

2013 - 2014

# Activity report

Institut  
Pasteur  
de Lille



[www.pasteur-lille.fr](http://www.pasteur-lille.fr)



# A vision for the future : The **CROSS-** **disciplinary** **research centre** on **longevity**

With its prestigious scientific legacy and discoveries which have marked its history for the past hundred and twenty years, Institut Pasteur de Lille boasts an exceptional, world-renowned concentration of transdisciplinary skills. Relying on complementary themes and its partnership positioning, it has engaged today in the construction of a major project around longevity.

This project, which provides a continuum from fundamental approaches to the patient's bedside, is oriented towards pathologies that concern us all. Mixed research teams (Institut Pasteur de Lille, Lille University, Inserm, CNRS) have joined forces around a common project, on longevity.

## Research excellence combined with a health approach to provide the best answers

Institut Pasteur de Lille today hosts a fundamental research centre divided into six units, with multidisciplinary, cross-cutting skills. It is organised around the following axes :

- Infectious, parasitic and inflammatory diseases
- Neurodegenerative diseases
- Cardiovascular diseases
- Metabolic diseases, diabetes, obesity
- Cancer
- Research for new prescription drugs

Over the past ten years, these teams have endeavoured, together with their research partners, to get structured around excellence laboratories and facilities financed as part of the PIA (investment programme for the future), including :

- a LabEx dedicated to Alzheimer disease (**DISTALZ**)
- a LabEx dedicated to studying diabetes (**EGID**)
- a research centre on infection and immunity (CIIL) involved in the **ParaFrap** LabEx
- an EquipEx dedicated to genomics (**LIGAN-PM**)
- an EquipEx dedicated to cellular imaging pharmacological screening (**ImaginEx Biomed**).

Institut Pasteur de Lille's campus boasts an exceptional concentration of high level facilities and technology platforms whose mission is to serve all the researchers in the regional scientific community.

It also features a large molecule library – The chemical library – where thousands of tests are conducted every year, helping in the discovery of new prescription drugs.

And ever since its creation, health prevention and education have been among the fundamental missions of Institut Pasteur de Lille. Its professionals mingle on a daily basis with researchers, developing reactive synergies that can thus quickly benefit the community.

## Grouping of the vital forces of Institut Pasteur de Lille around longevity

Longevity is today one of the main public health challenges all over the world. In 1900, there were ca. 100 centenarians in France. In 2014, there were 23,000. In 2060, the number will be close to 198,000. Soon, close to 25% of the population will be over 65. Living to 100 years old in good health is a real challenge for our society, that is already faced by health, economic, and political leaders worldwide. The last part of life is a major challenge for society.

Attempting to prevent dependency and preserving the independence of the elderly are key if society is to adapt to ageing. In this context, it has appeared indispensable to create regional scientific and medical dynamics capable of engaging the excellence teams and structures present in the region.

This is how in 2013-2014, a new project came into being on the campus, supported by the successful development of innovative tools and specific study models which help considering human beings from a global point of view as integrated biological systems where the mechanisms of diseases are often at work in an interrelated manner.

This common vision will strengthen the skills and tools that are already available to create a unique value chain in France : **CTRL** (*Centre Transdisciplinaire de recherche sur la Longévité*).

## Creation of CTRL, the transdisciplinary research centre on longevity

The transdisciplinary research centre on longevity (so-called CTRL) gathers research teams in a consistent and organised manner representing a major potential for development, both in terms of job grouping and creation, in the fields of fundamental and translational research, of the discovery of therapeutic drugs, and prevention and social care, economic prospects which may be developed in cooperation with our partners.

The longevity project will develop two main axes. The first axis is entitled «Age, immunity and infection». The purpose is to be able to reduce age-related infectious mortality (30% of deaths have an infectious origin after the age of 65). Researchers will focus on understanding the mechanisms of

immune-senescence and will try and improve the efficiency of vaccines for older patients. The other objectives are : the prevention of age-related comorbidities, in particular chronic respiratory infections and inflammatory

diseases frequent among older patients ; the study of the influence of age on the microbiome ; understanding the relation between chronic infections and cancers.

The second axis «Age, genes and environment» find its origin in epidemiology studies which combine health condition, genes and environment. The strategy is to compare full genomes of people with pathologies to those of healthy individuals. Candidate genes, which are in a way a sign of genetic weakness,

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are thus identified by their association to an increased risk of developing, for a given individual, a neurodegenerative disease, diabetes, a cardiovascular disease, a stroke, cancer, all these pathologies being widely represented in the Lille region.

The next step is to establish a causal link between the candidate genes thus identified and the disease thanks to experimental cellular and animal models. This strategy will help discover biomarkers and new prescription drugs thanks to the screening of molecules from our chemical library. The ultimate objective is to improve preventive care management for these diseases. It will be possible to launch prevention

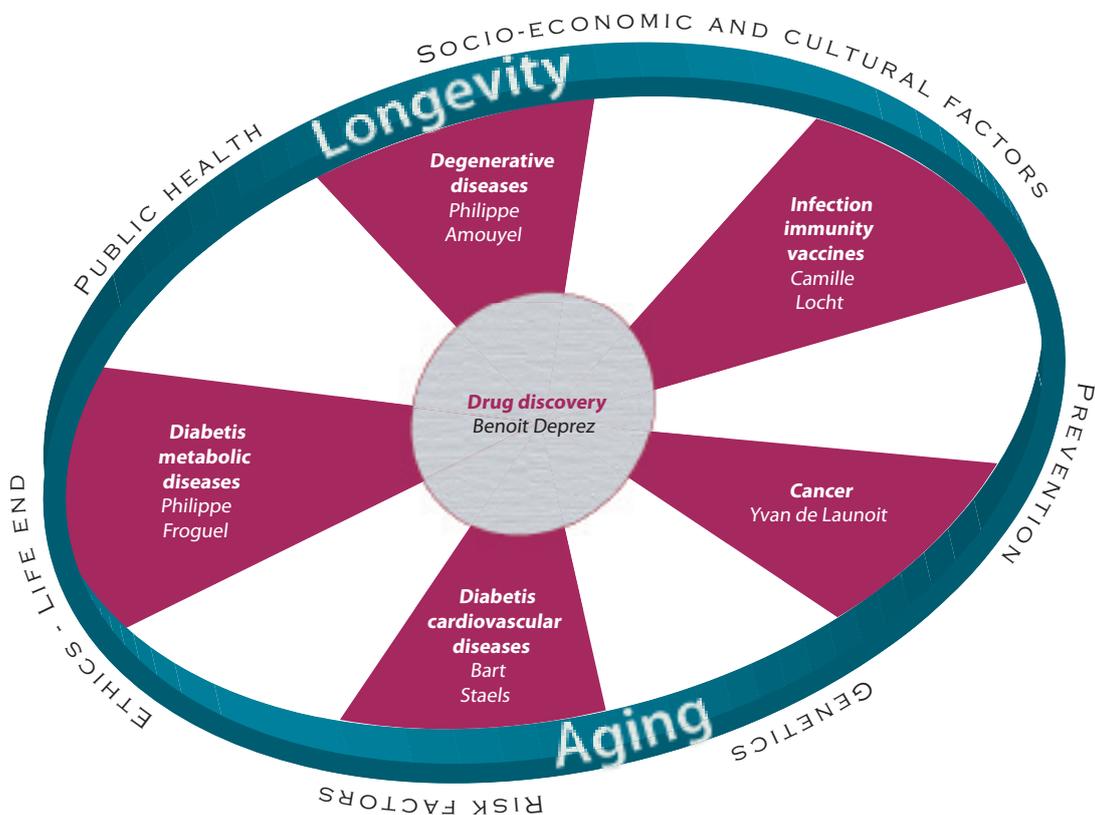
clinical trials with adapted structures on a significant number of patients. These trials will benefit from an access to populations from the health prevention and education centre, from the nutrition department, from the vaccination centre of Institut Pasteur de Lille and the clinical services of public and private hospitals.

All these activities will help develop a great number of regional cooperation programmes, in very diverse areas relating to old age and disability, including studies in human and social sciences, in Public Health, in Public Health, in health economics or in treatment education.

## CTRL : the new backbone of Institut Pasteur de Lille

In addition to the prevention age-related diseases, the priority for Institut Pasteur de Lille researchers is first and foremost to help the population stay healthy as long as possible. The creation of CTRL represents the best way to pool the vital forces of Institut Pasteur de Lille, to promote the cooperation of geneticists, clinicians, epidemiologists, microbio-logists, biochemists, immunologists... around this objective.

*CTRL through scientific excellence, the international visibility of its teams and themes, is perfectly consistent with the regional priorities and with the regional strategic guidelines for research & innovation and with the strategy of the site of Institut Pasteur de Lille.*



## II - RESEARCH



- Cardiovascular diseases and neuro-degenerative diseases
- Cancers
- Cardiovascular diseases and metabolic diseases
- Genetic and metabolic diseases
- Inflammatory, infectious and parasitic diseases
- Discovery of therapeutic drugs
- Genetic toxicology laboratory
- Microbiological safety unit
- International relations
- Technology platforms
- Promotion of research
- Scientific papers



## Discovery of therapeutic drugs : a unique potential in France

Unit led by Pr Benoit Deprez (Lille University)  
Inserm U761 - Institut Pasteur de Lille,  
Lille University (School of pharmacy)



Thanks to chemical synthesis, analysis, molecular pharmacology associated to state-of-the-art screening technology, the unit led by Pr Deprez has made the link between the discovery of the molecular mechanism at the origin of the diseases and the creation of new active principles for prescription drugs.

**B**oth a scientific contact point and a partnership with the researchers of the Egid Labex and of the infection and immunity centre in Lille, the researchers of the unit design compounds that modulate the molecular targets selected with the biologists in the team. These compounds, which must be powerful, selective and bio available, are assessed in increasing complex models, from in vitro miniaturised tests to trials in animals suffering from the pathology studied.

To discover the first « hits » on these molecular targets, the laboratory has at its disposal the biggest academic chemical library\* in Europe (80,000 different products, i.e. over 1 million single use samples) In cooperation with the biologists, the unit's researchers rebuild and miniaturise the molecular mechanism at the origin of the disease studied in order to test, quickly and at a low cost, tens of thousands of compounds, and find

among them, those that will correct the molecular defect. In 2014, the Equipex ImaginexBiomed (see p 30) equipped the laboratory with an automated screening platform that is unique in France, managed with CILL.

Thanks to progressive adjustments in the chemical structure, researchers will design more powerful and selective compounds. But these two required properties are not sufficient. The compound must also reach its target in the organism as when it is metabolized or eliminated before reaching the relevant cell, it will have no therapeutic effect. Benoît Deprez and his team have therefore modelled the natural barriers that protect our organs from foreign chemicals, in order to check, before trials in animals, that the compound, which could become a drug candidate, will be able to cross them. This unique combination of know-how in pharmacodynamics and in pharmacokinetics make it possible to

study simultaneously what the compound does to the living system and what the living system does to the compound. It is the harmony between this two phenomena that makes the future drug.

*« For example, with Alain Baulard who has worked with Camille Lochet on the treatment of extensively drug-resistant tuberculosis, we have developed antibiotic boosters (See p 31). With Bart Staels (see p 24), we have been working on intestine or pancreas cells to find products that improve the management of sugars to treat diabetes » explained Dr Deprez.*

In parallel with the discovery of new drugs, the compounds we are preparing enable us to act « surgically » on the molecular components of the cell and study specifically the biological roles of a receptor or an enzyme of interest. This approach, called « chemical biology », is complementary to

genetic approaches used by our team members. With Bart Staels and Philippe Froguel, this is how we have been studying an enzyme whose role is still poorly understood, called Insulin Degrading Enzyme.

Currently, 4 treatments are being designed or developed. Around metabolic diseases and tuberculosis. One of them has been the subject of a cooperation between Bioversys and the GSK pharmaceutical company. ■

\*collection of chemicals



## Perspective

### Apteeus, personalised solutions for rare diseases

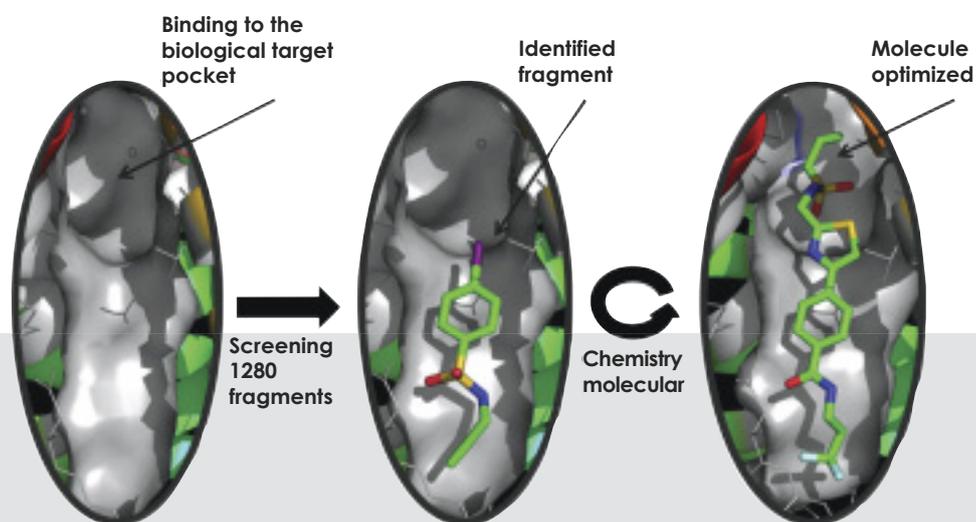
As we have seen above, and the pharmaceutical R&D process is very long, risky and costly. When it comes to rare diseases, it is unfortunately more economically viable to develop a drug de novo for each orphan disease. Dr Terence Beghyn and Pr Benoît Deprez have developed an innovative solution to individually manage patients with rare diseases.

APTEEUS offers clinicians and their patients suffering from rare diseases, a new service of clinical biology which meets at the emerging challenges of individualised medicine. APTEEUS's technology make it possible to test thousands of molecules from the existing pharmacopeia and directly on primary cells from the patient. « Within a few

days we identify the drugs that specifically correct the molecular defect of the patient and thus provide him/her with a new opportunity of treatment. »

The company focuses today on inherited metabolic diseases, and is currently using its miniaturised and automated technology on cells from patients with creatine transporter defect recruited from several centres in France. A clinical trial is scheduled for 2015.

*A start-up company stemming directly from the "Biostructure and drug discovery laboratory", APTEEUS was created in December 2013, and is currently incubated by Eurasanté, in partnership with Institut Pasteur de Lille & the Lille University.*



## Publishing

### Development of bioactive molecules through screening and fragment optimisation

The discovery of active molecules from small molecules, called fragments is an original approach developed by the drug discovery laboratory of Benoît Deprez. It relies on the individual identification through screening of molecules with less

than 18 atoms which can easily attach themselves to a selected therapeutic target in order to modify its biological function. The best fragment then identified is subsequently modified through medicinal chemistry in order to optimise its action on the desired target. At the end of these optimisation stages, the molecule meeting all the selection criteria shall then be tested *in vivo*.

*An example of this work is illustrated in an article entitled "Ligand Efficiency Driven Design of New Inhibitors of Mycobacterium tuberculosis Transcriptional Repressor EthR Using Fragment Growing, Merging, and Linking Approaches, Journal of Medicinal chemistry, 2014, 57, 4876–4888".*