From its creation, Louis Pasteur assigned three missions to our foundation: medical research, prevention of diseases and knowledge transfer. Our foundation’s ambition is to understand and prevent diseases by making science work for Public Health.

The research campus gathers 961 people, 330 of which are Institut Pasteur de Lille employees; 140 students study there (Masters and Ph.D. students, and post-docs). The foundation has contributed to the creation of a number of start-ups and hosts several companies. The research activity is conducted in partnership with Inserm, CNRS and the Lille University.

Our foundation is also a member of the wide network of Instituts Pasteur with 32 establishments scattered all over the world. This network has led to fruitful collaboration with many foreign countries.

Research on the campus of Institut Pasteur de Lille is organised in 6 main units. The themes are oriented to the pathologies which have a significant regional impact: cancer, Alzheimer disease, obesity and diabetes, cardiovascular diseases, infectious and respiratory diseases. One of the units is dedicated to discovering new therapeutically active molecules in a Drug Discovery Center.

We also have our own laboratories oriented towards genetic toxicology, environmental hazards and microbiological safety. We also host 3 Labex & 2 Equipex.

Faithful to our public health mission, we have been developing a health centre to serve vulnerable populations, which is oriented towards prevention through health checkups (~ 15,000 a year) vaccinations (~ 40,000 a year) and a Nutrition Department which includes a very active clinical studies centre. We have also taken part in a number of treatment education activities. In addition to students in research labs, we have also welcomed a great number of occupational trainees (3000).

For the years to come, our ambition is to develop a transdisciplinary research centre on longevity, which will gather all the teams working at Institut Pasteur de Lille. The emphasis will be put on preventing age-related diseases. This «longevity» project includes a first axis entitled «Age, infection and immunity», aiming at reducing age-related, infectious excess mortality (Infections are the cause of 30 % of deaths among people over 65). The purpose is to better understand the mechanisms of immune-senescence, to improve the efficiency of vaccines for older patients. The purpose is also to prevent age-related comorbidity (obstructive bronchitis and chronic inflammatory diseases), to study the influence of ageing on the microbiome, or to study the phenomena of cancerization during chronic infections. A second axis consists in identifying the genes associated with a risk to develop Alzheimer disease, cardiovascular diseases, cerebrovascular accidents, diabetes, obesity or metabolic diseases.

The «longevity» project will be able to feed on the great number of cooperation programmes with research labs in the Lille region, and also with public and private hospitals, retirement homes, economists, epidemiologists, ethicists, especially for issues related to end of life.

The foundation created by Louis Pasteur has remained faithful to its origins and works for the population of the Lille region.

Institut Pasteur de Lille is a private research foundation. It forms part of the heritage of the city of Lille. Our institution was created by Louis Pasteur himself in 1894, and has championed for over a century values such as generosity, opening up to society, sharing and scientific excellence. Albert Calmette, its first director, has shown us the way from the very origin, by fighting against infectious diseases, especially diphtheria and tuberculosis. Through relentless work, he would discover, with the help of Camille Guérin, the first effective vaccine against tuberculosis: BCG (bacillus Calmette-Guérin).

Professeur Patrick Berche
Directeur général
de l’Institut Pasteur de Lille
Partners of
Institut Pasteur de Lille

Supports
CONTENTS

L'Institut Pasteur de Lille

8 An original structure for research and health prevention
9 An institute close to the community from its creation
10 Mixed governance
11 A strategic position
12 A vision for the future: The transdisciplinary research centre on longevity

Research

16 Cardiovascular diseases and neuro-degenerative diseases
21 Cancers
24 Cardiovascular diseases and metabolic diseases
26 Genetic and metabolic diseases
29 Inflammatory, infectious and parasitic diseases
34 Discovery of therapeutic drugs
36 Genetic toxicology laboratory
37 Microbiological safety unit
38 International relations
40 Technology platforms
41 Promotion of research
42 Scientific papers
46 The biotechs of Institut Pasteur de Lille

Health

50 The Prevention and Health Education Centre
52 Medical biology laboratory
53 The nutrition Department

Dissemination of Knowledge

56 Scientific mediation and health information
58 Health education

Key Figures

60 Headcount
61 Budget - Donations and bequests
62 And…
I - L’Institut Pasteur de Lille

- An original structure for research and health prevention
- An institute close to the community from its creation
- Mixed governance
- A strategic position
- A vision for the future: The transdisciplinary research centre on longevity (so-called CTRL)
An original structure for research and health prevention

Institut Pasteur de Lille, created in 1894 by the Lille city council, is a non-profit making private foundation, declared of public interest in 1898. Its object is biomedical research, education & health promotion.

Institut Pasteur de Lille is one of four private foundations recognised in France by the French Ministry for higher education and research, the only one outside Paris, and in the international network of Instituts Pasteur (see p 38). It is financially and legally independent from Institut Pasteur in Paris.

Research excellence

With the biggest campus for biomedical research North of Paris, Institut Pasteur de Lille is located in the Lille city centre. This foundation, which is unique in France, employs 330 people, hosts 6 research units, 32 fundamental research laboratories - including three laboratories of excellence and an integrated research site on cancer-, three applied research laboratories, 9 technology platforms, including two facilities of excellence, where, across all departments, a total of 900 researchers, engineers and technicians work on the century’s major diseases: cardiovascular diseases, neurodegenerative diseases, infectious diseases and parasitoses, inflammatory diseases, metabolic diseases and cancers.

Public Health mission

Ever since its creation, health prevention and education have been among the fundamental missions of Institut Pasteur de Lille. Created over thirty years ago, the Prevention and Health Education Centre (CPES) is one of the largest health examination centres in France, it is also a public health skills platform to serve the community, public health players and health policies in the region. CPES also includes an international vaccination centre approved by the World Health Organisation.

High level training

Over 140 students are studying for their master’s degree or Ph.D. within the research teams. Every year, over 1000 occupational trainees come to Institut Pasteur de Lille to train on the following subjects: nutrition, addictive behaviours management and laboratory best practices.
An institute close to the community from its creation

The history of Institut Pasteur de Lille is emblematic of this special relationship that binds the community to this foundation.

In the late 19th century, three quarters of the planet had been wiped out by infectious diseases and penicillin hadn’t been invented yet. In 1884, a serious outbreak of diphtheria hit Lille. A former dean of the Science University in Lille, Louis Pasteur has just opened the institute that bears his name in Paris where one of his associates, Emile Roux, has developed a serum against diphtheria. A delegation of the Lille City Council went to Paris to consult with Louis Pasteur on the quickest way to get the serum to the Lille population.

Louis Pasteur proposed to create a laboratory to manufacture the serum in Lille. A laboratory, independent from Institut Pasteur in Paris, which will not only manufacture the serum, but will also conduct scientific research. This is how Institut Pasteur de Lille came into being in 1894.

Since the origin, while developing a high level scientific research, Institut Pasteur de Lille has always had a sense for serving the community, from Calmette’s antituberculosis free clinic, up to pilot activities in health prevention and education, its international vaccination service or its conferences for the general public.
Mixed governance

The Board of Directors of Institut Pasteur de Lille sees to the compliance with the foundation's fundamental values and statutes. The board defines the organisation’s strategy, its business model, and controls the implementation by the managing director.

The Board of Directors is made up of:

- **Representatives from local authorities**: The founding members (Lille City Council, Nord and Pas-de-Calais Départements), joined later by Somme, Aisne and Ardennes Départements, and more recently by the Lille region Regional Council and Métropole Européenne de Lille.

- **Representatives from the scientific and health community**: who contribute to the consistency of the foundation’s actions with its mission, among others, the Director of Institut Pasteur in Paris, the Director of the Regional Health Agency (ARS), the Lille Chief Education Officer and the Chairman of the Lille 2 University, and the Director of the Lille University Hospital.

- **joined by personalities from various backgrounds**, selected on their administrative and social, legal, financial, industrial or commercial skills for their capacity to understand the challenges of the foundation such as Préfet du Nord, the chairman of Chambre régionale des notaires (regional chamber of notaries) the chairman of Medef Nord Pas-de-Calais (Employers’ union).

There are 21 directors in total.

The **Board of Directors** is chaired ex officio by the **Mayor of Lille**. Martine Aubry has delegated this function to her fourth deputy: **Dr Jacques Richir**.

The director is a scientific personality. On 1 July 2014, **Professor Patrick Berche** was appointed **Managing Director of Institut Pasteur de Lille**, for a term of office of 6 years.
A strategic position

The Lille region’s health issues have initiated the creation and guided the scientific orientations of Institut Pasteur de Lille. The research of Institut Pasteur de Lille, on issues often more acute in a region with an industrial legacy which accumulates bad health indicators, today benefits the whole of the French population and beyond.
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 (CIIIL) 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 axis. 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,
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 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.

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.
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
Cardiovascular diseases and neurodegenerative diseases

“Public health and molecular epidemiology of age-related diseases” unit
directed by Pr Philippe Amouyel (Lille University)
UMR 744 Inserm, Institut Pasteur de Lille, Lille University

This unit studies cardiovascular diseases and neuro-degenerative diseases with an emphasis on cardiac arrests, strokes, and Alzheimer disease. Within this unit, a team is dedicated to epidemiology and the public health of cardiovascular and cerebrovascular diseases; Dr Florence Pinet (an Inserm research director) leads the «cardiovascular disease molecular determinants» team and Dr Jean-Charles Lambert (An Inserm research director), the «Neurodegenerative disease molecular determinants» team.

Cardiovascular diseases: Identifying the risks factors

Professor Philippe Amouyel’s team has developed an epidemiological research programme in order to better understand the role of cardiovascular risk factors (Genetics, excess weight, obesity, type II diabetes, high blood pressure, cholesterol, tobacco dependence...). The programme particularly focuses on studying cardiovascular diseases at a population level.
The work is relying on the records of morbidity of ischemic heart diseases and cerebrovascular accidents in Lille. Medical researchers investigate in public hospitals, emergency services and private hospitals with a cardiology or neurology department. A biological resource centre ensures the logistics and storage of biological samples and tissues.
The purpose of this studies is:
- To understand the evolution of the vascular pathology in terms of classification, management and prevention,
- To analyse the role of genetic and environmental determinants of cardiovascular diseases.
Institut Pasteur de Lille has been taking part in international studies such as MONICA (MONItoring of trends and determinants of Cardiovascular diseases), PRIME (PRospective sur l’Infarctus du MyocardE - Prospects on myocardial infarction) or EUROASPIRE (EUROpean Action on Secondary and Primary Prevention by Intervention to Reduce Events).
In addition, the research team conducts in the Lille region the Elisabet (Enquête Littoral Souffle Air Biologie Environnement - Coastal area breath air biology and environment study) study which studies the impact of pollution on the pulmonary and cardiovascular functions.
Through all these activities, researchers have been following up on the evolution of the vascular risk factors for the past 30 years, which means that the «Public health and cardiovascular disease epidemiology» team is actually a unique observatory for these diseases in France!
On the field

Three years with Elisabet

The ELISABET survey is a crosscutting study on a representative sample drawn at random from the voters list, of 1,669 residents of Métropole Européenne de Lille (MEL) and 1,607 residents of the greater Dunkirk area (CUD), aged 40 to 64. Recruitment started in January 2011 and was completed in November 2013.

During three years, it’s not Elisabet but rather Alina, Christine, Olivia or Angelina, doctors and nurses, who went and met the participants, and interviewed them at home and made a number of examinations for, before we can conduct statistical studies, we need to collect reliable results from the field.

The primary objective of the ELISABET survey is to compare the prevalence of obstructive lung disease in CUD hit by industrial pollution with that observed in MEL. The construction of the database and validation of exams were completed in late 2014. The analysis can now start.

In Lille, if we compare the results of ELISABET with the MONICA & MONA-LISA surveys, which are two population-based studies conducted in the past 15 years, researchers were in a position to confirm the decrease in the prevalence of cardiovascular risk factors, excluding obesity and physical activity among men.

Cerebral strokes in young adults: a susceptibility gene has been identified

Researchers have discovered a susceptibility gene involved in the arising of the major cause for cerebral strokes among younger subjects: the dissection of cervical arteries. "We wanted to understand why certain young individuals suffer a stroke, while this affects mainly older patients," commented Pr Amouyel.

A high number of cerebrovascular accidents affecting young adults in the 40-50 age bracket are connected to the dissection of cervical arteries. The origin of this dissection is a bleeding which occurs in the very thickness of the carotid or cerebral arteries which will "tear" the artery (hence the term dissection) without rupturing the vessel. If the vessel inflates up to the point of forming a blood clot inside the artery, the blood flow is interrupted, the brain is no longer supplied, which leads to a stroke.

In order to find susceptibility genes for this condition, researchers have set up an international consortium comparing the genomes of 2,052 patients in a total of 12 countries (10 European countries, the United States & Russia), to those of 17,064 healthy people. They demonstrated that a specific form of the PHACTR1 gene was associated to a decrease in the risk of developing a dissection of cervical arteries. The same form of the PHACTR1 gene was associated, in other studies, to a lower risk of migraines and conversely to a higher risk of myocardial infraction.

Researchers have also identified two other genes potentially connected to the risk of dissection: The LNX1 gene and the LRP1 gene, already associated with migraine and abdominal aortic aneurysm.

But for these last two genes, extra investigations shall be necessary.

"It is obviously too early to draw a practical, immediate application of this discovery in a clinical context," commented Pr Amouyel, "since, for the moment, we do not know how to prevent potential dissections, but this information allows us to better understand the mechanisms involved. In the future, we hope to be able to identify more quickly the people at risk and find solutions to prevent the major functional consequences associated with cerebral strokes in young adults."

Common variation in PHACTR1 is associated with susceptibility to cervical artery dissection, S Debette et al, Nature Genetics, Nov 2014
Detecting and preventing heart failure

Following a myocardial infarction, the left ventricle may change shape and the patient then suffers from heart failure: the heart is no longer capable of pumping enough blood to meet the body’s oxygen demand. People who suffer from heart failure get out of breath and tire more easily. The survival rate five years after the diagnosis is approximately 50%. Heart failure concerns 10% of people over 70.

When the first signs of this heart failure appear at the ultrasound exam, one year after the myocardial infarction, the condition is already irrecoverable. So when Dr Florence Pinet proposed, in the early 2000s, to the Lille University Hospital cardiologists in the unit, to “recruit” patients in order to find earlier markers of this failure, there were all for it.

An Inserm research director, Florence Pinet is a specialist in proteomics, a approach that is complementary to genomics, aiming at studying proteins, their functions and interactions inside the cell. Together with Pr Christophe Bauters of the University Hospital, she has designed a research protocol around a cohort of patients which led them to discover, in 2010, a first biological marker for left ventricular remodeling following a first myocardial infarction.

Since then, researchers have refined the antibodies to develop an assay that can be used in clinical routine and have continued to search for new markers in order to offer a blood test that can be used to measure the risk of developing heart failure through from a simple blood sample. This discovery, patented by Institut Pasteur de Lille, is of interest to the diagnosis industry and should help better adapt treatments to myocardial infarction victims, through a better selection of the people who can benefit, at the right time, from assisted circulation or a heart transplant.

Heliotropism is also in your plates

Many studies have shown that the social and economic level directly influences the quality and the balance of the diet. But researchers have demonstrated that these differences are partly reduced in the South by the positive effect of the Mediterranean diet that benefits everyone, regardless of the standard of living and level of education. In 2011, as part of the Mona-Lisa study, the French sequel to the MONICA international study, they demonstrated that, in France, the level of education had a strong positive influence on the compliance to the recommendations of the National programme for nutrition and health (so-called PNNS) in the North and North-East but not in the South-West of France where the quality of the diet was higher due to the positive effect of the Mediterranean cultural environment.

Researchers have continued their investigations at European level as part of a European study, HELENA (HEalthy Lifestyle in Europe by Nutrition in Adolescence) which analyses the interrelations between eating behaviours, physical exercise, nutritional knowledge and genetic susceptibility factors in children aged 13 to 15. Results have shown that overall teenagers from the South of Europe (Greece, Italy & Spain) eat better than those from the North (Austria, Belgium, France, Germany & Sweden), and that the influence of the level of education and the parents’ occupations on the quality and the balance of the diet is more significant in the North compared with the South of Europe which benefits from the Mediterranean environment.

On the field

Close links with clinical care

If the samplings are kept and analysed at Institut Pasteur de Lille, blood samples come from patients hospitalised in the cardiology unit of the Lille University Hospital, and from other hospitals in the region and from the Rouen University Hospital. Through four different cohorts, precious blood samples from 2,500 patients are kept in freezers and regularly analysed. In the hospital centres, doctors run a battery of tests, duly defined in the protocols, study the cardiac function with ultrasound before sending the blood samples corresponding to the phenotypes of the patients required. Today, no less than five cardiologists work in the team that hosts in addition, every year, one or two 2nd year Masters’ medical students.

Alzheimer disease: The genetic lead

Alzheimer disease is a so-called neuro-degenerative brain pathology, this means that it causes the progressive disappearance of neurones. Two main lesions progressively invade the brain and cause the death of the nerve cells:

- senile plaques or neuritic plaques
- neurofibrillary degeneration

This is a deposit, outside the neurones, of the ß-amyloid protein,

which is an aggregate of another protein, the Tau protein, under the form of abnormal filaments inside the very neurones.

The lesions caused in the brain by Alzheimer disease remain silent for a long time, and then cause detectable signs as they spread and impact areas that are important to the brain function. So that when clinical signs appear, the disease has already damaged the brain quite often for over ten years.

For research to progress, we need to find markers that will allow us to identify the disease as soon as possible, before the first signs, which will be clinically detectable only five or ten years later. Current research focus on three types of markers: cerebral markers that can be detected with imaging, blood markers and genetic markers.

Jean-Charles Lambert’s team has successfully focused at Institut Pasteur de Lille. It has contributed to the discovery of nearly all genes known for their susceptibility to the disease.


11 new factors of genetic susceptibility in 2013

Between 1990 and 2010, only 10 genes were identified. To speed up the pace of discoveries, 4 major international research centres have coordinated their efforts around the IGAP (International Genomics of Alzheimer’s Project), launched in 2010, and screened the genomes of several thousand patients and healthy people in Europe and North America. Over 7 million mutations in total have been analysed, and, by the end of 2013, 11 new genes involved in the molecular mechanisms at the origin of the disease were thus isolated, bringing the total to 21. «As we speak, we only know half of the genetic component. The full sequencing of patients and controls will allow us to map out in details the genetic determinants of Alzheimer », believes Philippe Amouyel. The knowledge of these genes is precious to better understand the events leading up to the destruction of the nerve cells and to the loss of the intellectual functions which characterise this disease.

Currently, about 100 molecules are being tested but the topic remains complex, as Alzheimer disease activates several mechanisms which interact with the environment to enhance or inhibit the development of the disease: «We are interested by the brain, the most complicated organ in the human body» commented Pr Amouyel.

Institut Pasteur de Lille has set up a Fly Lab since 2012 where can be observed, in the eyes of vinegar flies, the effect of genetic modifications involved in Alzheimer disease. It is indeed possible to observe in the eyes of these small genetically modified insects the toxicity of the proteins involved in cerebral degeneration: Tau protein and amyloid protein. 75% of the neuronal genes of these vinegar flies have homologues in human beings and as Men, vinegar flies can memorise events in the short and long term. «Geneticists identify genetic markers associated with the disease, while we intervene later to check whether, by manipulating these genes, we can have an effect, whether positive or negative, on the toxicity of the Tau protein» explains Dr Bart Dermaut, in charge of the Fly Lab (Inserm Excellence Chair - Lille University). And thanks to the observation of the eyes of these little flies under microscope, the team led by Jean-Charles Lambert was able to prove the connection between the variation in the BIN 1 gene, which it contributed to identify in 2010, with a Dutch American team, and the Tau protein. Researchers hope to be able to demonstrate that by reducing the quantity of the protein produced by BIN1 in the brain, we will be able to reduce the toxicity of the Tau protein and thus prevent the formation of the lesions. Which would present an interesting new therapeutic approach since so far, 95% of the drugs developed, -without real success up to now- deal with the amyloid cascade, the other process coming into play in nerve cells degeneration.

Distalz was granted funds in February 2012 during the second wave of the «excellence laboratories» (so-called Labex) request for projects, as part of the «Investment programme for the future» financed by a national loan scheme (known as «Le Grand Emprunt»). A multi-site laboratory coordinated by Pr Philippe Amouyel, DISTALZ (Development of innovating strategies for a transdisciplinary approach to Alzheimer disease) has concentrated its efforts on the 10 to 15-year period when the disease remains «hidden».

DISTALZ is a group of 7 research units of the highest international level (5 located in the greater Lille area ; 1 in Paris, 1 in Nice). 110 researchers coming from a great number of disciplines have joined forces to speed up the discovery of bio-markers and therapeutic targets, as well as the transfer of innovating solutions to treat this disease. These go beyond the medical sphere by addressing the ethical and social aspects generated by the detection and the care management of this scourge.

While teams and technology platforms have been strengthened, a European-scale training programme has been designed as a complement to this approach. In addition to making emerge a top research programme that is legible nationally and internationally, this project also shows the excellence of the region and the federating role of our Institut around this disease. The close co-operation programmes with Université de Lille, Université de Nice Sophia Antipolis, Université de Paris-Sud, Lille University Hospital and AP-HP, Inserm and CNRS are as many assets to overcome the disease.
Scientific cancer research on the Institut Pasteur de Lille campus is conducted by six research teams. Since the discovery of the first genes of cancer, the oncogenes, in Lille, researchers have attempted to identify the molecular mechanisms through which a normal cell becomes a tumoral and eventually metastatic cell.

From a biological point of view, cancer results from the onset of a dysfunction in certain cells in the body. These start to multiply anarchically and grow out of control, first locally, and then in the surrounding tissue, and eventually at a distance where they form what is referred to as metastasis.

"There are nearly as many different cancers as there are patients. Each tumour is associated to a different molecular mechanism. There is no longer breast cancer but a dozen diseases which are taken care of based on their own characteristics and those of the patient. For 15 years now, targeted therapy has been a reality, a reality that we try to improve every day" noted Yvan de Launoit.

With this in mind, his teams focus more specifically on the blood network specific to cancer cells to find a way to starve them while continuing to feed healthy cells. They have also studied the role of receptors, including the Met receptor, which regulate at the surface of the cells, their survival, growth and migration. The deregulation of the Met receptor is responsible for the most deadly cancers (lung, colon, aerodigestive tract) and is revealed by the presence of fragments of the Met receptor, called soluble Met. If we manage to detect the soluble Met fragment, the patient will be able to benefit from a treatment targeting only this fragment to limit collateral damage.

Researchers also observe how the cells of the immune system those that are in charge of defending our body against aggression, are capable of identifying and then destroying newly appeared cancer cells, more particularly in liver cancers. They try and understand why normal cells change to cancer cells during aging (in skin cancers) and including how to detect and fight metastases in prostate cancers. They try to decipher the mechanisms of tumour dormancy which allow cancer cells to leave the primary tumour to lodge themselves in new organs and remain dormant there, sometimes for many years before waking up. ■
From the lab to practical applications

**Innobiochips** make solutions for miniature biological analysis and diagnosis: peptide and protein biochips which allow to perform several dozen simultaneous analyses from a reduced biological sample. This start-up company, founded in 2008, relies on the know-how and skills developed by the «cancer chemistry and biology» laboratory, led by Dr Oleg Melnyk, a Research Director at CNRS. The company offers a range of made-to-measure services: peptides synthesis, anti-body characterization, multiplex protein assays and other custom analyses. These biochips enable for example researchers who work on small animals or from collections of high-value samples, to retrieve a maximum of information from a small sample. Innobiochips is also present on the market of miniature diagnosis: thanks to its biochips it is possible to retrieve in a single operation, several dozens of different pieces of information and therefore obtain a comprehensive diagnosis in one single analysis.

Another product of research in the cancer chemistry and biology laboratory X’ProChem has been marketing since 2012 an innovative technology: protein synthesis from a chemical reaction. These 100% chemical properties are custom-made to meet requirements that classic recombining methods cannot synthesise, such as toxic, membrane proteins or proteins equipped with a probe so it can be traced in cellular imaging.

It received an award in July 2014 as part of the 2014 national competition for the creation of innovative technology companies, in the «emerging» category. **EAT Cell Biotech** proposes to assess ex-vivo and in-vivo the impact of a new drug candidate on the immune system in general and on Tregs in particular, this special population of white blood cells that maintain the right balance in our immune system so it can protect our organism against aggressions, without making us sicker than the aggression itself would. Know-how stemming from the research led in the «Immunoregulation of virus-induced cancers» laboratory by Dr Nadira Delhem, a lecturer at the Lille University. «Several clinical trials for the treatment of cancer had to be stopped in phase 2 or 3 because they boosted the lymphocytes T-reg. We have developed a method-ology that helps us assess ex-vivo and in-vivo the impact of a new drug candidate» explained Dr Delhem. This fledging company is incubated by CNRS, EuraSanté and Institut Pasteur de Lille.

---

**Perspective**

**An integrated research site on cancer**

A member of cancéropôle Nord-ouest, the «Tumourigenesis mechanisms and targeted therapy» unit has also been a stakeholder, since its labelling in October 2012 by Institut national du cancer (INCa), of the new integrated research site on cancer (SIRIC) : ONCOLille.

Under the coordination of Pr Eric Lartigau, scientific director of Centre Oscar Lambret, ONCOLille gathers the Lille players in fundamental and clinical cancer research: 18 laboratories, over 300 researchers who join forces from investigations at the heart of cells up to applied research through human and social sciences.

The two key areas of work for ONCOLille are:
- The resistance of the tumour and its host to local/regional treatment.
- Dormancy and persistence of the tumour after treatment.

This research revolves around four technology platforms: clinical research, animal models, imaging and biology. This latter platform is coordinated by Yvan de Launoit, director of the Lille Institut de Biologie (CNRS) located on the campus of the Institut Pasteur de Lille site.
All cells, including cancer cells, produce small vesicles, called exosomes which have the capacity of transporting part of the cell material. On the Institut Pasteur de Lille campus, a research team coordinated by Dr Nadira Delhem, a lecturer at the Lille University, focused more specifically on the role of these cancer exosomes in nasopharyngeal carcinomas (NPC). The team has demonstrated that these are actually tumour boosters. In addition, the team has obtained very promising results, which prove the efficacy of a treatment capable of targeting and neutralising these exosomes.

Nasopharyngeal carcinoma is a cancer of the upper respiratory and gastro-intestinal apparatus associated to 100% of cases of infection by the Epstein Barr virus. CNP is the third human cancer most frequently associated with a viral infection, after liver cancer, and cervical cancer. Currently, CNPs is inoperable when diagnosed. These can only be treated with radiotherapy possibly combined with chemotherapy. Unfortunately, all of these treatments show limited efficacy and have significant side effects. Hence the importance of finding alternative therapeutic measures.

NPCs, like most other virus induced cancers, are paradoxical tumours for, in spite of the massive presence of leucocytes, (Immune system cells that ensure the defence of the organism), they develop very quickly. Researchers have therefore tried to find the cause of this virulence and have managed to highlight the « evil » role of exosomes.

They have demonstrated that NPC cells cultured in vitro released large quantities of exosomes. These exosomes have a three-way action:

- they interact with healthy cells to change them into tumoural cells and help the cancer grow,
- they multiply the T-Regs exponentially and recruit them massively. T-Regs are “suppressor” cells for our immune system, preventing it from efficiently fighting cancer, for example,
- and they even change T lymphocytes, the « good little soldiers » of our immune system, into T-Regs.

The effect all of these various modes of action is to limit the immune response of the organism, thus allowing cancer and opportunistic infections to develop more quickly.

After identifying these mechanisms, the scientists have succeeded in synthesizing a drug candidate capable of attaching itself onto the exosomes of CNP and neutralising them. Incidentally, a patent was applied for, for this therapeutic tool in June 2014. The proof of concept has now been provided. However, before any clinical trial on humans, the efficacy of this treatment shall have to be confirmed by new laboratory tests.

**Cardiovascular diseases and metabolic diseases: hypercholesterolemia, cardiovascular complications**

"Nuclear receptors, cardiovascular diseases and diabetes"

A unit led by Pr Bart Staels (Lille University)
Unité Inserm U 1011 - Institut Pasteur de Lille

Research in Pr Bart Staels’ team (Lille University) is oriented to molecular pharmacology of diabetes and its cardiovascular complications. The unit particularly focuses on the regulation of the genes involved in these pathologies and the consequences of their deregulation with a specific interest for nuclear receptors which represent potential therapeutic targets, using functional genomic and molecular pharmacology techniques.

Nuclear receptors are proteins which act on the genes. When the expression or the function of these receptors is altered, the genes are modified and diseases such as the metabolic syndrome, obesity or high blood pressure can develop. Bart Staels’s team has been trying to propose a therapeutic approach to modify or counter these alterations, by working particularly on the nuclear receptors of the peroxysomes proliferator-activated receptors (PPARα) family involved in the metabolic control and inflammation, of FXR, the receptor of bile acids which also plays its role in the way our body metabolise glucose; and finally Rev-erb and ROR that have a role in the way our biological clock works. Finally, the team has been working on intestinal hormones which trigger the secretion of insulin in response to the ingestion of a meal.

The immune system plays an important role in the triggering and the chronicity of cardiovascular diseases. If the link between inflammation and atherosclerosis (accumulation of bad cholesterol in the blood vessels) has been known for a long time, it has been established much more recently for type 2 diabetes, obesity or the metabolic syndrome. This is why David Dombrowicz (Inserm Research Director), has studied the evolution of immune cells, lymphocytes and mastocytes (cells typically involved in allergic reactions) in cardiovascular diseases in order to find out whether all or part of these cells could be therapeutic targets.

Giulia Chinetti (Inserm Research Director), has been concentrating on the macrophages, the «grave digging» white cells which are capable of destroying damaged cells and foreign bodies but become deregulated in the adipose tissue in obese patients or in the vascular wall in case of atherosclerosis. In cooperation with Pr Brigitte Jude and Pr François Pattou’s teams from the Lille University Hospital, the team has studied the macrophages coming from atheromatous plaque from patients operated for atheromatous carotid stenosis or visceral adipose tissue extracted during obesity surgery, in order to propose a therapeutic approach to modify or counter this accumulation of macrophages in the tissue as well as to regulate their function.

Philippe Lefebvre (Inserm Research Director), has studied the modifications, induced by metabolic diseases of the action mechanisms of the nuclear receptors and the way...
these proteins regulate metabolism. This type of approach helps better understand the mechanisms at play inside the cells, find new therapeutic targets there, and better predict and/or limit the side-effects of molecules that may interact with these targets.

Boosting the respiratory capacities of muscles

There are two types of muscles: the muscles used for sustained efforts (as for a marathon) and those used for intense, short duration efforts (as for a sprint). Researchers have focused on the first type, which uses as a priority the oxidation of fatty acids to produce the energy the muscles require for contraction. These are specifically very rich in mitochondria, these small cellular structures that produce energy by consuming oxygen. Researchers have found that Rev-erb-a, a protein, has some control on the activity of mitochondria within the muscle. « Mice with a deficiency in Rev-erb-a cannot raise their oxygen consumption during physical exercise and are incapable of sustaining a prolonged effort » explained Hélène Duez. Their mitochondria are abnormal. Conversely, mice who have an overexpressed Rev-erb-a gene, see their performance improving in endurance exercises.

Rev-erb-a modulates the quantity of mitochondria in the muscle and their efficacy, i.e. the quantity of oxygen consumed to produce the energy required for muscle contraction. « If we give deficient mice the molecule that help activating Rev-erb-a, this provokes changes similar to those induced by training for athletes. We can say that this molecule creates a molecular signature similar to that of training programmes » explained Hélène Duez.

The results of this study will help, for example, develop new therapeutic strategies in the treatment for example of myopathy where the muscle function is impaired. In the longer term, researchers hope that Rev-erb-a could for example help re-synchronise the biological clock, which is often disturbed among type 2 diabetes patients, by promoting ways usually activated by exercising.

Rev-erb-a modulates skeletal muscle oxidative capacity by regulating mitochondrial biogenesis and autophagy.

Estelle Woldt & Al, Nature Medicine, July 2013
Genetic and metabolic diseases: diabetes and obesity…

Genomics and metabolic diseases
unit led by Pr Philippe Froguel (Lille University)
CNRS UMR 8199 - Institut Pasteur de Lille - Lille University

Common genetic mutations however only explain 20% of the diseases. So researchers are looking at rarer mutations that only affect a very small percentage of the population but increase exponentially the risks of developing certain diseases. Thanks to the very high-throughput human genomic platform, that is unique in France, and their genetics expertise, Pr Philippe Froguel’s team (Lille University) was the first one to identify the genes responsible for type 2 diabetes and obesity.

"I worked on obesity because 80% of obese patients have diabetes and because I thought that the genetics of obesity would help us make progress in diabetes genetics but at the end of the day, genetics have described other processes. What we know of genetics today enables us to better understand diseases. But for healthy people, genetics cannot predict anything" warns Pr Froguel. "To know your health future, sequencing your genome, as some companies on the web may offer, is about as reliable as reading your horoscope."

After having explored genetics, Pr Froguel’s team has oriented part of its research to epigenetics. Epigenetics study changes in the way genes work that are not caused by changes in the DNA sequence. These are changes that appear mainly during the foetal period. Epigenetics, is the short term adaptation of the genetic material to its environment. This is fundamental as it enables us to read the genetic code differently. It explains, for example, the differences that exist with identical twins. To conduct these studies, researchers use modelling in stem cells, in the wake of previous successful researches for certain types of cancer. Philippe Froguel’s team have cultured stem cells from pancreatic cells and fat tissue from diabetes patients to test drugs.

When all these genetic and epigenetic anomalies are clearly identified, the scientists hope to be able to propose preventive actions and individual care, for true personalised medicine."
Pr Froguel and Pr Staels joined forces with Pr Pattou from the Lille University Hospital in 2009 to create the European Genomic Institute For Diabetes (Egid). Egid is the leading research institute dedicated to diabetes in France with part of the teams working from Institut Pasteur de Lille. In 2011, it obtained the LabEx label (excellence laboratory) as part of the first wave of the French «Investment Programme for the Future» financed by a national loan scheme (known as «le Grand Emprunt»).

Egid is the association of three world-renowned, excellence groups in genomics and molecular pharmacology and a surgical team specialising in obesity and diabetes biotherapy. The synergy between the teams helps make progress in the identification of the risk factors for the various types of diabetes, better understand the mechanisms underlying the onset and the worsening of the disease, and in fine improve patient care management.

The complementarity of the genetic, pharmacological and clinical approaches is at the core of this project which gathers today over 150 researchers with a target of 250 in 2020.

On 12th September 2014, the foundation stone of the Egid building was laid on the Lille University Hospital site. If most researchers will work in the new building, Pr Froguel & Staels’ teams will continue to be part of Institut Pasteur de Lille and part of the team members will remain on site. Pr Philippe Froguel is at the helm of the LabEx.

Préparation de l’échantillon d’ADN avant séquençage

This could explain the increased risk of cancer for certain diabetes patients

Certain chromosome abnormalities are particularly frequent among type 2 diabetes patients who develop vascular complications in their eyes (retinopathy), kidneys (nephropathy) or hearts. This discovery could, in part, explain the excess mortality from cancer for these patients.

One diabetes patient out of three develop vascular or nervous complications. In 2012, other studies demonstrated that «chromosomal clonal mosaic events» (CMEs) appear in the DNA of ageing blood cells. Type 2 diabetes is also known to accelerate the ageing process.

Researchers have been wondering if the disease could not cause, as old-age does, the appearing of chromosome abnormalities of the CME type in blood cells. Results: Patients with CMEs are 4 times more frequent among diabetes patients.

In addition, scientists have demonstrated that diabetes patient with CMEs develop a more severe form of the disease compared with others, with vascular complications. «The presence of certain chromosome abnormalities of the CME type could, in part, explain the high frequency of cancers among Type 2 diabetes patients» assessed Philippe Froguel, who is already considering the clinical development of this discovery: «A genetic analysis of CMEs could be offered to patients suffering from severe diabetes to detect potential pre-cancer conditions.»

Association between large detectable clonal mosaicism and type 2 diabetes with vascular complications.

Amélie Bonnefond & Al, Nature Genetics. 14 juillet 2013

Publishing
For 6 years now, Bertrand and his family have been supporting the study on diabetes by joining the cohort of «200 families against diabetes». A good decision indeed, for the discoveries of researchers have changed the daily life of his eldest daughter. «In my family, diabetes is passed down from one generation to the next. My great-grand-father, my grand-father and my mother have all had it. I suffer diabetes myself since the age of 13.» As Bertrand is tall and slender, with diabetes starting in his teens and on which the most common medication had little effect... The least we can say is that Bertrand is not your typical diabetes patient. «I was a mystery, including for my endocrinologist, but even if the medication could not fully stabilise me, I could live a normal life.» When, at the age of 16, his eldest daughter is diagnosed overnight with a 3-g diabetes, and has to get two injections of insulin a day, Bertrand thought this mystery may well interest Science. «I had been asked to take part in the cohort, but never accepted. But then, I thought that if the work done on our blood and our DNA could one day prevent other children from having as hard a time as my daughter, it had to be done.» What a surprise it was for Bertrand when researchers called him, in the summer of 2012, to tell him that they had identified his type of diabetes, MODY 13, a form of diabetes with only five recorded occurrences in the world to date. And above all, that its mechanisms of action were known and that an old drug may be more effective for this form of diabetes than all the therapies tested up to now. «We are reborn. Since I changed drug, my rate of glycosylated hemoglobin has been the same as a non-diabetes person and I feel much better. For my daughter, the change is even more dramatic. It was an ordeal with insulin not working properly. In less than a month, she could live a normal life again.»

Weight gain : something to do with your saliva ?

Doctor, I don’t eat more than others but everything I eat makes me put on weight. Why? An international team coordinated by Professor Philippe Froguel may have found an explanation to this capacity to put on weight. «We had no preconceived idea », adds Pr Froguel, « but we have highlighted marked differences in the region of chromosome 1 : salivary amylase. Instead of having only two copies of this gene (One from the father and one from the mother) the number of copies varies from 1 to 20 and the less you have, the heavier you are. » In addition, the quantity of copies of salivary amylase has a direct effect on the intestinal flora. We have observed a direct correlation between a low rate of salivary amylase and the development of certain bacteria that can be found in great quantities in the intestine of obese children or adult with nonalcoholic steatohepatitis (NASH).

If this discovery, that can be easily transposed in a mere salivary test, opens new leads for researchers, it doesn’t provide them with immediate solutions in the treatment of obesity. Should we adapt the doses of slow sugar in the alimentary bolus depending on the rate of salivary amylase? It is too early to tell. But these works have unveiled a weight gain process in which the role of saliva and of the intestinal flora have been clearly identified. Low copy number of the salivary amylase gene predisposes to obesity. Mario Falchi & Al. Nature Genetics, 30 mars 2014
Inflammatory, infectious and parasitic diseases

Lille infection and immunology centre (CIIL)
A unit led by Dr Camille Locht (Inserm Research Director)
Unité Inserm U 1019, CNRS UMR 8204, Institut Pasteur de Lille, Lille University

Understanding infection and immunity, including the deregulation of the immune system, requires multidisciplinary, integrated approaches. These global approaches have been developed within the Lille infection and immunology centre (CIIL), the biggest research unit set up at Institut Pasteur de Lille with 15 complementary teams.

Part of Pasteur’s «legacy», bacterial and parasitic infections, as well as inflammatory diseases, are still today major causes of morbidity and mortality, killing every year over 14 million people throughout the world. And this is only the tip of the iceberg, as the morbidity and long-term impact of these infections on other conditions, such as chronic inflammatory diseases, cancers, cardiovascular and neurodegenerative diseases, are considerably higher.

A centre coordinated by Dr Camille Locht (Inserm Research Director), who has discovered a booster vaccine against tuberculosis and a nasal spray vaccine against whooping cough, CIIL is made up of 15 research teams who interact with one another, as well as with many other laboratories throughout the world. These teams today gather over 200 researchers, engineers and technicians with complementary expertise who cover a wide spectrum of disciplines, including molecular epidemiology, virology, molecular and cellular bacteriology and parasitology, up to the immunological base of infectious and non-infectious diseases and to the development of clinical applications.

In concrete terms, the scientists are looking for a treatment against tuberculosis and particularly extensively drug-resistant TB, type C hepatitis, malaria, bilharziasis, plague, toxoplasmosis, whooping cough, inflammatory diseases, whether intestinal or pulmonary (Asthma, respiratory allergies, chronic bronchitis). The 15 teams are divided in three major fields: parasitology, molecular and cellular microbiology, immunity and inflammation.
As far as parasitology is concerned, research is concentrating on *Toxoplasma gondii*, agent of toxoplasmosis, *Plasmodium*, agent of malaria, schistosoma, agent of bilharziasis or certain intestinal parasites.

Toxoplasmosis is a harmless condition in the overwhelming majority of cases that presents major risks for foetuses and patients with a weaker immune defence system. The *Toxoplasma gondii* can remain dormant for years while forming cysts in the brain. When the cysts awaken, they provoke serious lesions: meningoencephalitis, loss of sight, partial paralysis, tremor, or coma. « We are trying to identify the genes responsible for this encystment » explained Stanislas Tomavo (CNRS Research Director). The specificity of toxoplasma is to be half animal half vegetable, but it isn’t the only parasite like this. This is also the case for other apicomplexa parasites such as *Plasmodium*, the agent responsible for malaria, or *Cryptosporidium* which causes crypto-sporidiosis, a disease of the intestinal tract. « By looking for similarities between these parasites and the vegetal world, we are trying to manipulate the toxoplasma’s genes. If we succeed, discoveries could be transposed to other apicomplexa parasites » points out Dr Tomavo.

No less than two teams are attempting to unravel the mysteries of malaria. The team led by Raymond Pierce (CNRS Research Director), has been studying the molecular process underlying the development and the reproduction of parasites in order to identify new therapeutic targets. « We are focusing on the signalling pathways and the transcription of the genes that control the growth and the reproduction of parasites » added Dr Pierce.

The team around Sylviane Pied (CNRS Research Director), has focussed on the immune response to a primary infection by *Plasmodium falciparum*, the parasite responsible for malaria. These studies combine fundamental research and clinical research in cohorts of African or Indian patients. Field research has been conducted thanks to a collaboration network, including in Gabon and India. This integrated approach should allow researchers to better understand the host-pathogen relationship and identify new vaccine and/or therapeutic targets.

In Sylviane Pied’s team, Gilles Riveau (CNRS Research Director), has been working on the malaria-bilharziasis co-infection in order to understand the specific immune reaction of people confronted simultaneously to both parasitosis. On the African field, Gilles Riveau has been directing a structure called Espoir pour la santé (Hope for health) which combines research in immuno-epidemiology of bilharziasis and malaria and clinical trials. It is in this centre that was completed in 2012 the third phase of clinical trials (efficacy phase) of Bilhvax, a paediatric vaccine candidate against bilharziasis. This clinical trials phase was entirely conducted with public funding, including strong support from the Lille region. The first results, analysed in 2013 and 2014, showed good tolerance of the product but its efficacy remains to be improved.

Finally, the biology and diversity of emerging eukaryotic pathogens team led by Eric Viscogliosi (CNRS Research Director), has studied many parasites lesser-known by the general public. Past work include recommendations for professional of the fishing industry on fish parasites (ANR Fish-Parasites, 2010-2013, research programme followed by the original programme: ABC Fish in 2014). The team has also worked and will continue to focus its efforts in the years to come on the study of intestinal parasites such as the *blastocystis* protozoan, responsible for skin breakdown and digestive disorders including the irritable bowel syndrome or *Cryptosporidium* involved in the development of cancers of the digestive tract.

**Perspective**

19 French teams, including two located at Institut Pasteur de Lille, respectively coordinated by Stan Tomavo & Sylviane Pied, have been taking part in ParaFrap, the French alliance against parasitic diseases, an excellence laboratory (LabEx) approved in October 2012 and codirected by Stan Tomavo with Artur Scerf (CNRS, Institut Pasteur) and Fréderic Bringaud (CNRS, Bordeaux Segalen university).

ParaFrap gathers the best of parasitic research in France on malaria, sleeping sickness, toxoplasmosis, leishmaniases, theileriosis and amoebiases. This LabEx offers the advantage of working in close partnership with the countries where these diseases are endemic allowing Ph.D. students from these countries to come and complete their training in the ParaFrap teams.
The **molecular microbiology** teams, work on bacterial respiratory infections (Tuberculosis and whooping cough), type C hepatitis, MERS-Cov or even plague.

For over 20 years, Camille Locht and his team have been analysing the mechanisms of the development of whooping cough and tuberculosis, from molecular research up to therapeutic or prophylactic applications. «We have been trying to understand the mechanisms induced by these germs that make people sick in order to improve the efficacy of vaccines, and find new antibiotics and new diagnoses» explained Dr Locht.

For tuberculosis, the Lille researchers are working on the development of a booster vaccine which could help extend the efficacy of the initial BCG. This vaccine candidate should soon be tested on humans and could also turn out to be an excellent diagnosis test to screen healthy carriers. As far as treatments are concerned, researchers have found, in cooperation with Benoit Deprez’s «biostructure and drug discovery laboratory», how to make the tuberculosis bacillus more sensitive to antibiotic treatments.

As for whooping cough, the team has worked on the development of a nasal spray vaccine which should make it possible to vaccinate young children at birth (see page 32).

The young team led by **Priscille Brodin**, (Inserm Research Director), has studied the intra-cellular chemical genomics of mycobacteria, thanks to a unique high-throughput imaging system. They have just made an important discovery concerning Buruli ulcer (See opposite) but have mainly focused on *Mycobacterium tuberculosis*, the agent of tuberculosis. They have identified new inhibitors to the bacillus of tuberculosis inside the host cells, which could be used as a base for new drugs and have studied the biological markers of the reactivation of latent tuberculosis.

The genomics technology platform coordinated by **Yves Lemoine**, a professor at the Lille University, has...
also developed a research programme on the study of the virulence regulation of Bordetella pertussis (The agent responsible for whooping cough).

The team led by Jean Dubuisson (CNRS Research Director), have studied the biology of the virus of type C hepatitis. They have tried to understand how the virus enters the liver’s cells and develop there. «We have shown that the sugars present in the viral envelope contribute to reducing the recognition of the virus by the immune system. We have also participated in the characterization of the cellular protein involved in the penetration of the virus. Finally, we have identified and characterised the inhibitors of this virus» explained Dr Dubuisson. In 2013, Dr Anne Goffard, a clinical virologist and lecturer at the Lille University, joined this team to try and characterise MERS-CoV, the coronavirus that is very deadly in the Arabian Peninsula.

The team led by Florent Sebbane (Inserm Research Fellow) have reproduced the mechanism of the infection in laboratory in order to better understand the molecular mechanisms underlying the spread of the plague. More particularly, they have tried to identify the genes that help the bacteria be more efficiently transmitted by the flea as well as those responsible for the disease in mammals.

A structure coordinated by Frank Lafont (CNRS Research Director), the «Laboratory for cellular microbiology in the cell-pathogen interface» has studied, using a panel of imaging techniques that is unique in Europe, the future of the cells and their reaction to infection in order to identify the common mechanisms to respond to an attack and the mechanisms specific to each pathogen. «Our work is complementary to genetic research. We try and understand how pathogenic bacteria, bacterial toxins or parasites enter the cell in order to identify cellular targets to create new therapeutic tools» explained Dr Lafont.

Successful trials in humans for the nasal spray vaccine against whooping cough

The candidate vaccine developed by Dr Camille Loch’s team is a strain of genetically attenuated, Bordetella pertussis, the agent of whooping cough, formulated into a totally pain-free nasal spray. «This type of vaccine offers the double advantage of being cheaper to produce than so-called second generation, injectable vaccines, that developing countries cannot afford, and of being adapted for very young children. For even in Western countries where the vaccination coverage is excellent, infants cannot be immunised before they are 2 to 6-month old» explained Dr Loch. In order to develop the formula of the nasal spray and test this candidate vaccine, Camille Loch has steered CHILD-INNOVAC, a European research consortium. The vaccine was developed in Lille, produced by a bio-technology company in Belgium and the clinical trials were conducted in Sweden.

In total, 10 European partners have worked on this program that has also tested the possibility to combine, in a single nasal spray vaccine, protection against several pathogens. Researchers have provided the proof of concept of the efficacy of a vaccine that combines protection against whooping cough and the respiratory syncytial virus (a virus that triggers bronchiolitis in infants). The first success of this European project was to develop a vaccine whose harmlessness could be tested in humans within 2½ years (Against 5 to 7 years for most projects of this type).

The vaccine has no side effects, even at a high dose. Additionally, in all subjects for whom the vaccine worked, immune responses were triggered. The next step will consist in administering higher volumes to try and increase the efficacy rate in the mucous membrane of nose and sinus and improve the stability of the vaccine over time, with the objective of a future industrial development.

A phase I clinical study of a live attenuated Bordetella pertussis vaccine - BPZE1; A single centre, double-blind, placebo-controlled, dose-escalating study of BPZE1 given intranasally to healthy adult male volunteers, Rigmor Thorstensson & al. Plos One janvier 2014

Perspective

An award-winning structure in January 2011 as part of the first wave of equipment for the future, ImaginEx BioMed (excellence imaging in biomedicine) offers a continuum of techniques on a single platform that includes chemists, biologists and bioinformaticians. This platform is directed by Dr Frank Lafont (CNRS Research Director) and helps identify new therapeutic targets and develop at a faster pace drugs whose action on many pathologies (Alzheimer, diabetes, infectious diseases) can be tested simultaneously. The ImaginEx BioMed structure uses facilities mainly located at Institut Pasteur de Lille but also in Villeneuve d’Ascq and the hospital sites of the Lille University, in partnership with Inserm & CNRS. It is managed by Communauté d’Universités et d’Etablissements Lille Nord de France.
Six teams have been working more specifically on immunity and inflammation issues, both in the pulmonary and intestinal fields.

The team of pulmonologists led by Anne Tsicopoulos (Inserm Research Director), has been trying to better understand the mechanisms at play in asthma at the level of the tissue inflammatory cells and of the lymphocytes (the leucocytes involved in immunity). The researchers have been analysing how the cells and their mediators orchestrate the inflammatory reaction and tissue remodelling, in order to find new therapeutic targets.

The team led by François Trottein (CNRS Research Director), has been focussing on two pathogenic agents of considerable clinical importance: the flu virus (virus influenza A) and Streptococcus pneumoniae (pneumococcus). Its first objective is to identify the early immune mechanisms triggered during an infection by the flu and pneumococcus. In addition, it has been trying to define the cellular and molecular factors of the host creating a predisposition for secondary bacterial infections following a flu infection, chronic obstructive pulmonary disease (COPD) and during obesity. Finally, the laboratory has developed new therapeutic strategies in order to strengthen the defence mechanism against respiratory infections.

The laboratory of Dr Mathias Chamaillard focuses on studying the dynamics and the role of the gut microbiota in the pathogenesis of common human illnesses, such as colorectal cancer and inflammatory bowel diseases (IBD). His group has adopted a wide-ranging, integrated approach to studying host-microbiota interactions via gnotobiotic, biochemical and deep-sequencing technologies. His studies are the first to have described an unexpected role of both NLRP6 and the major Crohn’s disease predisposing NOD2 protein in the protection against intestinal inflammation and tumorigenesis afforded by gut bacterial communities. Furthermore, he also demonstrated that epithelial barrier function and wound healing relies on a novel non-hematopoietic function of IL-33.

As for the team led by Bruno Pot (Institut Pasteur de Lille Research Director), they have been studying the positive effect of probiotics (microorganisms with beneficial effects on health) on the prevention and treatment of intestinal inflammatory diseases. The team is more particularly interested in the mechanistic aspects of the interaction between the probiotics selected and their hosts. This includes focusing on deciphering the role of wall components and their interaction with NOD2 in anti-inflammatory capacity of lactic bacteria. They have also been analysing the potential role of probiotics in the prevention or treatment of opportunistic infections such as Clostridium difficile or Salmonella and the potential role in the fortification of the immune system.

Since 2012, the team led by Lionel Poulin (Inserm Research Fellow), have studied the dendritic cells that «decode» the pathogens’ information for the immune system. Better understanding these mechanisms would help improve the efficacy of vaccines or better target them.

On the influence of tobacco on intestinal diseases

Cigarette smoke is one of the environmental factors capable of influencing the onset and development of chronic inflammatory bowel disease (IBD). In addition to the deleterious effect on lungs, smoking increases twofold the risk of developing Crohn’s disease (CD). In addition, tobacco increases the risk of attacks, speeds up post-surgery relapse and worsens the evolution of CD, which requires resorting to immunosuppressant more frequently. Conversely, tobacco has a beneficial impact on ulcerative colitis (UC): the risk of developing UC is 2.5 times lower among smokers, and the disease occurring among smokers seems to be less severe.

One hypothesis that might explain this dichotomy is that the effect of tobacco is different in the colon and in the small intestine. A research group coordinated by Philippe Gosset & Muriel Pichavant (Inserm Research Fellows) has shown that the NKT cells, immune cells particularly sensitive to the effects of pollution (at least at the level of the lungs), are essential players in the protection of the colon by cigarette smoke. In the colon, the NKT cells exposed to cigarette smoke have the capacity of reducing the production of proinflammatory cytokines. Results underline the importance of these cells through their reactivity to environmental stimuli. Thus, the NKT cells could constitute a new therapeutic target capable of controlling the inflammatory reaction in UC.

Colonic Inflammation in Mice Is Improved by Cigarette Smoke through iNKT Cells Recruitment, Muriel Montbarbon & Al, Plos one on line 23 avril 2013
Both 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 CIL.

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 Locht 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

---

* 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.
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.

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.

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”.

*collection of chemicals
The genetic toxicology laboratory directed by Dr Fabrice Nesslany (Institut Pasteur de Lille Research Director), has been studying the mutagenic, i.e. potentially carcinogenic, activity of substances present in our environment.

He has conducted, among others, regulatory stories to assess the genotoxic potential (primary lesion of DNA) and the induction of mutations (stable and irreversible changes to the genetic heritage transmissible from cell division to cell division) for many types of substances. This reference laboratory is one of the biggest centres for genotoxicity in France. With a very wide field of competence (human health, animal health, cosmetics, chemicals, plants/vegetable, nanotechnologies, environment...), the experts from the genetic toxicology laboratory have been cooperating with the pharmaceutical, cosmetics, food, chemicals... Industries

The laboratory has also taken part in research programmes at national and European level aiming at assessing the genotoxic potential of nanoparticles, heavy metals, mycotoxins, and even compost from biodegradable packaging... Dr Nesslany’s project is to develop a new technology platform specialised in the analysis of endocrine disruptors, these molecules that belong to various chemical families (phthalates, bisphenol A, PCB, polybrominated & perfluorinated compounds, certain type of pesticides, parabens, etc.) that can be found in the environment and permanently in consumer products (Cosmetics, plastics, packaging, cleaning products, electronics, toys, etc).

**Development of reference tests for the research of generalotoxicity of nanoparticles**

Nano particles are defined as particles between 1 and 100 nanometers in size. The growing human exposure to nanoparticles requires to take into account with their genotoxic potential. However, the current in vitro genotoxicity tests are not adapted to nanoparticles. The nanoparticulate form can generate specific risks, cross physiological barriers (The blood-brain barrier, the feto-placental barrier, the cellular and nuclear membranes etc.), transport impurities through adsorption, or generate degradation and solubilization products from the materials they are made of.

Only one regulatory agency, Agence nationale de sécurité des médicaments et des produits de santé (ANSM) in France issued, in 2011, recommendations for the toxicological assessment of nanodrugs that Dr Nesslany helped draft. Recently, the Genetic toxicology laboratory researched a reference nanoparticle in order to validate a number of in vitro genotoxicity tests. In this study, the laboratory has assessed the possibility to use tungsten carbide and cobalt nanoparticles (WC-Co NP) as reference positive control in various models of regulatory or non-standard genotoxicity and through various cell types, i.e. a total of five in vitro models including the comet trial recommended by ANSM.

Result show that WC-Co NPs can be used as reference nanoparticles but also confirmed that the assessment of the toxicity of nanoparticles remains very complex and highly dependent on the experiments conditions and the cell type.

The Microbiological safety unit (so-called USM) has studied the behaviour of microorganisms in the environment, and more particularly the response of microorganisms to an environmental stress.

The axis of research revolves around the study of the response of different microbial species (Bacteria or viruses) to the conditions or their environment whether natural or connected to human activities. The contribution of the knowledge on the impact of a type of environment on the spread or the destruction of the microorganisms has proved a major asset in the control of microbiological risks.

USM also conducts specific studies for several industries where the awareness is raised on the management of contamination, such as the hospital sector or the cosmetics industry.

Nosocomial infections concern one hospital patient out of 20. There has even been a slight increase since 5.1% of hospital patients were infected in 2012 against 4.97% in 2006 according to the survey of the French Institut de veille sanitaire. This is why it was relevant to develop fabrics, bedlinen and uniform for healthcare professionals that block infections in hospitals.

USM has been studying the antimicrobial properties of these technical fabrics within the «advanced materials and textiles» scientific interest group. Its research has included assessing the compared microbial load in treated and nontreated bed linen and healthcare professional uniform fabrics as part of programme Crosstexnet. This study led to a paper in "Advances in Microbiology" in November 2013.

"The fabric has proved its efficacy in laboratory but remains difficult to handle in hospitals in the current washing conditions. A specific washing scheme might need to be developed so as not to destroy the efficacy of the fabric treatment." observed Michèle Vialette.

In 2014, as part of the project VIRNOS, deliberately started researching molecules which could give the textile virucidal properties against enteric viruses responsible for gastroenteritis. The fabric could be used to manufacture hospital linen and protection masks.
International relations: A wide spectrum of partnerships

Dr Nathalie Mielcarek
International relations manager

Institut Pasteur de Lille has always developed a determined policy of international partnerships. The teams cooperate with universities, laboratories, companies or not-for-profit organisations from over 53 and different countries. Over half of our partnerships are located outside European borders: in Africa, in Asia, in America and also in Australia.

Our Institut is an active member of the international network of instituts Pasteur (RIIP)* which gathers 32 institutes on 5 continents. «This is a great network which allows us to work in close connection with our colleagues who work at the very heart of countries where a number of pathologies we are studying are endemic», observed Nathalie Mielcarek. Some of the instituts were created at the local government’s initiative. Others, like us, are private foundations recognised of public interest. For the past two years, we have strengthened our presence in the network where we are the second largest structure. RIIP signed in 2012 a co-operation agreement with WHO in the fields of response to epidemics and global health security and has developed a great number of collaborative projects.

In 2013, for example, as part of this network, Instituts Pasteurs in Tunis,
Madagascar Lille joined forces with the EPLS biomedical research centre in Saint-Louis, Senegal (See opposite) to assess a diagnosis test to detect latent tuberculosis developed at Institut Pasteur de Lille by Dr Camille Locht’s team.

« It is essential to have a good knowledge of the reality of the field and the working conditions of researchers and health care professionals in the countries most impacted by the pathologies we are studying. As part of this network, we organised in co-operation with Institut Pasteur à Paris and Institut Pasteur de Madagascar a medical bacteriology course in Madagascar in November 2014, thus enabling African professionals to acquire and develop the latest theoretical and practical knowledge without having to travel to Europe. We have adapted this training program to the local issues by studying more specifically the infections that affect the African continent. This was so successful that we would like to make this course a permanent fixture with the support of public and private donors ».

In addition to its involvement in RIIP, Institut Pasteur de Lille has reinforced its scientific co-operation with Université de Lille on international partnerships. As an example, we have been receiving for several years young American students in our labs for a 3 to 6 month placement. Institut Pasteur de Lille signed in September 2014, with the Lebanese University a framework cooperation agreement on microbiology research and training formalising the relationship developed for many years between the two organisations. Institut Pasteur de Lille has also welcomed a number of foreigners on site : 37% of research directors are foreign citizens, with a majority of Belgians. 19% of post-docs and 33% of Ph.D. students come from abroad. Regardless of positions, among the scientists working on campus, 60% come from Europe, 20% from Asia, 14% from Africa & 6% from America.

### A presence on all continents

Researchers not only cooperate with the countries where certain diseases are endemic, they organise extra-muros laboratories closer to, and with the populations concerned.

« Espoir pour la santé » (EPLS), a biomedical research centre came to light in Saint Louis, Senegal, in the wake of the ESPOIR programme, initially financed by the European Union and supported by Inserm and the Lille region, for the implementation of a clinical trial of Bilhavax, a vaccine against bilharziasis. A structure coordinated by Gilles Riveau, EPLS has diversified its biomedical and epidemiologic research activities around infectious diseases, such as tuberculosis and malaria, and metabolic diseases too. In addition, the centre has also developed the function of clinical research platform, has proven over the years its capacity to conduct phase I to phase III clinical trials. These scientific and clinical research activities are part and parcel of the diploma courses that EPLS offers to Bachelor, Master and Ph. D. students, in partnership with Senegalese universities. On 15 January 2013, Institut Pasteur de Lille and EPLS signed a framework agreement which reinforces the scientific and human partnership between Lille and Saint Louis.

The « immunology system and genetics of the infectious diseases » Franco-Indian associated international laboratory (LIA SIGID) was officially created on 14 November 2012 in Bhubaneswar (India). This is a « laboratory without walls » gathering, in India, 4 fundamental research institutes and two clinical research centres and, in France, two laboratories one in Paris and the other at the Institut Pasteur de Lille. « This associated laboratory is the result of long and fruitful co-operation for nearly 30 years, explained Dr Sylviane Pied, coordinator of the French side. This gathers three networks that have decided to join forces to better understand how humans, in their environment, respond to aggression transmitted by insect bites. LIA SIGID is a platform for immunology and genetics of infectious diseases. For the moment, we have been focusing our efforts on the most widespread parasitic infections in India, such as malaria or leishmaniasis, but we are trying to validate a model which could be also used for the study of diseases transmitted by bacteria or viruses. » All LIA SIGID partners met in France for the first time on 5th and 6th February 2015 during an inaugural symposium at Institut Pasteur de Lille.
Technology platforms

- **Imaging microscopy & cytometry**
  Inserm U 761, Inserm U 1019, CNRS UMR 8204, Institut Pasteur de Lille, Lille University
  Manager: Frank Lafont
  BiolImaging Center Lille-Nord de France (BICeL), represents the most important part of EquipEx ImaginEx BioMed (See p 30).
  Website: www.bicel.org

- **Transcriptomics and Applied Genomics**
  Transcriptomics and Applied Genomics Group [TAG]
  Inserm U 1019, CNRS UMR 8204, Institut Pasteur de Lille, Lille University
  Manager: Yves Lemoin and, since 1st January 2015, David Hot
  High-throughput genomics platform specialised in microbial genomics. Since 2012, TAG has joined the genomics platform of Genes diffusion for the implementation of a common structure called Pegase-biosciences, in order to propose cooperation and services pooling the skills of each entity.
  Website: www.pegase-biosciences.com

- **Peptide Chemistry**
  Peptide Chemistry, Systems, Biology
  CNRS UMR 8161, Institut Pasteur de Lille, Lille University
  Manager: Oleg Melnyk
  Peptide chemistry and protein chemical synthesis.
  Website: www.csb.ibl.fr

- **High-throughput screening (HTS)**
  Inserm U 761, Institut Pasteur de Lille, Lille University
  Manager: Benoît Deprez
  Platform combining a chemical library with all the High-throughput screening tools (with the exception of techniques based on high-throughput confocal imaging which are available on the microscopic imaging platform).
  Website: www.deprezlab.fr

- **Pharmacokinetics**
  ADME-PK screening lab
  Inserm U 761, Institut Pasteur de Lille, Lille University
  Manager: Benoît Deprez
  Platform allowing for the quality and quantity characterisation of the future of experimental active principles in animals.
  Website: www.deprezlab.fr

- **Nuclear magnetic resonance**
  CNRS UMR 8576, Institut Pasteur de Lille, Lille University
  Manager: Guy Lippens
  Nuclear magnetic resonance (NMR) spectroscopy helps probe the molecular structure by making the natural magnetisation of nuclei interact with a magnetic field.
High security laboratory and animal house  
Institut Pasteur de Lille  
Manager: Jean-Pierre De Cavel  
Animal house for research and experimentation  
NSB3 high biological security laboratory bellowing for the secure handling of infectious biological agents (prions, viruses, bacteria…) or others (toxines, radiation…).

Genomic Analysis Laboratory  
Inserm U 744, Institut Pasteur de Lille, Lille University  
Managers: Philippe Amouyel and Nathalie Fievet-Verrecas  
Logistics and follow-up of large collections of human biological samples with patients recruited mainly from epidemiological studies based on the cardiovascular, metabolic and neurodegenerative disease themes.

Genomics and metabolic diseases  
EquipEx LiGAND-PM (Lille Integrated Genomics Advanced Network for Personnalized Medicine)  
CNRS UMR 8199, Institut Pasteur de Lille, Lille University  
Manager: Philippe Froguel  
The Lille Ligan-PM platform for the sequencing of the genome can establish the list of mutations which could explain the clinical signs for each patient, predict the possible evolution of his/her disease, and predict the efficacy or side-effects of existing drugs.  
Website: www-good.ibl.fr

Proteomics and analysis of modified peptides  
Proteomics and modified peptides platform (P3M)  
LabEx ParaFrap, Institut Pasteur de Lille, CNRS, Lille University  
Manager: Stan Tomavo  
Platform dedicated to the analysis of parasites’ proteins.

Promotion of research  
The department for the commercialisation of research, directed by Pr Yves Lemoine, follows up on approximately 50 patents filed jointly by Institut Pasteur de Lille and its partners who are, according to teams, Inserm (represented by Inserm-transfert), CNRS and the Lille universities (Represented by Société d’acceleration du transfert de technologies SATT Nord), or even, depending on the type of works, other French or foreign universities.
2013

Genome-wide association studies identify 18 new loci associated with serum urate concentrations 

Köttgen A, Albrecht E, Teumer A, Vitart V, Krumsieck J, ..., Yengo L, ..., Frooguel P, ..., Bouatia-Naji N, ..., Gieger C. 
Genome-wide association studies identify 18 new loci associated with serum urate concentrations 

Supply P, Marceau M, Mangenot S, Roche D, Rouanet C, ..., Debbie AS, Willery E, ..., Locht C, Gutierrez MC, ..., Brosch R. 
Genome-wide association studies of smooth muscle disease identify new loci associated with smooth muscle disease 

NOD2-mediated dysbiosis predisposes mice to transmissible colitis and colorectal cancer 

Supply P, Marceau M, Mangenot S, Roche D, Rouanet C, ..., Debbie AS, Willery E, ..., Locht C, Gutierrez MC, ..., Brosch R. 
Genome-wide association studies of smooth muscle disease identify new loci associated with smooth muscle disease 

Here the list of scientific international publications with impact factor is greater than 10. All publications are available on our website.
On the Institut Pasteur de Lille campus, bio-technology companies, market, throughout the world, analysis or diagnosis products, directly stemming from fundamental research conducted in Lille.

Genoscreen

Genoscreen proposes analytical services in genomics on all types of genomes (Human, animal, vegetable, microbial) and bio-computing analyses and training, both for academic research teams and for hospital or industrial research. This 100% French biotechnology company was created on the Pasteur-Lille campus in January 2001 and employs today approximately 30 employees. 80% of its turnover is made outside the greater Lille area, of which 30% is exported. Over these last years, own research programmes, conducted in partnership with research units from Institut Pasteur de Lille, Inserm and INRA have helped develop very competitive applications in areas such as the genetics of Alzheimer disease, microbial molecular typing or the control of biodiversity.
**Innobiochips**

Innobiochips make solutions for miniature biological analysis and diagnosis: peptide and protein biochips which allow for several dozen simultaneous analyses from a reduced biological sample. As there were coming from the research world, the young company naturally contacted researchers who work on small animals or from collections of high-value samples, to retrieve a maximum of information from a small sample. Innobiochips is now tapping the miniaturised diagnosis market: thanks to its biochips it is possible to retrieve in a single operation, several dozens of different pieces of information and therefore obtain a comprehensive diagnosis in one single analysis. Innobiochips, a company employing a dozen people today, moved to Eurasanté in late 2014.

**Lunginnov**

Lunginnov produces Endocan a biomarker of the state of blood vessels which can be used to treat sepsis and cancers. Endocan or endothelial cell specific molecule (ESM-1) was discovered in 1996 by Philippe Lassalle and his colleagues from the pulmonary immunity team at CIIL (CNRS, INSERM, Institut Pasteur de Lille). Its biochemical structure was characterised in 2001.

Endocan biomarkers assess the dysfunction of the endothelial cells that make up blood vessels. A relevant element in the event of sepsis (The number of symptoms which lead to organ failure) or cancer.

**X’Prochem**

X’ProChem markets proteins synthesised from a chemical reaction. An innovative technology directly stemming from academic research in Oleg Melnyck’s laboratory. These 100% chemical properties are custom-made to meet requirements that classic recombing methods cannot synthesise, such as toxic, membrane proteins or proteins equipped with a probe so it can be traced in cellular imaging.

The first papers published on protein chemical synthesis date back to the 30s, but we had to wait for the 2000s before a cost-effective, easily repeatable method is developed at Institut Pasteur de Lille.

**APTEEUS**

APTEEUS has developed an innovative solution for the individual care management of patients with rare diseases. APTEEUS’s technology make it possible to test thousands of molecules from the existing pharmacopeia and directly on primary cells from the patient. APTEEUS’ administrative headquarters are located at the school of pharmacy with a laboratory on the Institut Pasteur de Lille campus.
III - Health

- The Prevention and Health Education Centre
- Medical biology laboratory
- The nutrition Department
Ever since its creation, health prevention and education have been among the fundamental missions of Institut Pasteur de Lille. Created over thirty years ago, the Prevention and Health Education Centre (Centre de prévention et d’éducation pour la santé) is one of the largest health examination centres in France. It is also a public health skills platform to serve the community, public health players and policies in the Lille region.

It encompasses three main activities, Prevention - health education, epidemiological studies, medical advice to travellers and vaccination.

Prevention and health education

The health checkup, a true diagnosis for health prevention

Every year, 15,000 health checkups are carried out in the Lille and Tourcoing health examination centres as well as branches in Lens, Arras or Boulogne. These examination centres are the results of close partnership with sickness insurance funds of Lille-Douai, Artois, Flandres, Roubaix Tourcoing and Côte d’Opale.

The Sickness Insurance dedicates more specifically these checkups to the most vulnerable people (precarious social position, isolation, populations who do not benefit, or not properly, from the prevention action of general practitioners (GPs), because they are not consulting with them or have not appointed one, people who are not included in the organised follow-up, detection or vaccination schemes offered to them...) which accounts for over 50% of the clients of the centres. During half a day, they undergo a series of medical tests (Blood tests, hearing test, ECG, diet survey…) carried out by CPES professionals: doctors, nurses, dieticians, and medical sports specialists. The full checkup is then sent to the GP.

“We realised a long time ago that there are limitations to standardized checkups that only refer patients to the GP for any question, especially since over the past years the checkups are mainly proposed to people in a precarious social position, who combine a number of issues and are far from familiar with the health system. Many partnerships with not-for-profit organisations have now been established to facilitate access to rights and to the health programme” explained Dr Dominique Bonte, CPES director.

“In addition to referrals, it is also important to work with the person on motivation so this person is in a position to commit to a reachable objective. Pointing the finger at people is out of the question... we’d rather encourage them to go further and behave in a way that is better for their health.” Here, we don’t talk about prohibiting, dieting, forcing people to exercise, but rather about wellbeing behaviours.
The Tremplins (springboard) programmes, a global approach to health

To encourage people to change for these well-being behaviours, CPES has developed fun schemes with workshops and events. A number of Tremplins (springboards) are offered: practical workshops on nutrition, on exercising for overweight people, on memory for seniors, treatment education for diabetes patients, individual interviews to limit risk behaviours (tobacco, cannabis, alcohol: knowing when you are going too far), custom programmes for companies or communities… These schemes have particularly interested the Sickness Insurance and the regional health policymakers (Agence régionale de santé, Conseil régional Nord - Pas-de-Calais, Conseils généraux) who finance part of these activities and include CPES in the steering of national or regional programmes and use CPES expert services for training health stakeholders. Institut Pasteur specialists work on cardiovascular prevention, addictive behaviours, vaccination or to support professionals or volunteers.

Epidemiological studies

As it is used to full health examinations with its checkup programme, CPES is an excellent tool that is regularly used as part of the observation of cohorts in public health. CPES takes part in two major epidemiological studies. The Constances (standing for: patients of health examination centres) study launched in March 2013 is the largest epidemiological cohort ever made in France, gathering, between now and 2016, a representative sample of 200,000 adults aged 18 to 69 at the start of the study. The Constances project is under the scientific and technical responsibility of the cohort team of the Research centre in epidemiology and population health - Inserm U1018 - Université de Versailles St-Quentin, in cooperation with the support and training technical centre of the health examination centres (CETAf). Constances’ objective is both to provide descriptive information on the health status of the French population and its evolution and to make up a database that is relevant for epidemiological research. 16 health examination centres are taking part in the study. Esteban (Health study on environment, biomonitoring, physical activity and nutrition) is a new national study started in April 2014, which concerns at the same time the environment, nutrition, physical activity and frequent chronic diseases. Supported by the French Ministry for social affairs and health, and the French Ministry for environment, sustainable development and energy, this study is conducted by InVS, the French Institute for Public health surveillance. Esteban has concerned in mainland France a sample of 4000 adults aged 18 to 74 and 1000 children aged 6 to 17. The specificity of the study resides in the number of health themes it covers: environment, biomonitoring, eating habits, physical activity, frequent chronic diseases and their risk factors. As it combines a health examination, a nutritional aspect and assay of environmental biomarkers, it will help obtain a comprehensive review of the health and environmental exposure of the population living in France at a given time. 73 health examination centres are taking part in the study.

Recognition of excellence

CPES was ISO 9001 2000 certified in January 2009 for the delivery of health prevention examination on the Institut Pasteur de Lille site. This scope was extended, on 30th January 2013, to extra muros examinations as well as treatment education and health education actions (CETAf national programmes).

Dr Dominique Bonte, director of the CPES, was appointed medical coordinator of the health examination centres for the North of France in April 2014. She is at the helm of network 2 grouping the Lille region, Picardie and Haute Normandie, i.e. a total of 13 centres, which is a sign of the recognition of the whole Lille team’s know-how.
Medical advice to travellers and vaccination

An international vaccination centre

The international vaccination centre of Institut Pasteur de Lille, located within CPES, is approved by the World Health Organisation (WHO), and delivers over 40,000 vaccines a year. It is the largest international vaccination centre north of Paris. It is open to the public for compulsory or recommended vaccines and also for tropical medicine consultation (before and after a trip).

A reference centre against rabies

Institut Pasteur de Lille is an antirabies reference for Nord & Pas-de-Calais Départements. Vaccination against rabies is one of the oldest activities of Institut Pasteur. Every year, several dozens of people come to the clinic after having been bitten or scratched by an animal (Dog, cat, bat...).

Influenza vaccination campaigns in companies

Institut Pasteur de Lille organises on-site vaccination campaigns against flu, upon request from companies and/or local authorities in the Lille and Paris regions every year between October & December. In addition, since 2013, CPES has been co-steering the ARS’ regional programme for improvement of the vaccination coverage.

Medical biology laboratory

directed by Dr François Regnault
Institut Pasteur de Lille

The laboratory has been carrying out all types of Medical biology examinations health checkups proposed by CPES (Health prevention and education centre) as well as the biological monitoring of clinical studies delivered by various research and clinical studies centres (Scientific and logistics advice, selection and management of the analytical platform, development and validation of analysing methods, preparation of sampling kits, storage of samples...). The laboratory is also a major stakeholder in the prevention of colorectal cancer and as such has conducted close to 370,000 Hemoccult detection tests 2013 in 2014 for nine French Départements. The certification of LBM’s activities according to the NF EN ISO 15189 standard is scheduled for 2015.
The nutrition department has been conducting applied research projects in nutrition and public health training professionals, and conduct assessment missions in the nutrition area.

Created in 1982 upon the initiative of Dr Jean-Michel Lecerf, an endocrinologist and nutritionist doctor, the centre was from the onset oriented towards health education and the training of health & social professionals. For about twenty years, it has also been offering training and expertise to companies in the agro-food and catering industries. In 2012, they opened Nutrinvest, a clinical research centre in nutrition.

With a multidisciplinary team (Doctors, nutritionists engineers and dieticians), the nutrition Department is in a position to support all food industry stakeholders institutions (consumer, industrialists, producers, institutions...), with a cross-cutting analysis of nutrition. These professionals work as early on as possible to train and advise all food chain stakeholders: from industrialists to authorities and health professionals, through collective catering professionals. This pluralism ensures full independence from private interests. They are also at the origin of the creation of the alternative menu to the consumption of meat for collective catering, the development with the Lactalis group of the Primevère margarine, the first French margarine free of trans fatty acids and enhanced in omega 3, and the designing of Nutrissimo Junior®, an educational board game.

The Nutrition Department has also been actively participating in recognised bodies such as Anses, ANIA, and ARS Nord Pas-de-Calais. It is also a major player in the Nutrition Santé Longévité du Nord - Pas-de-Calais cluster.

A fully rewritten and redesigned children version of Nutrissimo®, the game invented by the nutrition department in 1994, Nutrissimo Junior® is a board game for schoolchildren from 6 to 12. With modern graphic arts and nutritional information complying with the French national nutrition and health programme (so-called PNNS), this new game offers hours of fun while revisiting good habits and behaviours in terms of diet and physical activity. Nutrissimo Junior® is also a useful educational tool for: parents, carers, teachers, and counsellors. The Nutrissimo Junior® game came out in November 2013. Thanks to corporate sponsoring, this game was distributed to community structures working around children eating habits and training was offered to support the staff concerned.
Public Health division

The public health and training division is made up of dieticians/trainers who work in cooperation with a number of recognised bodies (ANSES, ANIA, ARS, Regional Council…) on a number of diet-related themes. In addition, as an example, dieticians implement “nutrition and physical activity” projects for City Councils and companies and design educational material. The division has also been offering training sessions on the following themes: education and food balance, children and senior diets, health and food, agro-food industry, collective catering… Events on very targeted themes (Autism, Alzheimer…) and conferences (Entretiens de nutrition, nutrition workshops…) are also organised every year. Institut Pasteur de Lille’s Entretiens de nutrition will celebrate their 17th anniversary in 2015.

Expert assessments and clinical studies

The expert assessment division offers support to companies in the creation and development of products. Its offer relies on:

- advice and assistance in nutritional and dietetics regulations,
- assistance to product formulation and filing of PNNS (Nutrition and health national programme) applications,
- study of the impact of processes on nutritional quality,
- writing of scientific papers for publication, desktop research reports and applications for health claim,
- nutrition audits of existing products,
- nutritional labelling and justification of health claims,
- management and delivery of clinical studies in nutrition.

It is made up of engineers who are agro-food and nutrition specialists and Ph.D. students.

NutrInvest, centre for clinical studies in nutrition

In late 2012, Institut Pasteur de Lille opened NutrInvest, a clinical study centre in nutrition, to test the effects on health of a method, ingredients or food products, particularly those developed by companies, before they are put on the market. This is also a structure for clinical and biological evaluations for epidemiological studies. For approximately 15 years, the nutrition Department had been conducting clinical studies upon request from industrial partners. The objective of these studies is to measure the effect of a type of food, a nutrient, a diet, a cooking method, a non-drug remedy on biological, clinical, anthropometric, psychological and behavioural parameters. But given the increasing number of requests, the Institut has decided to create a dedicated structure. With NutrInvest, the expertise division has the capacity to support and carry out a clinical study from A to Z on IPL’s campus, from scientific design to data analysis and clinical interpretation. The whole intervention phase: medical checks, follow-up of subjects, distribution of products, etc. can be done within the centre. « Developed after clinical studies on prescription drugs, nutritional clinical studies are organised in the same way. Volunteers are protected in the same way and before we can start, our studies must be validated by the French National agency for the safety of drugs and health products and by a committee for the protection of people » explained Elise Clerc, in charge of the expertise division.
IV - DISSEMINATION OF KNOWLEDGE

- Scientific mediation and health information
- Health education
The dissemination of knowledge, including to enable individuals to better care for their health, has been an integral part of the missions of Institut Pasteur de Lille. This dissemination is illustrated through a series of general public conferences, participating in a number of national or international events, opening a museum which tells the story of Pasteur, Calmette and Guérin in Lille, scientific workshops for the younger public and, in 2013, the publishing of a book "La passion d’épauler" (A passion for support).

5-7 conferences draw crowds
For the past ten years, one Tuesday a month from 5 to 7, researchers from the Institut and their partners organise a general public health conference, the 5 to 7 conference, giving each time an update in a specific field about research, prevention and treatments. These free conferences have been getting so popular that the Institut has had to organise preregistration for the past two years. Every month, except July and August, over 200 people fill up amphitheatre Buttiaux.

A museum at the core of the history of scientific discoveries
Set in the old tuberculosis prophylaxis centre created by Albert Calmette, the Institut Pasteur de Lille’s Museum relates the lives and works of Louis Pasteur, Albert Calmette & Camille Guérin, the discoverers of the BCG vaccine. With 3,000 visitors a year, the museum is very popular with schoolchildren coming as part of group visits and guided tours.

Not-to-be-missed events
Opening of the laboratories for science day in October and Europe day in May, activities and exhibitions at the Museum for the European Heritage Days in September, conferences and film debates for Brain Week in cooperation with Inserm in March... Institut Pasteur de Lille never misses an opportunity to make Science accessible to all.
Kid Campus: A day in the life of a researcher

Every year, in January and February, Institut Pasteur de Lille takes a gulp from the Fountain of Youth by devoting an afternoon to ten-year-old schoolchildren and inviting them to put themselves in the shoes of researchers. The “Kid Campus” workshops were designed to be both educational and fun, with a pragmatic approach of research, to give children a new outlook on science… and why not stimulate new career interests.

The Kid Campus workshops are in 4 parts:

1. A visit of the Institut Pasteur de Lille Museum…
   helps children understand the history, the values of the Institut and discover the basics of microbiology.

2. A “hygiene and germs” demonstration…
   reviews the basic rules of hygiene and let children observe through a microscope moulds, bacteria, or yeast, all these microorganisms they unknowingly mingle with every day.

3. Manipulation in a science classroom
   After donning the researchers’ uniform, coat and gloves, the youngsters complete a task at a bench.

4. Free discussion between the researcher and the class
   This is the opportunity for children to know everything about the job of researcher.

Every year, a dozen teams devote six weeks to welcoming over 400 pupils around the following themes: Malaria, vaccination, prescription drugs, fat, viruses, mucosa, DNA (Of the onion and the banana), cells, bacterial pathogens, nutrition and diabetes.

Perspective

“La passion d’épauler”:
An exceptional book for the 150th anniversary of the birth of Albert Calmette

Albert Calmette (1863-1933) was the first director of Institut Pasteur de Lille and was a science pioneer, of exceptional stature and humanism. This is why Institut Pasteur de Lille wanted to pay tribute to him for the 150th anniversary of his birth in 2013 through a collectable book.

This original work combines the life and works of Albert Calmette with testimonials from iconic personalities of the Lille region. These personalities identify with the vision, humanism, successes and sometimes failures of the first director.

Gérard Mulliez and Jef Aérosol, Line Renaud and Mr Dupond-Moretti, Chantal Ladesou and Christophe Bonduelle… unlikely encounters indeed, still, these personalities have gathered around the values that have built Institut Pasteur de Lille.

All the proceeds from the sale of this book will go towards the financing of research.

« La passion d’épauler », Du Quesne publishing, November 2013, €30.00
Since its foundation, education has been an integral part of the missions of Institut Pasteur de Lille. Every year, over 1000 people attend continuous education sessions and over 130 young scientists are welcomed by the laboratories of Institut Pasteur de Lille to develop their research projects.

Institut Pasteur de Lille offers training in three main areas in which its expertise is unanimously recognised: scientific techniques and safety, nutrition and addictive behaviours.

Scientific and safety courses cover a wide spectrum of skills that are necessary to technical and scientific personnel: virology, parasitology, proteomics, bioinformatics, genomics, genotyping, imaging, cellular biology, mutagenesis, genotoxicity, statistics, animal manipulation, regulations, biological safety and OHS.

The nutrition Department offers training sessions adapted to various professionals likely to deal with the issue of eating habits with certain audiences: health professionals (doctors, nurses, dieticians), medical and welfare personnel, catering or agro food industry personnel, in addition to two not-to-be-missed events: «Entretiens de nutrition» in June more specifically dedicated to doctors and dieticians and «Ateliers de nutrition» in December for professionals in the social sector.

Finally, the doctors specialising in addictions from the Centre for prevention and health education have been organising specific training sessions for professionals working with tobacco and/or cannabis users. Institut Pasteur de Lille is also pedagogical partner of the professional Bachelor’s degree in organisational management, with a major in food safety and quality (SQA1) at IUT A in Lille.

The education department started rolling out in 2013 an e-learning platform with self-training modules.

As soon as the order of 4 August 2014 was published, that authorised the derogatory manipulation of the group 4 Ebola biological agent for the purpose of biological tests for patients, the education department and the high-security laboratory organised themselves to offer a day and a half of both theoretical and practical training. The first training session was delivered on 18th and 19th December 2014. This new course is now included in the catalogue.
V - Key Figures

- Headcount
- Budget
- Donations and bequests
- and...
Key figures about Institut Pasteur de Lille...

**Headcount**

**961 EMPLOYEES ON CAMPUS** INCLUDING:

- **330 INSTITUT PASTEUR DE LILLE EMPLOYEES**
  - INCLUDING **229 WOMEN**
  - INCLUDING **101 MEN**

- AND **564 EMPLOYEES FROM OTHER RESEARCH ORGANISATIONS** (INSERM, CNRS, UNIVERSITIES)

- AND **67 TRAINEES STAYING MORE THAN 2 MONTHS**

- **23 NATIONALITIES ON CAMPUS**
In 2014, Institut Pasteur de Lille devoted €14.7 million to research, including salaries, operational costs and infrastructures, and €10.7 million to education & Public Health activities.

Its income comes:

- from a government subsidy (as a private research foundation declared of public interest),
- from research contracts obtained from national (ANR) and international bodies (EEC),
- from donations and bequests,
- from sponsoring, and
- from royalties relating to the discovery of new drugs and vaccines.

Institut Pasteur de Lille committed in late 2012 to increase the share of private financing. This accounts for 9 - 10% of its budget.

Between 2012 and 2014, the amounts coming from private individuals and company donations were multiplied by 4.5.

In 2013, the costs for fundraising stood at 30%. In 2014, this ratio was momentarily degraded due to the sharp decrease in bequests and donations resources that fluctuate by nature.

Institut Pasteur de Lille allocates all the donations coming from the generosity of private individuals to the resources made available to research on its campus.
Key figures

And...

50,000 sqm of laboratories

10 Technology platforms

368 Scientific papers in 2014

Over 40,000 vaccinations delivered

15,000 Health checkups
The teams of the transdisciplinary research centre on longevity of the Institut Pasteur de Lille, in 2015

6 mixed research units:

U1167 Inserm - Université de Lille - Institut Pasteur de Lille
Pr Philippe Amouyel

U1177 Inserm - Université de Lille - Institut Pasteur de Lille
Pr Benoît Deprez

U1011 Inserm - Université de Lille - Institut Pasteur de Lille
Pr Baert Staels

UMR 8199 CNRS - Université de Lille - Institut Pasteur de Lille
Pr Philippe Froguel

U1019 UMR 8204 Inserm - CNRS - Université de Lille - Institut Pasteur de Lille
Pr Camille Locht

UMR 8161 CNRS - Université de Lille - Institut Pasteur de Lille
Pr Yvan de Launoit

Laboratories and equipment of excellence:

3 LabEx: DISTALZ - EGID - ParaFrap
2 EquipEx: LIGAN - ImaginEx BioMed

2 applied research units:

Service Toxicologie génétique: Fabrice Nesslany
Unité Sécurité microbiologique: Michèle Vialette

2 health prevention services

Service de Nutrition: Dr Jean-Michel Lecerf
Centre de prévention et d’éducation pour la santé: Dr Dominique Bonte