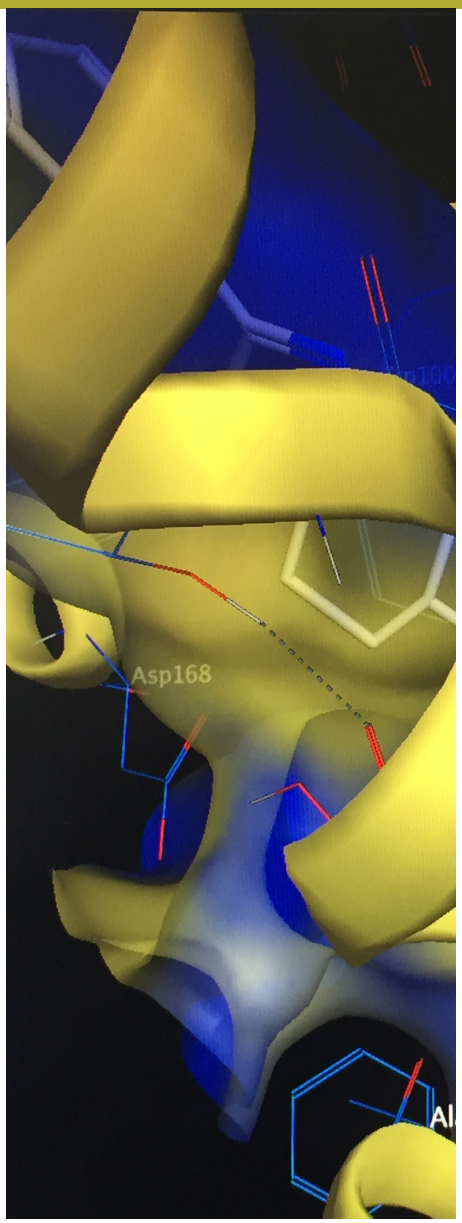
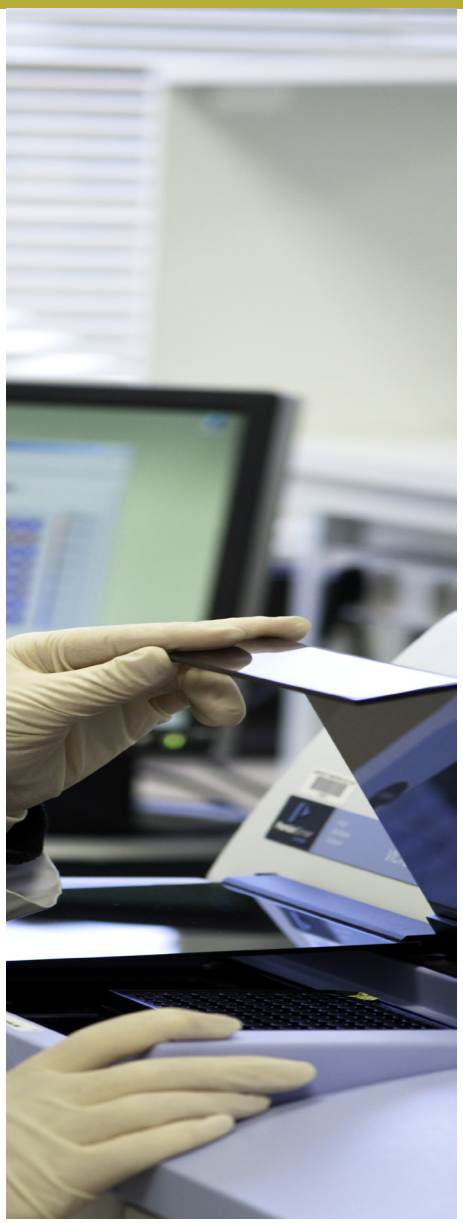
Drugs & Molecules for Living Systems

Lille Drug Discovery & Chemical Biology Laboratory





Inserm U1177 - Université de Lille 2 - Institut Pasteur de Lille
Médicaments et Molécules pour Agir sur les Systèmes vivants
www.deprezlab.fr

Discovery Across Boundaries

Presentation

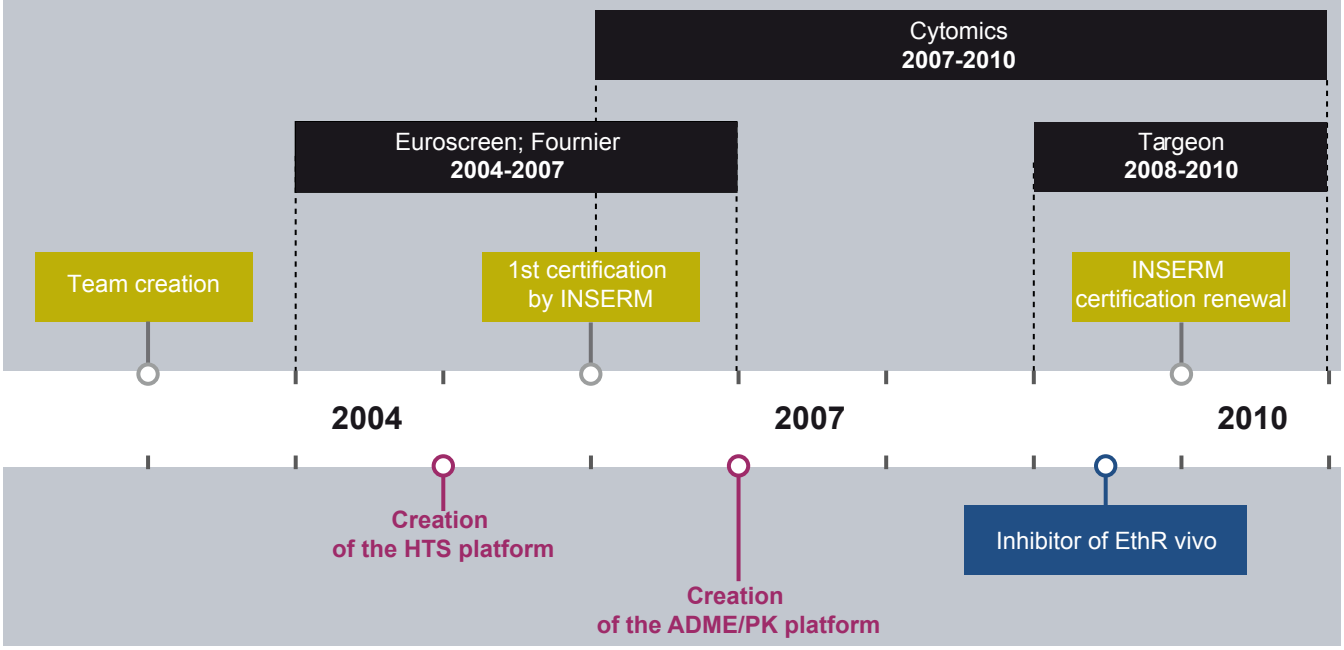
Mission

Our mission is to expend the human therapeutic armamentarium. We aim at designing and evaluating qualitatively and quantitatively chemical means of intervention in living systems (cells, organisms, men). We design and study compounds that selectively modulate molecular targets to understand (**chemical biology**) & treat infectious & metabolic diseases (**drug discovery**).

Where do we come from

The laboratory was created in 2003 by Pr. Benoit Deprez and was labelled INSERM in 2006 and renewed since then. It is affiliated to three institutions: Université de Lille2, INSERM and Institut Pasteur de Lille.

The laboratory is one of the founders of PRIM, the Regional Interdisciplinary Research on Drug Discovery Center.



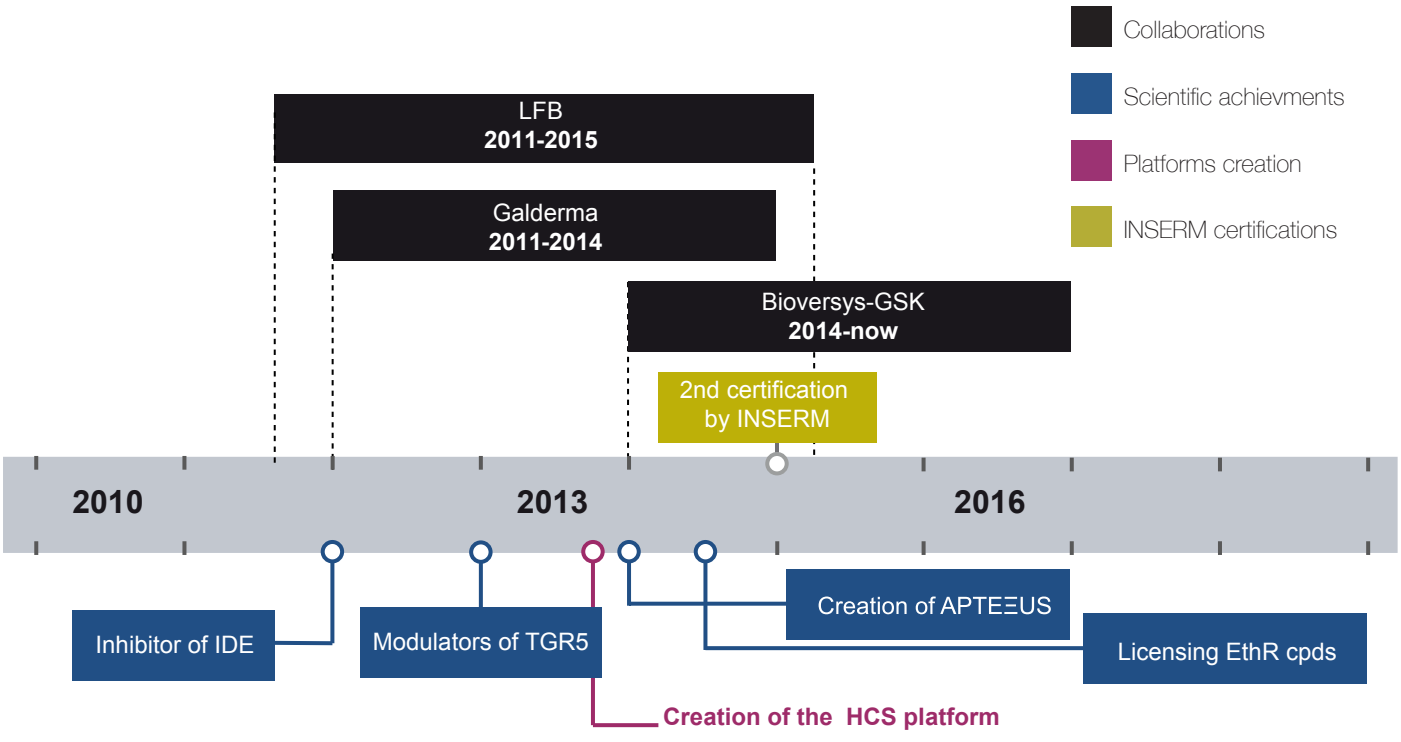
Economic and Scientific Environment

With more than 200 labs of 4800 researchers and 3000 PhD students, Lille and its region is a key scientific spot in Europe. Lille is the location of a dynamic network of laboratories, universities, engineer schools, medical and pharmacy schools, research institutes and biotechnology firms. In that stimulating and strong scientific research community, our team works within the framework of :

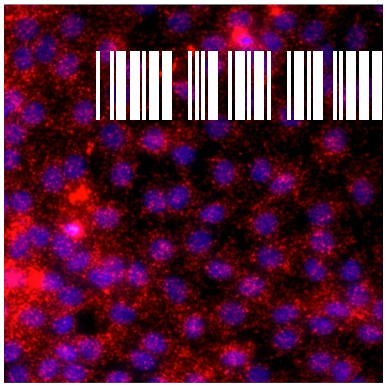
- the IDEX
- the Universities
- INSERM
- the Institut Pasteur de Lille ,
- CNRS
- the bioincubator Eurasanté (Nutrition Heathcare Longevity Cluster),
- the Regional hospital

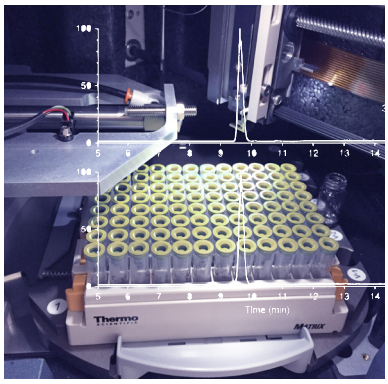
Location

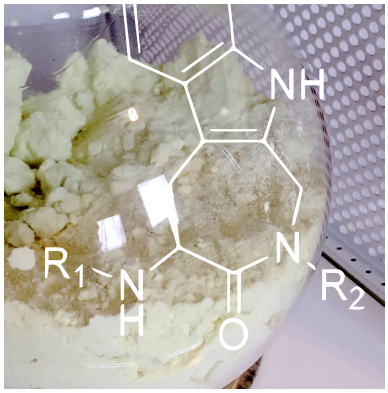
We are located both at the School of Pharmacy and at the Institut Pasteur de Lille. Being on both biomedical sites make our contacts with our main collaborators easier.

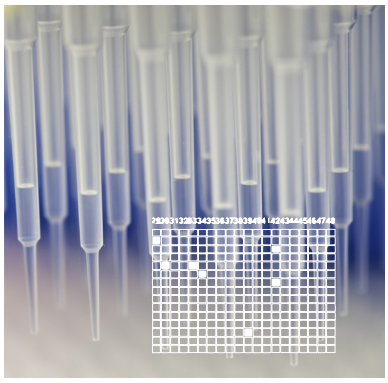


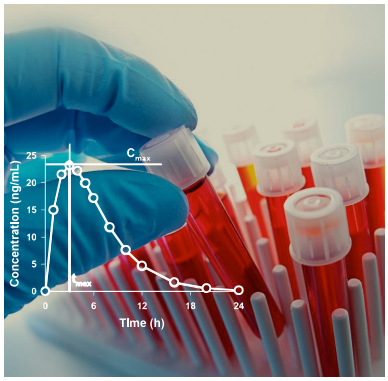
Expertise











Domains of expertise*

Our laboratory uses Chemical Biology and Drug Discovery tools* for its projects:

Target identification & validation

High-Content Screening

High-Throughput Screening

Fragment based discovery

In situ click chemistry

Medicinal chemistry

Molecular Modeling

X-ray

Biacore

Biochemistry

Cellular biology

In vitro ADMET, rodent PK and bioanalysis

** Report to specific leaflets*

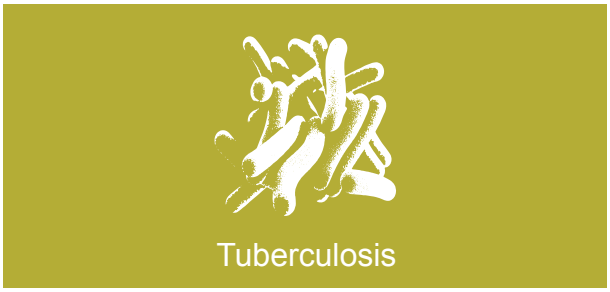
9,000 building blocks	18 patents	8 Post-Docs*	500,000 screening points
2 drug candidates	7 technicians, engineers	450 ADME / PK studies	10 researchers PhD
5 PhD students*	105 publications	1 start-up	90,000 compound library

** On average*

Key Figures since 2006

Scientific Achievments

Our professional expertise allows us to produce compounds for chemical biology and early stage drug-discovery. We focus mainly on infectious and metabolic diseases.



The increasing number of multi- (MDR), and extensively (XDR) drug resistant tuberculosis strains forces the discovery of new therapeutic alternatives. The project initiated in 2005 aims at designing new inhibitors of mycobacterial transcriptional regulators to achieve a complete reprogramming of thioamide antituberculous drugs in bacteria. We successfully made the proof of concept of **EthR** as a new biological target. We work on development of compounds with a new mode of action (with Bioversys, TB alliance & GSK).

Willand, N., et al Nature Med.,**2009**, 15: 537-544.

Flipo, M., et al J.Med. Chem,**2011**, 54(8): 2994-3010.

Flipo, M., et al J.Med. Chem, **2012**, 55(14): 6391–6402.

Flipo, M., et al J.Med. Chem,**2012**, 55(1): 68-83.

Villemagne, B., et al J. Med. Chem,**2014**, 57(11): 4876-4888.

We developed 2 different strategies to validate new therapeutic targets for malaria (collaboration with Univ. Antwerp & MNHN). The first approach, "Drug-to-Genome-to-Drug" strategy, allowed the optimization of tadalafil analogues to inhibit **PfPDE**. The second approach using screening of our in-house library of metalloprotease inhibitors, allowed the discovery of the first inhibitors of **PfAM1**, which in vivo distribution provided insights into the validation of this new target.

Flipo, M., et al Bioorg. Med. Chem.,**2007**, 15(1): 63-76.

Flipo, M., et al, J. Med. Chem.,**2007**, 50(6): 1322-1334.

Beghyn, T. B., et al J. Med. Chem.,**2011**, 54(9): 3222–3240.

Beghyn, T., et al J. Med. Chem.,**2012**, 55(3): 1274-1286.

Deprez-Poulain, R., et al J. Med. Chem.,**2012**, 55(24): 10909-10917.

ERAPs are implicated in the last steps of proteolytic processing of antigens and control in part their presentation to immuno-competent cells. In that context, modulators of these enzymes will find therapeutic applications in auto-immune, infectious diseases and cancer. Thanks to a “Target-hopping” strategy, we have discovered modulators of these enzymes (collaboration with NDCR Athens, Univ Southampton).

This project is spun from the University in a start up project called **APTEEUS,** which won the OSEO creation award in 2012. We use a collection of 1,400 marketed drugs and screen them independently of any reported clinical side effect. This concept is primarly applied to diseases where the cause of the disease is a perfectly characterized molecular alteration of physiology (mostly heritable rare, monogenic disease).

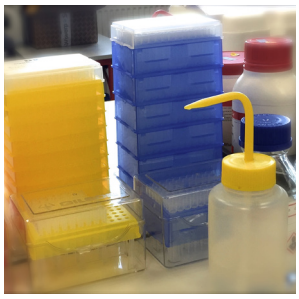
Innovation.

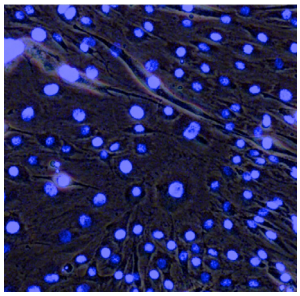
Discovery.

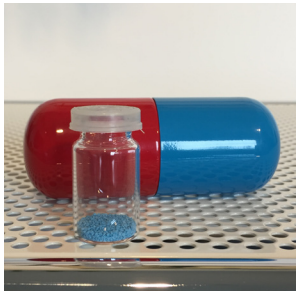
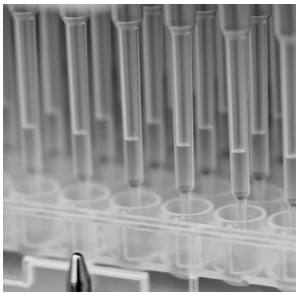
Quality.

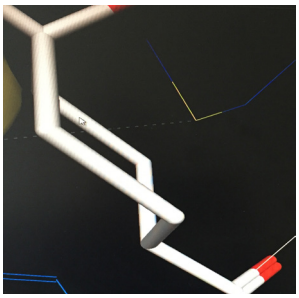
Ideas. ***Cure.***

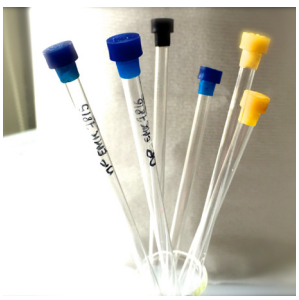
Technology.



Scientific Achievments

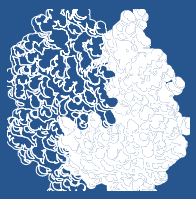
Diabetes

Our project (collaboration with U1011 Lille, Necker, Univ Chicago) aims at developing chemical probes to understand the biological roles of Insulin-degrading enzyme, **hIDE** and at optimizing them into therapeutic leads. We have significantly contributed in the field by discovering by HTS the first dual-site ligands of IDE. Also we recently discovered by an original in-situ click chemistry strategy an inhibitor whose effect has been evaluated vivo.

Deprez-Poulain, R., et al Nature Comm.,**2015**, 6.

Charton, J., et al. Eur. J. Med. Chem.,**2015**, 90, 2, 547–567.

Charton, J., et al. Eur. J. Med. Chem.,**2014**, 79, 184-193.



Cancer & HCV PPI

In the C-Dithem consortium, we have developped libraries to tackle tprotein-protein interactions in collaboration with Dr Villoutreix and Sperandio, who perform virtual screening. We have validated this focused library on **HDM2/p53** and **Bfl-1/ Bim** interactions implicated in cancer. Also, in collaboration with CIIL we have developed an HTS assay using a Bioluminescence Resonance Energy Transfer (BRET) an d dual BRET/high content screening (HCS) readout, to monitor **CD81-CLDN1** interaction, important for HCV entry. These assays are currently used to optimize our compounds.

Mathieu, A. L., et al J Biomol Screen,**2014**, 19(7): 1035-1046.

Couturier, C., et al. Front. Endocrinol.,**2013**, 3.

Metabolic syndrom, Obesity, Diabetes

This project (collaboration with Pr Staels, Pr Pattou) aims at discovering small, non-steroidal, potent and selective agonists of the **TGR5**. Following a screening of 20,500 compounds, we have identified 5 chemical series. To avoid target-based side effects of systemic agonists, we develop topical agonists that would only target endocrine L-cells to trigger GLP-1 secretion. Our compounds bear both a pharmacophore and a kinetophore

Osteoarthritis

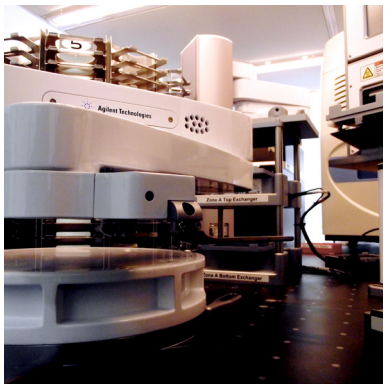
ADAMTS4&5 are metalloproteases of the extra-cellular matrix whose over-expression or enhanced activity lead to pathologies such as osteoarthritis. We have contributed in the field by screening and optimizing inhibitors of these enzymes that display an atypical zinc-binding group (collaboration with Univ Leuven, Univ Oxford).

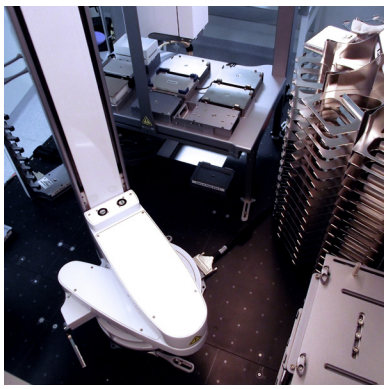
Maingot, L., et al Bioorg. Med. Chem. Lett .,**2010**, 21: 6213-6216.

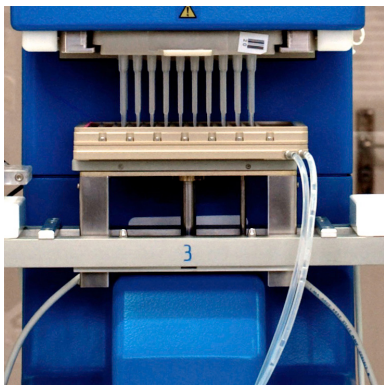
Maingot, L., et al Eur. J. Med. Chem.,**2013**, 69: 244-261.

Elbakali, J., et al Fut. Med. Chem.,**2014**, 6(12): 1399-1412

Equipments







Facilities & Platforms*

All our platforms are accessible for services & collaborations.

High-Throughput Screening

The **screening facility** set up at the Institut Pasteur de Lille is operated by six biologists, with liquid handling systems (CyBI™-Well, Biomek™ NX, Zephyr™), automated multi-mode fluorescence/ luminescence readers (Mithras LB940 Research III, Victor™3V), a lightcycler 480 and a cell culture unit . Screening techniques span from Fluorescence, Thermal Shift Assay, Mass Spectroscopy,...

High Content Screening

We are part of the **HCS Equipex ImagInEx BioMed cluster**. This platform allows the screening of siRNA or compounds in complex systems, using liquid handling systems like Echo acoustics™.

ADME, PK & Bioanalysis

We perform both in vitro ADME experiments and in vivo PK in rodents, using our state-of-the-art LCMSMS and LCTOF systems.

Libraries & Cpd management

We have assembled a 90.000-compound library formatted in 96- and 384-well plates. The sample management system ensures the longest possible lifetime for all the samples. To manage compounds and associated results, a LIMS system has been implemented in the Unit using Access, Oracle/ Isis databases and Pipeline Pilot™.

Chemistry

We have state-of the art equipements for Parallel synthesis, Solid phase synthesis, Green chemistry, microwave and solvent free techniques, Pd or Cu catalyzed reactions, as well as analytics and NMR.

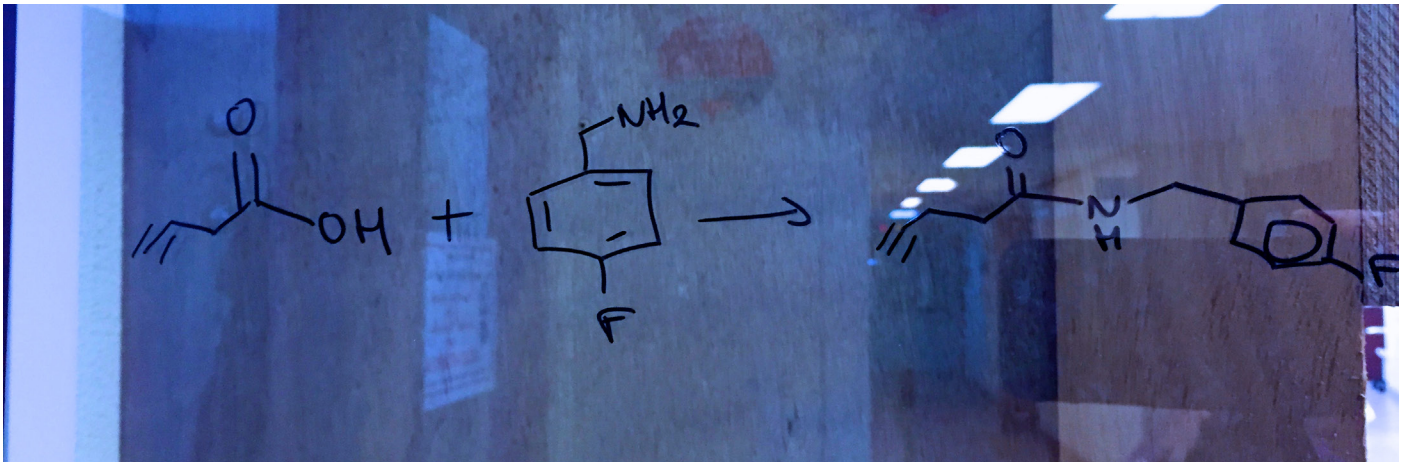
** Report to specific leaflets*

Collaborators

We collaborate with academic and industrial teams around the world.

We work with the high rated biology teams in the Region, becoming the «medchem arm» of both the CIIL (Centre d'Infection et d'Immunité de Lille) and the Labex Egid on metabolic diseases. In parallel, we have sustained relationships with several labs abroad. Since 2003, we have been collaborating with several industries: Fournier Pharma, Ferring, Euroscreen, Cytomics, Targeon, Imabiotech, Galderma, Genticell, LFB, Amakem and Bioversys/GSK.

We are members of national and international networks:
C-Dithem : Consortium for Discovery and Innovation in Therapy and Medicine
PRIM : Regional Pole for interdisciplinary research on medicines & drugs
GDR 3056 « ChemBioScreen»
Equipex « Imaginex BioMed » the BioImaging Center Lille-Nord de France
MINOTAUR: Antigen presentation



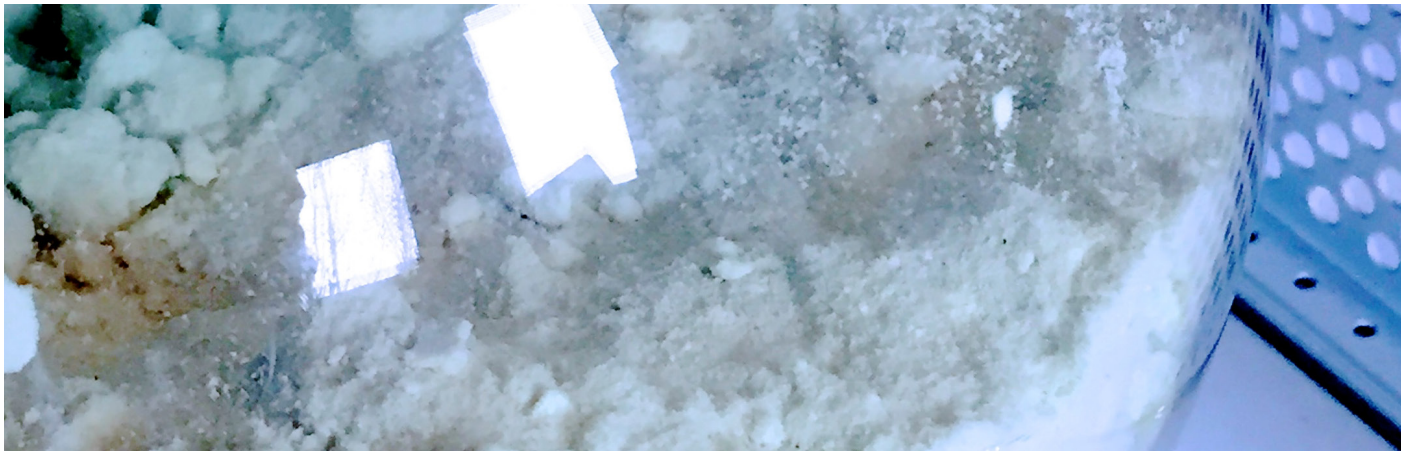
A. Bourin PhD, Researcher, Medicinal Chemist, Amakem, PostDoc 2008-2011: *"Coming from U. Cergy-Pontoise with a strong background in organic chemistry, I found this postdoc experience essential for me to be recruited in the industry as a medicinal chemist. This lab ideal to improve onself in the drug discovery field."*

M. Bourotte PhD, Researcher, Medicinal Chemist, In the team since 2011: *"Since 2011, I have been principal investigator in a dermatology program and senior researcher for an infectiology program both in close collaboration with pharmaceutical companies. A great advantage is to have access to a wide range of building-blocks (> 8000) and state of the art equipment. This allows my team to be both creative, reactive and productive."*

A. Herledan, study Engineer, Biologist, In the team since 2011: *"I develop miniaturized, fast and robust assays for medium to high throughput screening and phenotypic assays in collaboration with both academics and pharma companies. The large chemical library and the cutting-edge robotic platform offer the best supporting environnement for drug-discovery projects. Furthermore, campaigns and screening hit confirmation are performed using good laboratory practices to ensure traceability and quality of data"*

M. Lasalle PhD, PharmD - Medicinal Chemist, PostDoc Univ British Columbia, PhD student, 2011-2016 : *"After a PharmD & a Ms in Chemistry, I did my PhD in the lab working on the TGR5 project. I enjoyed having access to a wide technical plateau and interacting with experts in the drug discovery field. I found stimulating that the lab goes beyond the traditional academic work towards clinical candidates to solve health problems."*

B. Villemagne PhD, Medicinal chemist Assistant Professor, PhD student 2009-2013, in the team since 2015: *"I joined the lab as a Ms, then PhD student working on FBDD of new antituberculosis compounds. After a postdoc in medicinal chemistry in Birmingham (UK), I came back as an assistant professor. For a young researcher, the large number of collaborations ans the high quality of the lab meetings are unique opportunities to acquire knowledge in different fields spanning from organic synthesis, drug discovery, biology,...This remarkably stimulating environnment combined with the very high diversity of equipment allows researchers to carry out their project in the best conditions."*



People, Education

Who we are

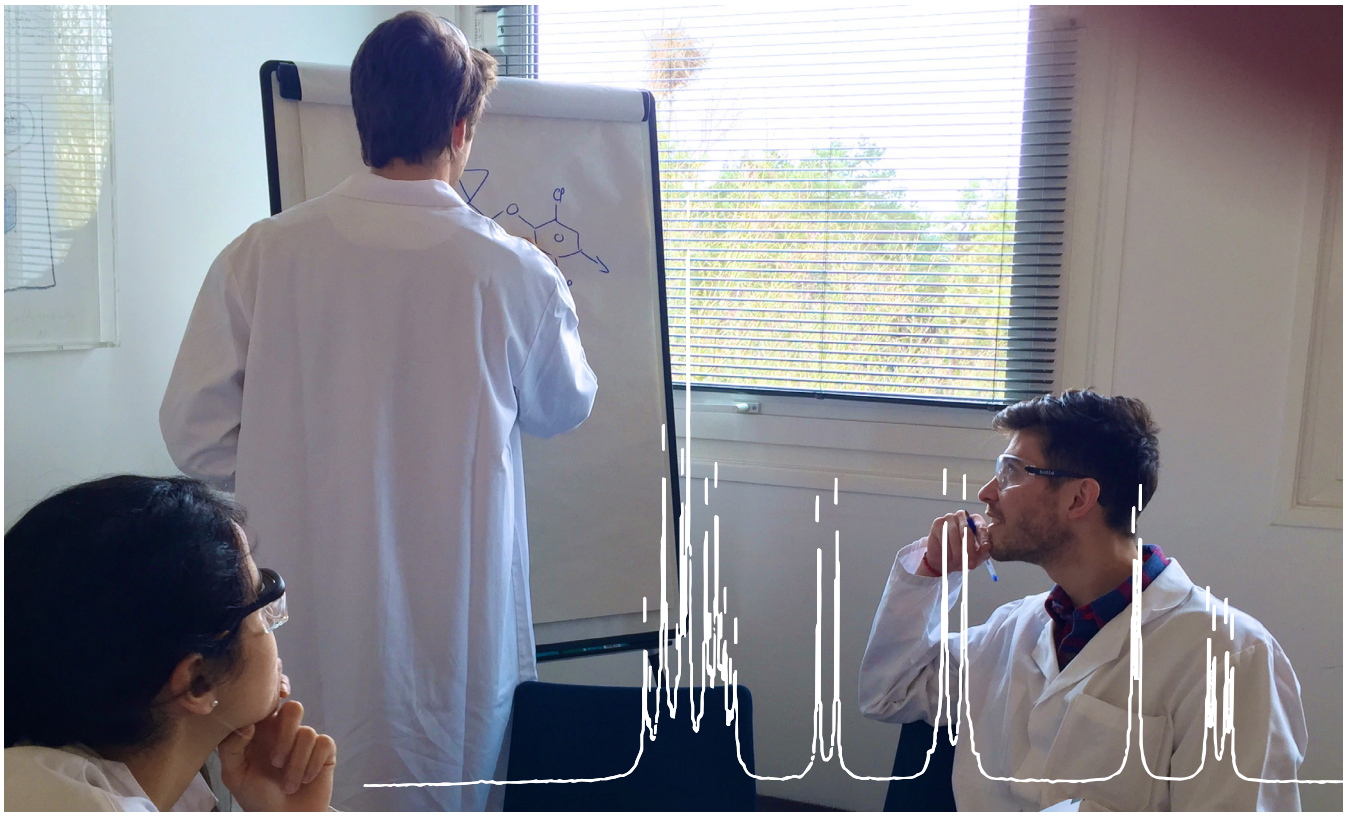
Our researchers are PhDs in Organic, Medicinal or Bio- chemistry or Cell biology. Some of them are also PharmD. Some of our team members have worked in the industry and biotech for several years.

We train PhD and Master students in chemistry and biology and welcome 3-5 new PhD students and 5 new PostDocs each year in the laboratory. Our laboratory is willing to provide future jobs to our fixed-term researchers, engineers and technicians when their contract comes to an end. As an example, 93% of our post-docs find a job when they leave our laboratory (55% of which are permanent positions).

Education

Our academic staff teaches at PharmD level and in different Master degrees : Biology (Biologie Santé) , Drug discovery (Sciences du Médicament) and Organic Chemistry (Chimie et Sciences du Vivant). Specifically we teach:

medicinal chemistry, organic chemistry, general chemistry
pharmacology, physiology
drug case studies
business models, project management
HTS, HCS
ADME/PK




VAPOUR TEMP. °C
ROTATION rpm
BÜCHI Rotavapor R-205
POWER
ROTATION
0
MAX.
2

Contacts

UMR1177 Lille Drug Discovery & Chemical Biology Unit
Médicaments et molécules pour agir sur les systèmes vivants
www.deprezlab.fr

UMR1177
Faculté de Pharmacie
3 rue du Pr Laguesse
F-59006 LILLE Cedex
France

UMR1177
Institut Pasteur de Lille
1 rue du Pr Calmette
F-59021 LILLE Cedex
France

Phone : +33.3.20.96.49.47
Fax: +33.3.20.96.47.09
Mail: u1177@univ-lille2.fr

Inserm
Institut national de la santé et de la recherche médicale

Université de Lille 2 Droit et Santé

Institut Pasteur de Lille

l'Europe s'engage en Nord-Pas-de-Calais avec le FEDER

Liberté • Égalité • Fraternité