evaluation of tumor infiltration by microscopy
- Measurement of tumor cell apoptosis by caspase 3 activity reporter probe (µMyc-DEVD)

Examples of partnerships

TNFR2 blockade for modulation of antitumor immune response after hematopoietic stem-cell transplantation – Blocking the tumor necrosis factor receptor-type 2 (TNFR2) pathway induces the complete loss of the protective function of regulatory T cells (Tregs) in a model of graft-versus-host disease (GVHD) prevention that relies on Treg-based cell therapy. In this study, we tested the possibility of amplifying the antitumor response by targeting TNFR2 in a model of tumor relapse following hematopoietic stem-cell transplantation, a clinical situation for which the need for efficient therapeutic options is still unmet.

Partners: IMRB, Inserm - Université Paris-Est Créteil Val de Marne, Créteil (Pr José Cohen)

Terms

- **Research partnership**

CLINICAL AND PRECLINICAL EVALUATION OF EFFICACY AND TOXICITY OF CAR-T CELL (ALL/AML) TREATMENTS

Keywords

ATMP development | ALL | AML | Cell therapy | Immunotherapy | CAR-T cells | Preclinical research (TRL 4-5) | Clinical research (TRL 6-8) |

OPALE entity

U976 - HIPI

Head

Prof. Sophie Caillat-Zucman

Responsable d'équipe

Contact

Dr. Sandrine Palcy

Responsable du Business Development

Preclinical and clinical evaluation of the efficacy and toxicity (pre-regulatory) of CAR-T cell therapy treatments.

Combining expertise from the preclinical to the clinical stage, to assess the potential of the therapeutic solution.

Description

Scope of research activities

Preclinical and clinical research for the development of new CAR-T cell therapies.

- Preclinical (in vivo) evaluation studies of CAR-T cells (new CARs, new targets, new CAR+ cells)
- Ancillary studies: identification of predictive markers of CAR-T cell efficacy/toxicity
- Clinical protocol: immunomonitoring of patients treated with CAR-T cells

Conduct of studies

- Assessment and definition of project requirements
- Study design and project implementation
- Analysis and communication of results

Research infrastructure

Experimental and analysis platforms:

- Spectral cytometry (Aurora, Cytec)
- Imaging (IVIS, Incucyte)
- Animal facilities (immunodeficient NGS mice

Specifications

The platform

Assessing the anti-tumor potential of CAR-T cell therapies for hematological malignancies.

The studies

Mouse model to assess CAR-T cell efficacy and toxicity:

- Immunodeficient NGS mice
- i.v., i.p. or orthotopic injection of human tumor lines expressing the CAR target

In vitro model for evaluating CAR-T cell efficacy:

- Cytotoxicity tests (bioluminescence, Incucyte)
- 3D spheroids

Immunomonitoring of patients treated with CAR-T cells:

- Multiparametric cytometry
- Cytokine assay

Examples of partnerships

To test in humans the relevance of observations made in preclinical models of CAR-T cells.

Partner: Institut Pasteur /Inserm 1223 (Dr. Philippe Bousso, Unité "Dynamiques des Réponses Immunes »)

Terms

- **Research partnership**

PRECLINICAL STUDIES FOR THE DEVELOPMENT OF INNOVATIVE TREATMENTS FOR ACUTE LYMPHOBLASTIC LEUKEMIA

Keywords

Preclinical development | ALL | Targeted therapy | Chemotherapy | Preclinical research (TRL 4-5) |

OPALE entity

UMR - 1274

Head

Dr. Françoise Pflumio

Responsable de l'Entité

Contact

Dr. Sandrine Palcy

Responsable du Business Development

Preclinical studies for the development of innovative treatments for acute lymphoblastic leukemia (ALL), to assess the impact of drug candidates on leukemia cells and the development of normal T and B lymphocytes.

The models developed accurately represent the biology and heterogeneity of different types of leukemia and summarize the tumor microenvironment.

Description

Scope of research activities

Preclinical research using in vitro and in vivo models to assess the efficacy and toxicity (pre-regulatory) of new molecules:

- Monitoring the development of human T and B lymphocytes during normal and pathological hematopoiesis

Conduct of studies

Steps:

- Analysis of innovative product development strategy
- Study design
- Drafting of study plans
- Establishment of quotes to finance the study
- Organization, implementation and conduct of studies
- Analysis and communication of results

Research infrastructure

Experimental and analytical platforms:

- Flow cytometry
- Animal experimentation (dedicated staff)
- Animal facility
- Molecular bioengineering
- Microscopy
- Ex-vivo screening of biomolecules

Preclinical models:

- Immunodeficient mouse model of normal human hematopoiesis
- Mouse model of human leukemia
- T-ALL (including pediatric models) and B-ALL PDX

Specifications

The platform

Set of in vivo and in vitro tests for the evaluation and selection of drug candidates for the treatment of ALL.

The studies

Toxicity assessment on T lymphocyte development in immunodeficient mice:

- Human T cell development in mouse thymus: monitoring by flow cytometry

Evaluation of drug candidate toxicity in mouse models of normal human cell xenografts:

- Normal human hematopoietic development in vivo in the bone marrow of immunodeficient mice

Evaluation of drug candidate efficacy in PDX models of T-ALL and B-ALL:

- Monitoring of leukemic growth in vitro; development of screening molecules

Evaluation of efficacy of drug candidates in PDX models of T-ALL and B-ALL in immunodeficient mice:

- In vivo leukemic growth; development of molecule testing

Examples of partnerships

Study of the functionality of the ProTcell product in the regeneration of functional human T lymphocytes after treatment with chemotherapy or irradiation - The aim is to test the ability of the ProTcellR cell product, developed by Smart-Immune, to generate normal, functional human T cells in vivo in young and elderly immunodeficient mouse models.

Partner: Smart Immune

Terms

- **Research partnership**
- **Public aid to companies**
- **Collaborative project (multi-beneficiary partnership)**

PRECLINICAL STUDY OF HEMATOPOIETIC SYSTEM REGENERATION FOLLOWING EXPOSURE TO GENOTOXIC STRESS SUCH AS IRRADIATION AND CHEMOTHERAPY (ALL/AML)

Keywords

Preclinical development | ALL | AML | Targeted therapy | Chemotherapy | Preclinical research (TRL 4-5) |

OPALE entity

UMR - 1274

Head

Dr. Françoise Pflumio

Responsable de l'Entité

Contact

Dr. Sandrine Palcy

Responsable du Business Development

Study of the regeneration of the human hematopoietic system following exposure to genotoxic stress such as irradiation and chemotherapy.

The models developed accurately represent the biology and heterogeneity of normal hematopoietic cells and recapitulate the normal bone marrow microenvironment.

Description

Scope of research activities

Preclinical research to monitor hematopoietic development:

- Monitoring the development of human hematopoiesis
- Monitoring the impact of preclinical molecules on the human bone marrow niche using an in vivo humanized bonelet model in immunodeficient mice

Conduc of studies

Steps:

- Analysis of innovative product development strategy
- Study design
- Drafting of study plans
- Establishment of quotes to finance the study
- Organization, implementation and conduct of studies
- Analysis and communication of results

Research infrastructure

Experimental and analytical platforms:

- Flow cytometry
- Animal experimentation (dedicated personnel)
- Animal facility
- Molecular bioengineering (dedicated personnel)
- Microscopy
- Immunohistochemistry and immunoflurescence on sections

Preclinical models:

- Immunodeficient mice with human chimerism
- Immunodeficient mice with human ossicles: analysis of non-hematopoietic cells in the bone niche

Specifications

The platform

Set of studies to measure hematopoiesis regeneration using in vitro assays and/or chimeric immunodeficient mice irradiated or treated with chemotherapy.

The studies

Assessment of molecule toxicity on normal human hematopoietic development:

- Hematopoietic development in the bone marrow of immunodeficient mice: flow cytometry monitoring of human cells and the level/quality of human chimerism

Evaluation of the efficacy of drug candidates in vitro on differentiating human hematopoietic cells:

- Monitoring of lymphoid, myeloid and/or erythroid cell production in vitro; testing of molecules: apoptotic effect/cell death, growth alteration

Evaluation of the efficacy of drug candidates on the hematopoietic stem/progenitor cell (HSPC) compartment:

- Treatment of HSPCs in vivo or in vitro; testing of multilineage hematopoietic reconstitution in vivo after transplantation or in vitro in functional assays (CFC, LTC-IC)

Evaluation of the efficacy of drug candidates on the regeneration of human hematopoiesis in vivo and/or in vitro after treatment (chemotherapy, irradiation):

- Treatment of humanized mice in vivo; monitoring of hematopoietic regeneration in vivo after treatment

Examples of partnerships

Study of the efficacy of the G-CSF and Plerixafor combination on the mobilization of stem/progenitor cells from poorly mobilizing patients - The aim was to study the multi-lineage hematopoietic reconstitution functions of HSPCs mobilized in patients with the G-CSF and Plerixafor combination by transplantation into immunodeficient mice.

Partner: Institut Gustave Roussy (Prof. J-H Bourhis, Dr. S Amsellem)

Study of the effects of ultra-high dose rate irradiation on T-ALL and human hematopoiesis - This involved a comparative study of the effect of a given dose of Flash (high dose rate) and conventional (low dose rate) irradiation on leukemic development and normal hematopoiesis, in vivo in humanized mice.

Partners: Center Hospitalier Universitaire Vaudois (CHUV), University of Lausanne (Dr. M-C Vozenin)

Terms

- **Research partnership**
- **Public aid to companies**
- **Collaborative project (multi-beneficiary partnership)**

PRECLINICAL TESTING OF CAR-T CELLS FOR THE TREATMENT OF T/B ACUTE LYMPHOBLASTIC LEUKEMIA

Keywords

ATMP development | ALL | Gene therapy | CAR-T cells | Preclinical research (TRL 4-5) |

OPALE entity

UMR - 1274

Head

Dr. Françoise Pflumio

Responsable de l'Entité

Contact

Dr. Sandrine Palcy

Responsable du Business Development

Preclinical testing the efficacy of CAR-T-cell therapy in ALL, to assess the impact of CAR-T-cells on leukemia cells and lymphocyte development.

Availability of PDX models derived from patients with T/B-ALL (pediatric).

Description

Scope of research activities

Preclinical research using in vivo and in vitro models to assess the efficacy and toxicity of CAR-T-cells:

- Monitoring the development of human functional T lymphocytes in normal and pathological hematopoiesis

Conduct of studies

Humanizing mice with normal human stem/progenitor cells, monitoring normal or leukemic human hematopoietic development, testing CARTs directed against pathological cells, testing toxicity on normal cells.

Steps:

- Analysis of innovative product development strategy
- Study design
- Drafting of study plans
- Organization, implementation and conduct of studies
- Analysis and communication of results

Research infrastructure

Experimental and analysis platforms:

- Flow cytometry
- Animal experimentation (dedicated personnel)
- Animal facility
- Molecular bioengineering
- Microscopy
- Ex-vivo screening of biomolecules

Preclinical models:

- Immunodeficient mouse model of normal human hematopoiesis
- Mouse model of human leukemia
- Ex-vivo culture of T-ALL PDX (including pediatric models) and B-ALL

Specifications

The platform

Set of in vivo and in vitro tests for the evaluation of CAR-T-cells for the treatment of T/B-ALL.

The studies

Evaluation of developmental toxicity of normal T/B lymphocytes from transplantation of CD34+ cord blood cells into immunodeficient mice:

- Measurement of % and absolute number of T/B lymphocytes in thymus, spleen and bone marrow of humanized mice

Assessment of toxicity in mouse models of normal human cell xenografts:

- Measurement of % and absolute number of T/B lymphocytes in thymus, spleen and bone marrow of humanized mice

Evaluation of efficacy in PDX models of T/B-ALL:

- Measurement of human leukemic growth in humanized mice with T/B-ALL PDX

Assessment of in vitro efficacy:

- Measurement of human leukemic growth of T/B-LAL PDX in culture

Examples of partnerships

Development of new CART development conditions - The aim is to study whether the experimental conditions developed by the Smart-immune company can be used to produce effective and specific CART.

Partner : Smart Immune

Terms

- **Research partnership**
- **Public aid to companies**
- **Collaborative project (multi-beneficiary partnership)**

DEVELOPMENT OF SMALL MOLECULES FOR TARGETED THERAPIES (ALL/AML)

Keywords

Preclinical development | ALL | AML | Targeted therapy | Preclinical research (TRL 4-5) |

OPALE entity

URP-3518

Head

Prof. Hervé Dombret

Responsable de l'Entité

Contact

Dr. Sandrine Palcy

Responsable du Business Development

Translational research platform for the evaluation of small active molecules (or active peptides) for the development of treatments for AML and ALL.

Study of in vitro and in vivo combinations to select and validate molecules (or peptides), combinations of molecules or biomarkers.

Description

Scope of research activities

Preclinical research using in vitro and in vivo models of AML and ALL:

- Proof-of-concept validation: evaluation of drug efficacy, stratification of pathology subgroups
- Drug combination screening
- Identification of biomarkers

Conduct of studies

Step :

- Establishing the scope of research partnership in the form of milestones
- Update after milestone completion
- Go-no go" discussions for future pre-clinical or clinical development

Research infrastructure

Experimental and analytical platforms:

- Cell culture laboratory with fume hood, cell culture, flow cytometry, cell sorting, florescence microscopy, access to molecular biology (PCR, microarray, CHIPseq)
- AML and ALL cell lines, annotated biobank of AML and ALL patient samples (THEMA cohort), mouse models (xenograft, syngeneic), access to PDX via collaboration
- 1 permanent engineer and 1 assistant engineer

Specifications

The platform

Screening platform using 3D in vitro models (co-culture of mesenchymal stem cells, blast cells, NK cells) to mimic the complexity of the tumor environment.

Studies

In vitro efficacy studies on primary patient cells (AML/ALL):

- MTS, proliferation, apoptosis, autophagy, differentiation, combination index
- Feeder culture (fibroblasts, cytokines) of primary ALL cells

In vivo efficacy studies in PDX mouse model (AML/ALL):

- Survival

- Leukemic expansion by flow cytometry

Combination drug screening using a library of small molecules used in standard care:

- NEXT platform with measurement of cytotoxicity, differentiation, effect on bulk and leukemic stem cells

Identification of biomarkers using patient samples and cohort data, in preparation for an early-phase clinical trial:

- Biomarker-dependent flow cytometry, PCR, Western blot analysis

Examples of partnerships

New therapeutic strategies in acute leukemia - Cifre Thesis.

Partner: Servier

Preclinical evaluation of potential therapeutic efficacy of the MPS1 inhibitor S81694 in Acute Myelogenous Leukemia (AML) and Acute Lymphoblastic Leukemia (ALL) - In this study the preclinical activity of an inhibitor of the MPS1 kinase, a major kinase of the "spindle check point (SAC) was evaluated. The MPS1 inhibitor, S81694, shows promising anti-leukemic activity in different models of ALL and AML, with significant synergy:

- With TKIs in BCR::ABL-fused ALL
- Venetoclax in AML

Partner: IRIS (Institut International de Servier)

Terms

- **Research partnership**
- **Public aid to companies**

MANUFACTURING OF ADVANCED THERAPY DRUGS: EARLY CLINICAL TRIALS OF CAR-T CELLS (ALL/AML)

Keywords

Biomanufacturing | ALL | AML | Gene therapy | Cell therapy | CAR-T cells | Clinical research (TRL 6-8) |

OPALE entity

MEARY CIC-BT

Head

Prof. Jerome Larghero

Responsable de l'Entité

Contact

Dr. Sandrine Palcy

Responsable du Business Development

GMP-compliant manufacturing of ATMP clinical batches for early cell and gene therapy trials.

AP-HP MEARY Center for Cell and Gene Therapy is a leader in the manufacturing of Advanced Therapy Medicinal Products (ATMPs), offering cutting-edge expertise to industrial partners to support and carry out their cell, tissue and gene therapy clinical trials. It supports industrial partners in the technical and regulatory development of their processes.

Description

Scope

Manufacturing of clinical batches of experimental drugs for advanced therapy:

- CAR-T cells
- Mesenchymal stromal cells
- Treg cells
- T progenitors
- Etc

Project management

Steps:

- Assessment of the project and its development stage
- Analysis of the manufacturing process and quality controls to be implemented
- Drafting of contracts and quality agreements
- Technology transfer
- Drafting of regulatory dossiers
- Trial set-up and batch manufacturing

Research infrastructure

- ATMPs Manufacturing Department: ATMPs manufacturing facilities (235 m^2) encompass 6 ISO 4/5 clean rooms, with type 2 GMO containment
- ATMPs Quality Control Department: with its state-of-the-art equipment, the ATMPs quality control laboratory offers a wide range of control options, including control of raw materials, starting materials, reagents, intermediates and finished products
- Quality Assurance Department: regulatory support (technical-regulatory dossiers, clinical trial set-up) and quality management (GMP, audits, Pharmaceutical Quality Systems)

Quality assurance

- GMO approval n°5691 (French Ministry of Higher Education, Research and Innovation)
- ANSM authorization TIE/19/O/001 (Eudra GMP)

Specifications

The platform

A Cellular and Gene Therapy Center dedicated to the manufacturing of innovative therapeutic drugs:

- Pre-industrial development
- Clinical batch manufacturing (phases I-II)
- Regulatory support
- Setting up clinical trials

Supported projects

Experimental cell and gene therapy drugs for the early phases (phase I-II) of clinical development.

Examples of partnerships

Safety and efficacy of SMART101 in pediatric and adult Patients with hematological malignancies after T cell depleted allo-HSCT – The purpose of this study is to evaluate the safety and the efficacy of SMART101 (Human T Lymphoid Progenitor (HTLP)) injection to accelerate immune reconstitution after T cell depleted allogeneic hematopoietic stem cell transplantation (HSCT) in adult and pediatric patients with hematological malignancies."

Sponsor : Smart Immune

Terms

Projects are submitted to the MEARY Centre's Scientific Advisory Board for approval.

Contractualization may take the form of partnership/collaboration agreements, or service provision contracts.

MANUFACTURING OF INNOVATIVE THERAPY DRUGS: PROCESS OPTIMIZATION AND INDUSTRIALIZATION (ALL/AML)

Keywords

Biomanufacturing | ALL | AML | Gene therapy | Cell therapy | CAR-T cells | Clinical research (TRL 6-8) |

OPALE entity

MEARY CIC-BT

Head

Prof. Jerome Larghero

Responsable de l'Entité

Contact

Dr. Sandrine Palcy

Responsable du Business Development

Supporting manufacturers in the technical development of GMP-compliant manufacturing processes for experimental drugs.

The AP-HP MEARY Center is an integral part of an R&D and innovation ecosystem. Its comprehensive range of technological solutions and expertise enables it to support the entire development process, from transfer to clinical batches manufacturing.

Description

Scope

Manufacturing of clinical batches of experimental drugs for advanced therapy:

- CAR-T cells
- Mesenchymal stromal cells
- Treg cells
- T progenitors
- Etc

Project management

Steps:

- Assessment of the project and its development stage
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Supported projects

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Examples of partnerships

Treatment of B lymphoid hemopathies by injection of CAR-T cells - aimed at evaluating the safety, efficacy and duration of response of CAR-T CD22/19 in patients with high-risk, relapsed/refractory CD19+ acute lymphoblastic leukemia."

Project leader: Prof. Nicolas Boissel, Hôpital Saint Louis

DualCALM01 – A multicentric phase I/IIA study of dual-targeted CD19/22 Chimeric Antigen Receptor (CAR)T-cell therapy in pediatric and young adult patients with relapsed/refractory CD19 and/or CD22-positive B-cell precursor acute lymphoblastic leukemia (BCP-ALL)

Project leader: AP-HP

Terms

Projects are submitted to the MEARY Centre's Scientific Advisory Board for approval.

Contractualization may take the form of partnership/collaboration agreements, or service provision contracts.