D2ONCO

AUVERGNE RHÔNE-ALPES NETWORK FOR DRUG DISCOVERY IN ONCOLOGY

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D2ONCO

AUVERGNE RHÔNE-ALPES NETWORK FOR DRUG DISCOVERY IN ONCOLOGY

D2-ONCO, un réseau de recherche collaboratif

D2-ONCO est un réseau collaboratif dédié aux travaux de drug discovery en oncologie qui a pour objectif de promouvoir les expertises et compétences présentes en Auvergne-Rhône-Alpes et actives dans le développement de molécules thérapeutiques, faciliter le *continuum* entre la découverte de cibles biologiques et l'élaboration d'agents anticancéreux, et favoriser l'émergence et la réalisation de projets scientifiques innovants.

Les missions de D2-ONCO

Dans cette optique, le réseau D2-ONCO a pour vocation de :

- Recenser les équipes de recherche et les plateformes technologiques impliquées dans la chaîne de valeur du drug discovery en oncologie, en Auvergne-Rhône-Alpes
- Organiser/favoriser l'organisation de manifestations scientifiques
- Favoriser la mise en place de collaborations entre biologistes et acteurs du drug discovery
- Apporter un appui méthodologique pour la validation de cibles thérapeutiques
- Valoriser les projets en développement et créer des interfaces avec le secteur privé
- Informer sur les opportunités de financement

Vous souhaitez rejoindre D2-ONCO ?

Contactez-nous à aurad2onco@gmail.com.

CELL INVASION IN ANGIOGENESIS AND CANCER (IMAC)

U1036 INSERM UMR 1036 (BCI Biology of Cancer and Infection)

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CHAMPS D'EXPERTISE

During cancer progression, deregulated cell invasion contribute to metastatic dissemination. Cell invasion relies on the interactions between several cell types and cross-talks between signaling pathways. The emerging technologies of 3D cell cultures are developed for these cell signaling studies and for anti-metastatic drug screening.

ACTIVITES DE RECHERCHE / SERVICES

The incidence and associated mortality of kidney cancer has increased in recent years. Despite earlier detection, patients develop metastases or become resistant to current treatments that are short-acting. For this reason, new therapeutic molecules are currently being researched very actively. We have recently identified by a chemo-genomic library screening approach a new combination of molecules targeting CK2 and ATM protein kinases whose inhibition is particularly effective in inducing cancerous kidney cell death. In a preclinical study called COMBOREIN, our goal now is to test our molecules directly on tissue cultures derived from tumors of the patient's kidney.

COMPETENCES / MOYENS TECHNIQUES

We have developped different 3D cultures models of ccRCC emphazing the feasibility and the advantage of human ccRCC tissue slice culture as a preclinical model. We have generated 786-O spheroids that are treated with a panel of drugs. Dead cell quantification is recorded using an Incucyte microscope. We also used tissue slice culture from ccRCC PDX mice or fresh human renal carcinoma tissue (Urology department, CHU-Grenoble-Alpes) that are cultured in presence of drugs for 2 days. Slice tissue cultures are processed for fluorescent live and dead testing and immuhistochemistry analysis. This approach is feasible, thanks' to a preclinical Trail COMBOREIN (NCT03571438).

ANTICORPS ANTICANCER

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CHAMPS D'EXPERTISE

anticorps monoclonaux, résistance thérapeutique, modélisation préclinique

ACTIVITES DE RECHERCHE / SERVICES

Les objectifs de notre équipe sont d'étudier les mécanismes d'action des anticorps monoclonaux dirigés contre les cellules cancéreuses ainsi que les mécanismes de résistance à ces biomolécules afin d'optimiser le traitement par anticorps monoclonaux chez les patients atteints d'hémopathies ou de tumeurs solides.

L'équipe Anticorps Anticancer, composée de médecins chercheurs, de post-doctorants, d'étudiants et de techniciens, possède une expertise en modélisation préclinique (in vitro et in vivo) ainsi que dans l'identification et la validation de facteurs prédictifs ou pronostiques dans des échantillons cliniques, et le développement de nouveaux agents ou de nouvelles stratégies thérapeutiques.

Notre travail se focalise sur les anticorps monoclonaux utilisés dans le traitement des hémopathies malignes et du cancer du sein. Nous explorons la nature et le rôle des cellules accessoires impliquées dans l'activité antitumorale des anticorps monoclonaux ainsi que le rôle des cellules du micro-environemment tel que les adipocytes, cherchons à identifier de nouvelles voies de signalisation apoptotique induite par les anticorps dans les cellules cancéreuses, développons de nouvelles stratégies de sensibilisation et déterminons la pertinence clinique des observations réalisées dans les modèles précliniques.

MEDICINAL CHEMISTRY (MEDCHEM)

UMR 5063 Département de Pharmacochimie Moléculaire (DPM)

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CHAMPS D'EXPERTISE

Drug Design, Drug Synthesis, Natural Products, Membrane Proteins, Nucleic Acids, Epigenetic, From hit to lead, Cancer, Infectious Diseases, Chemical Tools, Chemical Biology

ACTIVITES DE RECHERCHE / SERVICES

The MEDCHEM research activities are focused on drug discovery and development for targeting major human lethal diseases: cancer, infectious diseases and neurodegenerative disorders. Our know-how is drug synthesis and optimization of hit compounds to bring them to first stages of preclinical studies. In the oncology field, we work on the synthesis and development of drug candidates acting as modulators of membrane proteins involved in the multidrug resistance phenotype or as epigenetic inhibitors. Beside, we focus part of our activity on the development of uncharged cyclopeptides as transmembrane vectors of anticancer drugs.

COMPETENCES / MOYENS TECHNIQUES

The DPM has its own chemical library which has been integrated into that of the ICMG, the federative institute that groups together the chemical laboratories on the site of the University Grenoble Alpes.

GENETICS AND CHEMOGENOMICS (GEN&CHEM)

UMRS_1038 Large Scale Laboratory (BGE)

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CHAMPS D'EXPERTISE

Cancer, Cell signaling, Cell trafficking, Drug screening, Endocytosis, Inflammation, Rare disease, Screening for Bioactive Molecules, Ubiquitin system, Ubiquitin specific protease (USP) Therapeutic targets

ACTIVITES DE RECHERCHE / SERVICES

The Gen&Chem team develops genetics and chemogenomics approaches for the study and targeting of proteins regulating cell signaling and trafficking. The team includes molecular geneticists dedicated to the acquisition of fundamental knowledge and the CMBA screening platform dedicated to Drug Discovery, i.e : to the identification of bioactive molecules valuable for both research and therapeutic purposes. This association aimed at mutually benefit from complementary expertise to strengthen both kind of activities and promotes translational research.

The research activity notably aims to provide fundamental insights into the role of the ubiquitin system in signal transduction and endocytosis of plasma membrane receptors (such as the EGFR or TNFR) that provide appropriate cellular responses to cell growth or differentiation signals. Special attention is given to deubiquitinating enzymes (DUBs) of the ubiquitin-specific protease subfamily that regulate membrane receptor trafficking and downstream intracellular signaling cascades. These DUBs are known therapeutic targets in several pathologies, including chronic inflammation, cancer or rare diseases but their substrates and mechanisms of action are still poorly known.

COMPETENCES / MOYENS TECHNIQUES

The research of the team is based on the implementation of molecular genetics, transgenesis, mutagenesis and cell biology strategies on murine or Drosophila fly models.

The screening platform for bioactive molecules (CMBA) is fully equipped to perform high-throughput screening campaigns (HTS) on either purified targets or living cells, including phenotypic screening by automated imaging using the high content screening methodology (HCS) (see also the dedicated form of CMBA platform).

STRUCTURAL BIOLOGY OF BACTERIAL MACROMOLECULAR COMPLEXES (SBBMC)

UMR 5086 Molecular Microbiology and Structural Biochemistry (MMSB)

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CHAMPS D'EXPERTISE

X-ray crystallography, Helicobacter pylori, stomach cancer

ACTIVITES DE RECHERCHE / SERVICES

Helicobacter pylori is is a Gram-negative bacteria that infect the gastric mucosa of about half of the world population and may cause chronic gastritis, peptic ulcer disease or gastric cancer. Although for most individuals the infection is asymptomatic, H. pylori will provoke gastric or duodenal ulceration in about 20 % of infected individuals and in 1-2% even gastric cancer. With around 750 000 cases of death/year, H. pylori-mediated gastric cancers are the third leading cause of cancer in the world. Although antibiotics are currently used to treat the infection, a rapid increase of antibiotic resistance causes more and more problems for a successful treatment as stated by the WHO.

The most virulent strains of H. pylori, i.e. more frequently associated with cancer, carry a highly sophisticated protein injection system, the cag Type 4 secretion system (T4SS). Using this type of molecular syringe, H. pylori delivers the bacterial protein toxin CagA into different types of host cells. The “needle” of the syringe is termed the pilus and is known to attach to the host cell. Once injected, CagA interferes with host cell signalling cascades, resulting in a reprogramming of these cells, eventually leading to their malignant degeneration. The structure of the cagT4SS and of its pilus, its assembly and how it injects CagA is still very poorly understood. Our team has focused its research program on 1) the determination of the cagT4SS structure and mechanism of CagA injection and 2) development of targeted inhibitors against H. pylori infection. Thus our group's activity fits very well with the CLARA Axis 2 : Infections, Immunity and Cancer

Our group studies key processes of Helicobacter pylorinfection at the molecular and structural level. We employ a large and complementary set of biochemical, structural and biophysical methods including: molecular biology, protein expression and purification, protein-protein interactions (Multi-angle laser light scattering, isothermal titration calorimetry, SPR) and structural biology (X-ray crystallography, electron microscopy and SAXS). Our expertise lies in the study of the assembly of large, dynamics macromolecular complexes.

COMPETENCES / MOYENS TECHNIQUES

X-ray crystallography, protein-protein interaction studies, cryo-electron microscopy.

GENIE PHARMACEUTIQUE (GEPHARM)

UMR 5007 Laboratoire d'Automatique, de Génie des Procédés et de Génie Pharmaceutique (LAGEPP)

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CHAMPS D'EXPERTISE

Pharmaceutical technology, Nanomedicine, Biomedical Imaging, Drug Delivery, Gene Delivery, Vaccine, Immunotherapy

ACTIVITES DE RECHERCHE / SERVICES

The LAGEPP (Laboratoire d'Automatique, de Génie des Procédés et de Génie Pharmaceutique) is a research laboratory of the University Lyon 1 and the French national Institute for scientific research (CNRS UMR 5007). It develops pluridisciplinary research in chemical engineering and pharmaceutical technology.

The "pharmaceutical engineering" team (GePharm) expertise encompasses several scientific domains devoted to physico-chemical characterization, formulation and biological in vitro evaluation.

This team mainly works on novel nanosystems for the administration of chemical and biological compounds intended for therapeutic and diagnostic applications. Different projects are ongoing and aimed at implementing conventional chemotherapeutic strategies with immunotherapeutic approach to fight cancers. Gepharm has the expertise to evaluate the druggability, to enhance bioavailability overcoming biological barriers and to provide targeting functionality to novel molecular candidates.

The team is composed of 3 Professors, 6 Associates Professors and 3 CNRS Research Directors.

COMPETENCES / MOYENS TECHNIQUES

The laboratory activity includes in-depth physico-chemical characterization of the formulation developed. The over facilities of the laboratory are listed in the webpage https://lagepp.univ-lyon1.fr/en/scientists-equipments-material/

Physico-chemical analyzes

- Rheometer (MCR 302, Anton Paar)
- Franz-type diffusion cell
- Chromatographic instruments (HPLC Merck, Agilent et GC 2010 Plus, Shimadzu)
- Dissolutest (DT12R, Erweka)
- Schulze Ring Shear Tester (RST-XS, Dr Dietmar)
- GRANULOMETER, (Mastersizer MS3000, Malvern, Zétasizer nanoseries ZS, Malvern)
- Spectrometer FT-IR Nicolet® IS50

Thermal analyzes

- Thermogravimetric Analysis (TGA) TG209F1, Netzsch
- Differential Scanning Calorimeters, DSC Q200, TA
- Dynamic Vapor Sorption, DVS Advantage ET, Surface Measurement Systems
- Water activity analyzer, FA-st/1, GBX
- Temperature and Climate Test Chamber, Vötsch
- Suntest cps+(Atlas)

Formulation

- Lyophilisateurs, Cryonext
- Microfluidizer LM 20, Microfluidics
- Géluleuse, (Bonapace)
- Simulateur de compression Styl'One (Medel'pharm)
- Machines à comprimer rotative (Piccola Riva, Korsch)
- Machine à comprimer alternative instrumentée (Korsch)
- Granulateur (Glatt)
- Mélangeurs granulateurs (Turbula)
- Lit d'air Fluidisé (Aeromatic-Fielder)

Imagery

- Reflectance laser probe (Lasentec FBRM ®)
- Light microscope (Leica DM LM)
- Cryomicroscope
- Light microscope in cold room (Leica MZ12, Leica 2000R)
- Temperature control Microscope Anacrismat®
- Video Probes: EZProbe-D25®L1200, EZProbe-D25®L220, EZProbe-D12-L800

CIBLES ET OUTILS POUR L'IMAGERIE MOLECULAIRE ET LA THERAPIE (TATOO)

Inserm U1240, UCA Imagerie Moléculaire et Stratégies Théranostiques (IMoST)

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CHAMPS D'EXPERTISE

Organic synthesis, radiolabelling

ACTIVITES DE RECHERCHE / SERVICES

The objectives of UMR 1240 INSERM/IMOST are the development of tools for theranostic strategies, in particular radiopharmaceuticals, with researches mainly dedicated to oncology.

Based on a two teams structure entitled respectively "Targets and tools for imaging and therapy" and "Translational research in functional imaging, radiopharmaceuticals and theranostic biomarkers", IMOST brings together specialists of complementary disciplines, (chemists, radiochemists, pharmacologists, molecular biologists, researchers in preclinical imaging, physicians), (as well as high technology platforms), which creates a scientific environment for drug development and rapid translation from bench to bed,

Researches are focused, on targeting strategies through the use of target-specific ligands conjugated to agents being radiolabeled for both diagnostic imaging and targeted radionuclide therapy (TRT), as well as drugs (hypoxia activated prodrugs) and nano-objects. Among the main three researches axis conducted by TaToo team, one deals with melanin/proteoglycan ligands, and on new vectors/targets for cancer. The second theme consists in targeting specific proteins involved in dissemination and metabolic reprogramming using radiolabeled antibodies and small ligands.

The last part develops methodological approaches for radiolabeling for imaging and radionuclide therapy, pretargeting radioimmunotherapy with click chemistry and functionalization of nano-objects.

COMPETENCES / MOYENS TECHNIQUES

IMoST is equipped with tools for organic synthesis and analytical controls, fully-automated radiolabelling for high energy radionuclides (e.g., 18F,124I, 64Cu, 131I, 177Lu), hot cells used for the handling of medium energy isotopes (e.g. 99mTc, 111In, 125I,..) radionuclides. For demonstrating the proof of concept, IMoST has cellular and post genomic equipments, as well as ex vivo and in vivo imaging facilities (spect-ct, PET, CT, whole body autoradiography for small animals, optical imaging), authorized housing for small animals and rabbit including shielded cages for animals injected with radiopharmaceuticals.

SYNTHESE DE MOLECULES D'INTERET THERAPEUTIQUE (SMITH)

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CHAMPS D'EXPERTISE

medicinal chemistry, heterocyclic chemistry, anticancer agents, protein kinase inhibitors, ALDH inhibitors, alternative splicing modulators, antibody drug-conjugates, drug candidates, pharmacological tools

ACTIVITES DE RECHERCHE / SERVICES

Organic synthesis towards the developement of new chemotherapeutic agents to treat cancer is the mainstream of our team. The aim of our research works is to provide chemical solution (pharmacological tools or drug candidates) to this issues from drug design to the evaluation in vitro and in vivo. Research challenges include: protein kinase inhibitors, alternative splicing modulators and antibody drug conjugates,...

COMPETENCES / MOYENS TECHNIQUES

Methodologies in heterocyclic chemistry, multi-step organic synthesis, small-weight molecule library in house

TEAM 2: THERAPEUTIC OPTIMIZATION IN ONCOLOGY

EMR3738 Therapeutic targeting in oncology (CTO)

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CHAMPS D'EXPERTISE

Oncology, Biomarkers, Pharmacokinetics-pharmacodynamics, Phase 1 trials (design, conduction, data analysis), metabolic studies, quantitative prediction of drug-drug interactions, mathematical models

ACTIVITES DE RECHERCHE / SERVICES

Our aim is to Optimize the benefit/toxicity ratio of cancer therapy.

We have 5 research strategies to reach this objective :

1. Innovative bioanalytics for measurement of anticancer drugs and endogenous products concentration to support pharmacokinetic-pharmacodynamic (PK-PD) modeling studies.

2. Development of semi-mechanistic PK-PD models allowing in silico prediction of the best administration protocols in terms of efficacy or toxicity.

3. Development of kinetic models of serum tumor biomarkers to define early markers of treatment efficacy or to predict PFS or OS.

4. Innovative phase I trial design to provide data required for optimizing drug dosing schedules by modelling and simulation.

5. Innovative pharmaceutical care :

- Prevention of iatrogenic risks with anti-cancer drugs
- Adherence to oral treatments and relationships to treatment efficacy and toxicity

Our team is composed of 3 clinical oncologists, 4 modellers, 2 biologists, 2 clinical pharmacists , 2 staff members and a variable number of PhD students and master students.

The team works in tight connection with the Investigational Center Of Treatments In Oncology And Hematology, a platform for phase 1 clinical trials which is labelled by the National Institute of Cancer (Inca). This unique platform brings together on the same site the Clinical, Analytical, Pharmacological, and Biomathematical facilities.

Our team benefits from its membership to the Lyon Cancer Institute, which receives more than 13000 patients per year, and from its collaboration network .

COMPETENCES / MOYENS TECHNIQUES

- Analytical facilities:

The laboratory has the necessary equipment to assay most of the antineoplastic agents : liquid or gas chromatography instruments, including 7 HPLC systems, 3 GC systems (1 equipped with mass spectrometry), 2 LC-MS/MS, 1 ICP-MS and 1 LC-ICP-MS.

- Clinical facilities:

the platform has access to full-time, as well as day-hospital beds, medical/surgical instrumentation, the ICU of Hôpital Lyon-Sud and the central cytotoxic reconstitution unit. The department is composed of a 10 bed hospitalization ward; a 10 bed chemodaycare unit and a out-patient consultation unit. About 50 patients a year with different types of cancers are eligible to early phase clinical trials.

- Biomathematical facilities:

The laboratory is fully equipped with a network of high powered computers allowing storage, intensive computing, confidentiality and data protection.

The established calculation tools are statistical (R®, Splus®, SAS®), mathematical (Matlab®) and specific to modelling individual pharmacokinetics and population PK-PD, NONMEM® / Monolix®(population kinetics, a mixed effect method allowing covariable analysis and the establishment of PK-PD relationships), ADAPT (individual linear kinetics, optimal sampling times), Simulo (therapeutic trial design),PKSim (PBPK model)….

DNA DAMAGE & REPAIR (DDR)

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CHAMPS D'EXPERTISE

DNA repair; Nucleoid organisation; Anti-cancer drug resistance; Protein-protein inhibitors; FRET; Fluorescence imaging; Structural Biology; Biochemistry

ACTIVITES DE RECHERCHE / SERVICES

The prime objective for every life form is to deliver its genetic material, intact and unchanged, to the next generation, despite constant assaults from both endogenous and environmental sources on the DNA. DNA lesions can block genome replication and transcription, and if left unrepaired can lead to mutations or wider-scale genome aberrations that threaten cell or organism viability. To counter this threat, cells have evolved several elaborate DNA damage response systems.

Research projects

1. Our team studies the molecular mechanisms underlying DNA damage recognition and repair in the radiation-resistant bacterium Deinococcus radiodurans. Our work focuses on two major aspects, which are:

- Dynamics of DNA Damage Repair Processes
- Recognition of DNA Lesions

Our goal is to use a combination of Structural Biology methods and Biophysical and Biochemical tools to decipher the complex molecular processes leading to efficient repair of DNA lesions.

2. Our team also studies the organisation and dynamics of Deinococcus radiodurans nucleoids that present several unusual features: they adopt a toroidal shape and are highly condensed.

Here our goal is to use structural biology and biochemical approaches together with live cell imaging techniques (conventional and super resolution PALM/PAINT fluorescence microscopy) to better understand the mechanisms underlying nucleoid organisation and chromosome segregation during the cell cycle.

3.Our team also studies DNA repair enzymes from humans and in particular we are studying the interaction between a DNA glycosylase, hNTH1, and a transcription factor, YB1. This complex is involved in anti-cancer drug resistance in solid tumours treated with cisplatin. In order to identify potential inhibitors of this complex, which could be used to resensitize drug-resistant tumour cells, we have developed a highly effective and low-cost FRET-based biosensor in order to perform high-throughput screening of chemical libraries.

Expertise in oncology:

DNA repair expert & solid experience in the study of protein-DNA and protein-protein interactions using diverse biochemical and biophysical approaches.

COMPETENCES / MOYENS TECHNIQUES

Methodologies:

- Structural Biology: Expression and purification of proteins, X-ray crystallography and small-angle X-ray scattering of proteins and protein-DNA complexes.
- Biochemistry: Development of in vitro DNA repair assays for Base excision repair enzymes and nucleotide excision repair proteins using purified proteins and fluorescently tagged DNA probes.
- Biophysics: Use of biophysical approaches (thermal shift assay, isothermal titration calorimetry, surface plasmon resonance, electrophoretic mobility shift assays, AlphaLisa technology, FRET) to study protein-protein, protein-DNA and protein-ligand interactions.
- Fluorescence imaging: Use of conventional spinning-disk confocal microscopy and super-resolution microscopy to localize proteins and DNA and probe their dynamics in live or fixed cells (mammalian cells and bacteria).

Technical facilities at IBS or on EPN Campus:

- M4D imaging platform; Biophysical and SPR/BLI platforms; High-throughput crystallization facility at EMBL; X-ray data collection at ESRF.

REGULATION AND PHARMACOLOGY OF THE CYTOSKELETON (RPC)

Centre de Recherche UGA / Inserm U 1209 / CNRS UMR 5309 Institute for Advanced Biosciences (IAB)

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CHAMPS D'EXPERTISE

Microtubules, post-translational modifications, kinases, Chemotherapy, Cancer

ACTIVITES DE RECHERCHE / SERVICES

Our team studies how the plasticity of the cellular microtubule and the actin filaments cytoskeleton is regulated in response to environmental cues, and deregulated in cancer. Microtubules targeting agents (MTA), such as vinca-alcaloids and taxanes, are widely used in the treatment of breast cancers. However they are toxic for many proliferating cells and peripheral neurons, inducing severe adverse effects. In addition, many tumors show resistance to these compounds. There is thus an urgent need to develop new drugs, less toxic. Increasing evidence indicates that functions other than mitosis may be involved in the therapeutic effects of MTA, such as regulation of microtubule dynamics in interphase. Thus, targeting microtubule-regulating proteins which are deregulated during cancer progression, is a promising alternative strategy. In this context, this team has focused on LIM kinase (LIMK), a kinase that controls both actin and microtubule dynamics and is overexpressed in many invasive cancers.

Upon LIMK inhibition, microtubules are stabilized and actin filaments are disorganized (Prudent et al., Cancer Res. 2012). Notably, the team has shown that pharmacological inhibition of LIMK has a strong effect on the growth and metastasis of breast tumors in animal models (Lagoutte et al., Sci. Rep. 2016; Prunier et al., Cancer Res. 2016). Such a treatment had no detectable undesirable side effect and showed efficacy even on taxane resistant tumors. A project of the team is the identification of microtubule-associated LIMK substrates and of the therapeutic interest of targeting LIMK in acute myeloid leukemia (INCA, PLBIO 2016-165). To that aim, we are currently invalidating LIMK in cells using the CRISPR/CAS9 system. We have observed that the modified cells show transitory phenotypes, that we would like to quantify.

The team has also recently selected an interesting compound that sensitizes cancer cells to low (1nM) doses of Taxol, with an original mechanism of action).

Moreover, the team plans now to select new pharmacological agents that target tubulin carboxy-peptidase, a microtubule-regulatory proteins that has been shown to be deregulated in breast cancer. Overall these projects can lead to the identification of attractive drug candidates to target breast tumors of poor prognosis.

COMPETENCES / MOYENS TECHNIQUES

We make an extensive use of phenotypic screening, i.e;.screening of chemical libaries using cell-based assays that probe for microtubule dynamics and functions.

We have acquired some expertise in the subsequent identification of the cell target of the compounds.

We also benefit from the close proximity of the platform OPTIMAL, to analyse in vivo the therapeutic efficacy of the compounds we are interested in on mice models of cancer.

MICROENVIRONNEMENT CELLULAIRE, IMMUNOMODULATION ET NUTRITION (ECREIN)

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CHAMPS D'EXPERTISE

L'objectif principal de notre équipe est de caractériser la réponse des cellules immunocompétentes (CICs) aux variations de leur micro-environnement. Celui-ci s'inscrit dans le domaine de l'immunonutrition.

ACTIVITES DE RECHERCHE / SERVICES

L'équipe développe des travaux de recherche dans le domaine de la prévention nutritionnelle des facteurs de risque néoplasique en relation avec la réponse immunitaire et le stress oxydant. Ces thématiques s'inscrivent dans les orientations du Centre de Recherche en Nutrition Humaine d'Auvergne (CRNH-A) et du Cancéropôle Lyon Auvergne Rhône Alpes (CLARA) en lien avec le Centre de Lutte contre le Cancer CLCC. L'objectif principal de notre équipe est de caractériser la réponse des cellules immunocompétentes (CICs) aux variations de leur micro-environnement. Celui-ci s'inscrit dans le domaine de l'immunonutrition avec deux objectifs majeurs :

1. Identifier les relations entre les altérations immunitaires/inflammatoires et les désordres métaboliques en lien avec le statut nutritionnel et immunitaire en situation physio-pathologique (notamment vieillissement, cancer).

Dans ce contexte, un des axes de nos travaux de recherche se consacre plus spécifiquement à l'étude des interactions entre les cellules épithéliales mammaires et leur microenvironnement (adipocytaire, immunitaire et inflammatoire) en situation d'obésité, considérée comme un facteur de risque d'apparition et de récidives du cancer du sein chez les femmes ménopausées.

Mots clefs : cancer, adipocytes, cellules immunocompétentes, surpoids/obésité, biomarqueurs, échappement thérapeutique, exercice physique, immunonutrition.

2. Maintenir/optimiser les capacités de réponse des cellules immunocompétentes par des interventions nutritionnelles ciblées dans une approche préventive et/ou thérapeutique.

Pour cela, une stratégie de modulation du dialogue entre les CICs et les autres tissus (sein, foie, intestin, tissu adipeux, poumon, microbiote) est développée par l'utilisation de bioactifs alimentaires immunomodulateurs (pré et probiotiques, vitamine D, bioactifs végétaux), afin de prévenir le risque de pathologie chronique associée au vieillissement. La recherche de nouvelles molécules extraites du monde végétale capables de cibler et moduler l'activité des CICs, susceptibles d'être utilisées à des fins préventives, constitue un axe en développement fort mené avec de nombreuses collaborations internationales notamment avec des pays africains (Mali, Congo, Cote d'ivoire, Bénin, Tunisie, Algérie…). Celles-ci ont déjà abouti à titre d'exemple au dépôt d'un brevet (2013) pour l'identification d'une nouvelle substance (un polyphénol : la guiéranone B) à activité anti-prolifératives et à un projet de valorisation pour cette molécule soutenu par la Société de Transfert et d'Accélération de Technologie (SATT) Grand Centre.

Mots clefs : bioactifs naturels, screening, VitD, probiotiques, bioactifs végétaux, phytochimie, cellules immunocompétentes, cellules tumorales, inflammation.

COMPETENCES / MOYENS TECHNIQUES

Nos travaux sont menés dans une démarche transversale alliant des modèles novateurs cellulaires (2 et 3D, organoïdes), animaux (régime hypercalorique, environnement enrichi, exercice physique) et des protocoles de recherche clinique. Pour cela, des approches moléculaires (transcriptomique, protéomique, métabolomique) et fonctionnelles (notamment via la cytométrie en flux/en image, imagerie, impédancemétrie) sont mises en œuvre. La recherche de nouveaux bioactifs végétaux pouvant cibler les CICs est réalisée via une approche bio-guidée. Selon les activités trouvées nous recherchons ensuite les mécanismes d'action moléculaire de ces composés par des approches expérimentales cellulaires (modèles d'organoides) et in vivo. https://www6.clermont.inra.fr/unh/Equipes-de-Recherche/ECREIN/Nos-outils-specifiques

DRUG RESISTANCE & MEMBRANE PROTEINS (DRMP)

UMR CNRS-UCBL1 5086 Molecular Microbiology & Structural Biochemistry (MMSB)

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CHAMPS D'EXPERTISE

Anticancer Drug resistance mediated by MDR ABC pumps (mainly ABCB1, ABCG2, ABCC1, ABCC2) and antifungal resistance mediated by yeast pumps (CDR1p, MDR1p);

ACTIVITES DE RECHERCHE / SERVICES

We study the efflux pumps Breast Cancer Resistance Protein(BCRP/ABCG2), Pleiotropic glycoprotein (P-gp/ABCB1), Multidrug Resistance Protein 1 and 2 (MRP1/ABCC1, MRP2/ABCC2), which confer resistance to multiple drugs (Multi-Drug Resistance, MDR) to cancer cells that overproduce them. BCRP and P-gp overexpression cause resistance to mitoxantrone of the acute myeloid leukemia; MRP1 is naturally overexpressed in neuroblastomas, and MRP2 is associated with resistance to cisplatin (Future Med Chem. 2015 7(15):2041). We also use the capacity of MRP1 to transport glutathione to over-sensitize to oxidative stress cells that overproduce it, and thus selectively induce their death (Chem Rev. 2014 114 (11): 5753). We develop molecules that induce via MRP1 a massive efflux of GSH and promote apoptosis (Eur J Med Chem 2017 130: 346 ; Biochem Pharmacol 2017 2017: 10 Curr Med Chem 2017 24 (12): 1186). We also study the Candida Drug Resistance 1 (CDR1) and of the Multidrug Resistance 1 (MDR1) MDR efflux pumps, which give a complete resistance to azole antifungals, thanks to which Candida pass from opportunists to pathogens in case of gingival or vaginal mycosis, until deadly in nosocomial diseases, for immunocompromised, eg, after surgery or AIDS patients (Advances in Cellular and Molecular Otolaryngology 2014 2(1) ; Curr Med Chem. 2017 24(30):3242).

We develop structural models of these and have identified critical residues for the transport of antifungals by mutating all the amino acids that constitute the membrane domain of these pumps. (Biochim Biophys Acta 2016 1858 (11): 2858 ; Biochem J. 2016 473 (19): 3127). These proteins expel drugs because of their “polyspecific” nature, which allows them to transport molecules with no structural similarity, a mechanism we seek to establish the molecular bases. We succeeded in positioning the binding sites of 2 drugs that P-gp carries (FEBS Let 2014 281 (3): 673). More recently, we established that the drug-binding pocket of MDR1 is surrounded by peripheral zones providing this polyspecificity (J Mol Biol 2018). Obtaining structural information at atomic resolution is absolutely fundamental to understanding the function and control it. Thanks to a collaboration with Geoffrey Chang in San Diego, USA, we also collaborated with an American team to solve the 3D structure of mouse P-gp in 2 conformations preceding drug binding (PNAS 2013 110 (33): 13386). We will release soon the x-ray and cryoEM structure of BmrA, an MDR ABC pump of Bacillus subtilis and after that of BCRP in complex with inhibitors that we develop. The membrane nature of these proteins is a constraint that leads us to develop tools and methods to solve them.

COMPETENCES / MOYENS TECHNIQUES

We develop cellular, enzymatic and structural models to understand how these pumps are organized and work. We develop inhibitors, in collaboration with chemists such as the MBLII141 which displays remarkable behavior and in vivo properties (Oncotarget 2014 5(23) :11957), and other compounds (J Med Chem. 2010 53(18):6720 ; J Med Chem. 2015 58(1):265 ; Bioorg. Med. Chem. 2018 26(2):421 ; Eur J Med Chem. 2016 122:408).

THese pumps are membrane proteins, a type of proteins not stable in aqueous solutions. We have thus developed a first generation of calixarene-based detergents bearing 3 negative charges (New J Chem 2008 32 (32): 1988). These detergents allowed to crystallize BmrA (PLoS One 2011 6 (3): e18036). Two patents from these works (WO2010116055 ; WO2009144419) have been licensed to the startup CALIXAR co-founded by Pierre Falson and Emmanuel Dejean in 2011. We just achieved a second generation of this type of detergents that displays a better interaction capacity, reinforced by hydrogen bonds provided by sugars. Some of them have quite remarkable properties of stabilization over time (more than 40 days at room temperature) and an increased resistance to thermal denaturation up of 30 °C (Angewandte Chemie, 2018 57(11):2948).

Our attempts to crystallize BmrA led us to optimize the size of the crown of detergent bound to the hydrophobic region of the membrane protein. We have developed and automated a method that uses the MALDI-TOF MS laser desorption mass spectrometry and validated it with several detergents and membrane proteins. With this method, it is now easy to model the detergent crown and predict its bulkiness (Sci Rep. 2017 7: 41751).

INGENIERIE ET INTERACTIONS BIOMOLECULAIRES (I2BM)

UMR 5250 Département de Chimie Moléculaire (DCM)

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CHAMPS D'EXPERTISE

peptides, glycoconjugués, acides nucléiques, vectorisation, ciblage tumoral, immunothérapie

ACTIVITES DE RECHERCHE / SERVICES

The activity of our laboratory mainly involves the synthesis of biomolecules (peptides, nucleic acids, oligosaccharides and a combination of these biomolecules), the structural and physicochemical characterization of these compounds, molecular systems and functional interfaces with "custom" properties for therapeutic applications (active vectorization, synthetic vaccines...) and diagnostics (molecular and functional imaging, sensor).

To date, we have designed several tumor targeted delivery systems encompassing for example "RGD" peptides that can be used to target cancer cells on which cell membrane integrins are up-regulated compared to healthy cells. Peptides labeled with fluorescent dyes or radiotracers were also developed for respectively the near-infrared optical guided surgery and tumor detection. In parallel, we develop mAb mimics or glycoconjugates that can be used for antitumoral immunotherapy by identifying the key residues involved in the recognition of the mAb with its epitope, by using Phage display, or templated combinatorial chemistry.

We are also involved in the synthesis of oligonucleotides (DNA and RNA) and their modified versions. In this context, we develop constrained G-quadruplex DNA (G4) that are found in the telomeric region as well as in promoter regions of oncogenes and are now considered as attractive anticancer targets. These constrained G-quadruplex systems are used for studying by SPR their interactions with synthetic compounds designed for anticancer activity.

We also develop the synthesis of aptamers DNA, which are used for diagnostic applications (aptasensor).

Our expertise essentially focuses on the synthesis of macromolecules via the development of a chemical scheme suitable for the assembly of functional units via the use of “click” chemistry. Our experience in chemical engineering facilitates the synthesis of highly sophisticated compounds. Our laboratory also involves researchers who share their expertise on the characterization of the interaction of macromolecules with their targets (protein, DNA, cells) by using analytical surface techniques such as surface plasmon resonance, bio-layer interferometry, quartz crystal microbalance with dissipation monitoring, and atomic force microscopy.

Al together, we can design, identify and provide to biologists new synthetic compounds for diagnostic and/or cancer therapy.

COMPETENCES / MOYENS TECHNIQUES

To prepare and to characterize our bio organic compounds we have access to the ICMG (Institut de Chimie Moléculaire de Grenoble) platforms such as the PSB (Plateau de Synthèse de Biomolécules) that contains automatic synthesizers, chromatography systems and the PCI (Plateau Caractérisation des Intéractions) that comprises SPR, BLI, QCM-D and AFM equipment.

In our team, we have a strong expertise in biomolecule chemistry such as peptide, nucleic acid and carbohydrate chemistry. To prepare sophisticated macromolecules, we use specific reactions such as chemoselective ligations that allow the ligation of all kind of biomolecules in aqueous solution.

Additionally, we have a complementary expertise in surface functionalization (SPR and QCM sensors, AFM surface) and in the characterization of biomolecular recognition by using the techniques described above.

SMALL MOLECULES FOR BIOLOGICAL TARGETS

Centre de RMN à très haut champ de Lyon
Centre de Recherche en Cancérologie de Lyon

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CHAMPS D'EXPERTISE

Fragment screening and Drug screening against soluble and membrane proteins, structural characterization of protein-small molecule interactions, affinity measurements, Bio-Layer Interférométrie, chemical synthesys, medicinal chemistry, cell assays

ACTIVITES DE RECHERCHE / SERVICES

The team project is dedicated to the development of small molecules targeting biological targets of interest, including soluble as well as membrane proteins such as the GPCR family of proteins. The team mainly focuses its research in the generation of compounds capable to bind binding sites different from orthosteric/active site as the allosteric sites and protein-protein interaction sites. In this context, one of the team objectives is the development of "linked" or "bivalent" compounds. All activities of the team can be provided as collaborations or services for academic and privates groups.

COMPETENCES / MOYENS TECHNIQUES

The team activity includes hit identification through fragment-based approaches, characterization of protein-small molecules complexes (structural investigation, affinity mesaurement) and hit-to lead optimization based on structural and medicinal chemistry skills.

- Structural characterization of protein-ligand complexes using NMR (the platerform at CRMN is opned for collaborations or services for academic groups as well as private compagnies)
- Biophysical characterization of protein-ligand complexes
- Chemical synthesys and medicinal chemistry
- Libraries : a non-focused fragment library and a kinase-focused library

ORGANIC AND MEDICINAL CHEMISTRY (COM)

UMR CNRS 6296 Insitute of Chemistry of Clermont-Ferrand (ICCF)

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CHAMPS D'EXPERTISE

design, molecular modelling, chemical synthesis, extraction, natural products, aromatics, peptidomimetics, metallocarbenes

ACTIVITES DE RECHERCHE / SERVICES

The team "Organic and Medicinal Chemistry "brings together an ensemble of expertise ranging from the design of original synthetic molecules by Molecular Modelling to the full achievement and characterization of the target molecules. The projects which are developed sit at the interface between chemistry and biology, with a particular focus on projects that have a link to cancer .

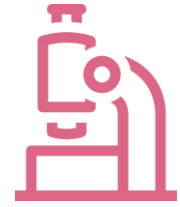
In particular the team COM is interested by the design and synthesis of heteroaromatic compounds (Indoles, Quinolines, Indazoles, Pyrimidines...) with protein kinases (Pim, DYRK1A, CLK1…) inhibitory potencies. The design and synthesis of folded peptide mimetics for mediation or inhibition of protein-protein interactions involved in apoptosis (biotic and abiotic helical BH3-domain mimetics as selective inhibitors of anti-apoptotic proteins) is also studied. In the context of anticancer immunotherapy, carbohydrate-based tumor-associated anticancer vaccine conjugates have also been conceived. The team has been developping vascular-disrupting agents (VDA) to target tumor angiogenesis. The extraction of plants to identify natural products with anticancer activity is also of interest.

COMPETENCES / MOYENS TECHNIQUES

ICCF Chemical library, member of the French National Chemical Library (GIS "Chimiothèque Nationale. Facilities such as mass spectrometry, NMR and X-ray diffraction are available from UCA Partner

CRIBLAGE POUR DES MOLECULES BIOACTIVES (CMBA)

UMRS_1038 Large Scale Laboratory (BGE)



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CHAMPS D'EXPERTISE

Automated assay development, Cancer, Cell signaling, Cell growth and differentiation, Drug Discovery, Molecular screening , HTS - High throughput screening, HCS High Content Screening, Inflammation, Rare disease, Therapeutic targets

ACTIVITES DE RECHERCHE / SERVICES

The CMBA screening platform aims at the identification of bioactive molecules valuable for research, pharmacological validation of therapeutic targets and drug development in cancer and other therapeutic fields. It is open to academic and industrial partners to promote translational research and Drug Discovery.

The CMBA is a member of the national infrastructure ChemBioFrance (www.chembiofrance.fr) which is a distributed infrastructure that interconnects the French national chemical library (Chimiothèque Nationale CN), the platforms for the screening and the pharmacokinetic studies (Screening-ADME), and molecular modeling laboratories (chemoinformatics).

The CMBA also works in close collaboration with medicinal experts of the Department of pharmacology of University Grenoble Alpes (DPM-Expert) for further hits analysis and drug development in the frame of the IBiSA labeled Grenoble Alpes Probes and Drug Discovery consortium (GAP2D) (https://www.ibisa.net/plateformes/detail.php?tri=&srch=&q=38).

An in-house sftware has been developed for chemical collections management and hits selection on robust statistical criteria (TAMIS) http://big.cea.fr/drf/big/english/Pages/BGE/GIPSE/TAMIS.aspx).

COMPETENCES / MOYENS TECHNIQUES

The CMBA platform is fully equipped to perform high-throughput screening campaigns (HTS) on either purified targets or living cells, as well as phenotypic screening by automated imaging using the high content screening methodology (HCS).

We propose pharmacological profiling of your extracts or in-house collection of molecules. We can also develop and adapt personalized and innovative assays to 96-well or 384-well microplates on demand for the automated screening of large collections of molecules available at CMBA platform.

A number of small to large chemical collections are available at the platform (including 2200 FDA-approved drug, commercial libraries and the national chemical library) totalizing more than 70,000 compounds.

CMBA-HTS Robotic Platform – Contact : Dr Caroline Barette, caroline.barette@cea.fr :

- Tecan's EVO200 workstation, 8-channel heads (hit picking) and 96 channels (suitable for 96 and 384-well plates)
- STX44 StoreX ™ LiCONiC Cell Incubator (42 Plates)
- Tecan's "HydroSpeed ™" automated scrubber
- Tecan's "Infinite® M1000" plate reader (absorbance, fluorescence (including FRET, HTRF, anisotropy) and luminescence (including BRET))
- Carousel Tecan, Orbital shaker,Barcode reader

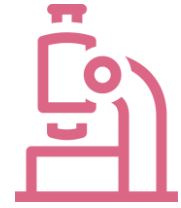
CMBA-HCS High Content Screening Platform –Contact : Dr Emmanuelle Soleilhac Emmanuelle.soleilhac@cea.fr
- INCell Analyzer 1000
- ArrayScanVTI

CENTER FOR DRUG DISCOVERY AND DEVELOPMENT (C3D)

Fondation Synergie Lyon Cancer

Translational Research and Innovation department, Centre Léon Bérard

Centre de Recherche en Cancérologie de Lyon



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CHAMPS D'EXPERTISE

Drug Discovery, screening, hit to lead, lead optimization, pharmacology, Medicinal chemistry, preclinical profiling

ACTIVITES DE RECHERCHE / SERVICES

C3D, Center for Discovery and Development is a unique academic drug discovery team created to fill the translational gap in oncology between fundamental research and patients. The aim of this plateform is to develop drug discovery programs based on validated target identified by basic researchers. The mission of the C3D is thus to provide the research teams with the means and technical support to identify, characterize and develop new cancer therapies (antibodies or small organic molecules). The C3D works in the early stages of exploratory research, up until the entry into clinical trials.

The challenges of the C3D are:

- To accelerate the transfer of academic research programs towards the clinic and to patients
- To create developmental partnerships between academic and industrial research.

- Organization

The operation of the platform is carried out by a steering committee comprising researchers, clinicians, IP responsives and the Head of C3D.
This committee selects the projects developed in the C3D, makes strategic decisions, both scientific and financial, and monitors the management and advancement of research programs. The committee is also aided by several independent experts who evaluate and orientate the scientific projects.

- Skills

Molecular and cellular Biology; Biochemistry; Medicinal chemistry; early-ADME; Regulatory preclinical development; Project Management

- Core activities

Drug discovery: hit to validated lead (biological- pharmacological activity); preclinical pharmacological profiling; target and biomarker validation; drug combination; drug repositioning; regulatory preclinical development (safety pharmacology, toxicity).

COMPETENCES / MOYENS TECHNIQUES

- **Equipment**

Automated liquid handling (robotic platform) ; multi-technology microplate readers (96 – 384 wells) ; 2 HPLC chains coupled to mass spectrometers ; Microscopy (fluorescence imaging) ; HP D300 dispenser ; Cell culture room; HCS platform: operetta CLS Perkin Elmer

- **Libraries**

The Prestwick library, 1200 FDA approved compounds ; a core library of 52 000 « drug like » compounds ; a protein-protein inhibition library: 13 000 compounds; a natural "like" compounds: 1200; a kinase inhibitor library of 590 compounds under development or already on the market.

- **Other facilities**

C3D has strong interactions with many other platform of the CLB like: the in vivo imagery platform, the bioinformatic platform, Anican and the LMT for the generation of animal models, the ex-vivo platform, and an anathomopathology platform for the study of biomarkers in animal models.

- **Competencies:**

Primary and disease relevant – secondary screenings (target or cell-based; multiple assay format and read-out technologies); incease of compounds potency (MedChem, SAR),
Early-ADME: kinetic solubility in assays medium, permeation (PAMPA), metabolic stability (microsome / S9), CYP450 inhibition, Cytotoxicity (chronic - acute toxicity).

PLATE-FORME CHIMIE NANOBIO (PCN)

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CHAMPS D'EXPERTISE

Spectrométrie de Masse, Résonance Magnétique Nucléaire, Microscopie Electronique, Cristallographie RX, Résonnance Plasmonique de surface, Bio-Layer Interférométrie, AFM, Chimiothèque, Synthèse peptides et acides nucléiques, Ingénierie de surfaces et

ACTIVITES DE RECHERCHE / SERVICES

La Plate-forme Chimie NanoBio (PCN) regroupe un ensemble de moyens techniques en chimie par mutualisation des équipements des 3 unités de recherche de l'ICMG (DPM. DCM et CERMAV). Elle est organisée en 9 plateaux techniques avec pour chacun d'eux du personnel technique et un coordinateur scientifique du domaine pour soutien et collaboration aux projets de recherche.

- **Plateau Résonance Magnétique Nucléaire (PRMN) :**

RMN en phase liquide et solide pour la caractérisation structurale de composés organiques ou inorganiques d'origine synthétique ou biologique, de molécules plus complexes (oligonucléotides, peptides, petites protéines, oligo et polysaccharides) ainsi que pour l'investigation de la physico-chimie d'assemblages.

- **Plateau Spectrométrie de Masse (PSM) :**

Identification et quantification de molécules très variées allant des bio-polymères complexes d'intérêt pharmaceutique (d'origine synthétiques ou biologiques comme les oligo- et polysaccharides, peptides et protéines, et oligonucléotides) jusqu'aux petites molécules de synthèse à visée thérapeutique ou non.

- **Plateau Synthèse des Biomolécules (PSB) :**

Plateau dédié à la production de biomolécules pour des applications thérapeutiques et diagnostiques : oligonucléotides aptamères et antisens, peptides bioactifs, marquages par des chromophores, des sondes électrochimiques et des fonctions pour l'accrochage sur surface.

- **Plateau Cristallographie (PRX) :**

Caractérisation structurale par diffraction des rayons X sur monocristaux de petites molécules (quelques centaines d'atomes) organiques ou inorganiques d'origine synthétique ou biologique. Détermination des centres asymétriques dans les structures chirales, résolution de l'aspect tridimensionnel impactant la réactivité.

- **Plateau Microscopie Electronique (PMIEL) :**

Caractérisation morphologique (imagerie électronique MET et MEB) et structurale (diffraction des électrons en MET), à température ambiante et à basse température, de polymères (naturels ou synthétiques), de colloïdes, d'assemblages macromoléculaires et de nano-objets, et de tissus végétaux.

- **Plateau Caractérisation des Interactions (PCI) :**

Caractérisation des interactions entre biomolécules (acide nucléiques, peptides, oligosaccharides, lipides) elles-mêmes ou en interaction avec des molécules de synthèses (en particulier de petite masse moléculaire).

- **Plateau Calcul Intensif (PCECIC) :**

Moyens de calcul pour le développement et l'application de la chimie calculatoire. Le plateau possède un savoir faire en chimie quantique, en dynamique et modélisation moléculaire, en méthodes mixtes et TD-DFT.

- **Chimiothéque :**

Offre d'une collection de molécules présentant une grande diversité et complexité structurales. Plus de 1000 produits formatés en microplaques prêtes au criblage et également une base de données virtuelle, soit 2991 molécules destinées au criblage virtuel.

- **Plateau Fonctionnalisation de Surfaces et Transduction (PFT) :**

Ingénierie de surfaces et transduction du phénomène de bio-reconnaissance.

COMPETENCES / MOYENS TECHNIQUES

PRMN

- Spectromètre 500 MHz (cryosonde Prodigy et TXI triple résonance 1H/13C/15N). Travail à basse température possible.
- 4 spectromètres 400 MHz (sonde Smartprobe, sonde BBFO, sonde BBO) dont un pour RMN solide.
- Spectromètre 300 MHz (sonde QNP)

PSM

- BRUKER autoflex speed : source MALDI, analyseur TOF /TOF (MS/MS possible)
- BRUKER amaZon speed : couplage avec UHPLC, sources ESI, ApCI et Direct Probe , analyseur Trappe Ionique (MSn possible)
- AGILENT 5977A-7890B : couplage avec phase gazeuse (CPG), sources EI et CI, analyseur simple quadripôle

PSB

- Synthétiseurs automatiques : ADN (ABI, Expedite) et peptides (Syro, ABI). HPLC en phase inverse analytique (1) et semi-préparatives (3) et en échangeuses d'ions (1).

PRX

- Diffractomètre Bruker AXS-Incoatec-Enraf-Nonius Kappa AppexII pour monocristaux équipé d'une microsource RX haute brillance à la longueur d'onde λ Kα du molybdène : 0,71073 Å.
- Diffractomètre Enraf-Nonius Kappa CCD pour monocristaux équipé d'une source classique de RX à la longueur d'onde λ Kα du cuivre : 1,54178 Å.

PMIEL

- Microscope électronique en transmission JEOL JEM 2100Plus 200 kV cryo/tomographie, Microscope électronique à balayage FEI Quanta 250 ESEM-FEG, Ultra-cryomicrotome Leica UC6 , station de congélation Leica EM-GP.

PCI

- Résonnance Plasmonique de surface, Bio-Layer Interférométrie, AFM, microbalance à quartz avec dissipation d'énergie, ellipsométrie.

PCECIC

- Le CECIC dispose en propre d'un cluster de calcul comprenant 560 cœurs de calcul et d'un serveur PowerEdge R520 doté de 8 disques de 4 To pour la sauvegarde des données.
- Le CECIC gère également, en relation avec l'UMS GRICAD, une plateforme de calcul intégrée comprenant près de 3500 coeurs de calcul, des systèmes de stockage à haute performance, un réseau de calcul ultra-performant et un système de refroidissement innovant (DLC).

Chimiothéque

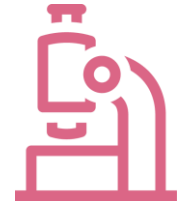
- 1 chambre froide (+4°C), 2 congélateurs sécurisé (-30°C et -80°C), scelleur de plaques par thermo-soudure.

PFT

- Métalliseur et spectromètre Raman de paillasse

CHIMIOTHEQUE ET SYNTHESE - COMPOUND LIBRARY AND CUSTOM SYNTHESIS

UMR5246 Institut de Chimie et Biochimie Moléculaires et Supramoléculaires (ICBMS)



RESPONSABLE

Arnaud COMTE

✉ arnaud.comte@univ-lyon1.fr

☎ 33 472 431 417

OU NOUS TROUVER ?

UCB Lyon1 - bat. Lederer - 1 rue Victor Grignard,

69100

Villeurbanne

@ http://www.icbms.fr/chimiotheque

CHAMPS D'EXPERTISE

Compound Library, chemical biology, screening, organic synthesis, SAR, structural optimization, custom synthesis

ACTIVITES DE RECHERCHE / SERVICES

The ICBMS compound library was created in 2001 to promote the screening of Lyon 1 University synthetic compound collection and to be in charge of hit-to-lead optimization process and various studies (synthesis of focused libraries, SAR models…) in collaboration with researchers in the fields of biology and biochemistry.

Currently, we offer two distinct technical ressources/services :

1) The Lyon 1 Compound Library: a collection of +3500 selected synthetic compounds (large chemical space, mostly non-commercial and highly original) in a format suitable for manual or automated screening

2) Our custom chemical synthesis services :

- Synthesis of various small molecules (API and bioactives, analytical standards, impurities, building blocks and reagents...)
- Use of various research areas available at ICBMS (with expertise in heterocyclic and organometallic chemistry, catalysis)
- Medicinal chemistry (SAR, analogues) and design of synthesis route
- Optimization and upscaling (from mg to g/kg) for non-GMP applications

Our fields of research and collaborations are mainly related to:

- oncology (design of TRAIL inducing molecules in cancer cells, kinase inhibitors...),
- rare diseases,
- antiparasitic or antibacterial compounds,
- inflammatory and cellular necrosis related disorders.

COMPETENCES / MOYENS TECHNIQUES

- Lyon 1 University - ICBMS Compound library : containing +3500 synthetic or natural molecules (functionalized heterocycles, fluorinated products, natural compound derivatives, peptides, amino acids and nucleoside analogues...)
- Standard organic chemistry equipement and 45m2 of dedicated laboratory space for multistep synthesis, acces to microwave synthesizer, high pressure vessels and reactors up to 10L.
- Synthetic know-how in various fields of organic synthesis (heterocyclic chemistry, organometallic catalysis, natural products...)
- Access at ICBMS to in-house NMR (300-500 MHz), mass spectrometry (GC and LC/MS) and various other methods for characterisation of compounds
- Access to an Hamilton automated liquid handling workstation

Information et contact

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Avec le soutien du

CLARA
CANCÉROPÔLE
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