

REPORT



2018



Vivre mieux
plus longtemps

WWW.PASTEUR-LILLE.FR

THE EDIT

LIVING LONGER IN BETTER HEALTH

is today possible as a result of ambitious research and early prevention. This is the meaning of the Longevity project implemented by Institut Pasteur de Lille.

If advances in matters of prevention, hygiene, nutrition and treatment of diseases have enabled clear progress in life expectancy over the past decades, there is still much to be done to improve life expectancy in good health and to develop effective prevention in light of age-related risk factors. Institut Pasteur de Lille teams strive relentlessly to that end by way of an ambitious longevity research programme and the deployment of prevention actions and expertise.

Numerous advances are being seen in the fight against cancers, Alzheimer's disease, diabetes, cardiovascular diseases, and infectious diseases as attested by our researchers' 342 publications and backed by the creation of new teams. In 2018, Institut Pasteur de Lille supported its longevity research programme thanks to ERDF, regional, state, and M.E.L. financing and also by the generosity of donors and businesses.

Within the Prevention in Health and Longevity Centre, the first Longevity Pathways undertaken in 2018 demonstrated the interest of early prevention on age related risks and the relevance of developing this model of preventive medicine. This completes the offer of health check-ups and health education the Institut undertakes within the scope of its general interest missions.

2018 was also affected by tax reforms which led to a decrease in donations in France, putting numerous projects and funding at risk. As such, I want to thank all the donors, companies, associations, and volunteers who brought us their support in 2018, those who will continue to help us, and all those who this year are preparing to join in our fight to gain ground against diseases.

In 2019, Institut Pasteur de Lille will celebrate the 120th anniversary of the first building's inauguration, an occasion to recall that since its creation in 1894, all the foundation's breakthroughs, first and foremost, the discovery of BCG, were only possible because of researcher commitment and the general public's generosity with donations, bequests, and business sponsorships.

In this story's continuum, it is the commitment of donors who stand side-by-side our researchers that will allow Institut Pasteur de Lille to support tomorrow's discoveries and to perpetuate its actions for the benefit of the population.

Together, let's accelerate research and act for tomorrow's health!

Many thanks for your support.



Didier Bonneau
Deputy managing director

6

8

18

40

50

54

62

70

74

2018 ACTIVITY REPORT

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Prevention in Health and Longevity Centre: Innovation for Aging Well

- Health Check-Ups Department
- Research within the Prevention in Health and Longevity Centre
- Nutrition and Physical Activity Department
- The International Vaccination Centre

TOWARD A BETTER UNDERSTANDING OF POLLUTION

Pollution Health Longevity: moving towards collective awareness

SUPPORT THE FOUNDATION, LET'S MOVE TOGETHER!

Thank you!

- Donations and bequests | Fundraising
- Business patronage
- Institut Pasteur de Lille Museum

BUILD TOMORROW'S FOUNDATION

Research, Prevention, Health, and Longevity: a foundation on the move

- A foundation that adapts
- Our CSR Commitments
- Scientific and Administrative Organisational Chart
- Employment/Resources

SCIENTIFIC PAPERS

PARTNERS AND SUPPORT

HIGHLIGHTS

2018

Entreprises et Cités
stands besides Institut
Pasteur de Lille

**CPSL visited by
Christophe Itier**,
High-Commissioner
for Social and
Solidarity Economy
and Social Innovation

**Pretty Month of
Europe: (Joli Mois
d'Europe)** laboratories
open to the public

Solidarity Concert

Launch of the **11th**
**edition of Kid
Campus**



Creation of the
Longevity Pathway



2018 Route du
Louvre Marathon



**2nd Smart
Move Challenge**
(Challenge
Bougeons Malin in
French) event with
Kiabi



**20th Nutrition
Interviews**

JANUARY

FEBRUARY

MARCH

APRIL

MAY

JUNE



Club
Gagnants
Meet-Up



Historical opening
of the tubes
containing the
**original BCG
strains**



Participation in the
second Youth Forum



**Mad for Biking ("La
Rage à Vélo" in French):**
Collective fundraising
during the Lille-Hardelot
bike race



Sale of the book titled
"La tentative de trop"
for the benefit of
Institut Pasteur de Lille



Signature of the
partnership with
API Restauration



**4th Institut Pasteur
de Lille Science
Day**



Horizon Campus #2018

Installation of **Bioversys** in Lille to intensify **R&D** on antibiotic resistance with Institut Pasteur de Lille teams

Institut Pasteur de Lille at the **Sports Village**

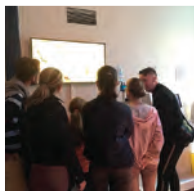


Junior **Nutrissimo Event** at Furet du Nord

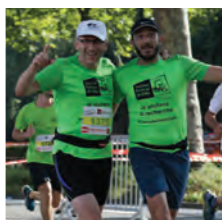


2nd Regional Meeting on **"Pollution, Health, Longevity"**

European Heritage Days



Braderie de Lille races



2nd edition of **"SOLID'AIR"** with Weembi



International BCG Symposium
Amphi IBL



17th Nutrition Workshop
"Prevention: How to talk about nutrition today"

Florence Pinet wins the 2018 "Danièle Hermann" Foundation award

JULY

SEPTEMBER

OCTOBER

NOVEMBER

DECEMBER

Alicia Mayeuf-Louchart wins the **L'Oréal-UNESCO Foundation** award



Support from the **Cyclo-Cancer Association**



Our sponsor **Franck Thilliez** visits the laboratories

2nd regional meeting on "Pollution, health, and the quality of life"



World day for generosity **"Giving Tuesday"**

Mobility Challenge: Institut Pasteur de Lille winner of the category "Best Participation Rate"



Support from Hubert-Felix Thiéfaine during his Lille concert



Longevity Conference at Lille Grand Palais



■

LONGEVITY OBJECTIVE



ACCELERATING RESEARCH AND ACTING ON TOMORROW'S HEALTH

Over the **past 60 years**, men and women have gained on average **a 14-year increase in life expectancy**. Life expectancy in a good state of health is increasing at a slower rate than life expectancy. In **2060**, France will count **250,000** 100-year olds, the question of aging well becomes essential.

But how are we aging? And more specifically, can we live better longer? At age 60, on average **life expectancy is 20 years**, ten of those in good health and the ten others with a gradual loss of autonomy. So, extending the period of life in good health is a challenge for research and public health.

A few figures:

- **Cancer:** leading cause of death, **400,000** new cases were detected in 2017
- **Alzheimer's Disease:** **900,000** people in France have not been diagnosed
- **Cardiovascular diseases:** **140,000** deaths per year, **1,000,000** cases of heart failure
- **Diabetes:** **3.3** million people in France are diabetic. **700,000** individuals unknowingly live with diabetes.



OVER AGE 60 IN FRANCE

24.8%

of the population in **2015**

29.4%

of the population in **2030**

32.1%

of the population in **2060**



NUMBER OF ONE-HUNDRED-YEAR-OLDS AND LIFE EXPECTANCY

16,000

ONE-HUNDRED-YEAR-OLDS

140,000

ONE-HUNDRED-YEAR-OLDS

82.4
YEARS

2015

88.5
YEARS

2050

Source: INSEE

Anchored in Hauts-de-France, Institut Pasteur de Lille is a major scientific actor recognised internationally for its expertise on identification of factors (“stressors”) which reduce the cells’ capacity to function normally leading to a decrease in the organism’s overall performance. These factors are of genetic, environmental, metabolic and nutritional, or infectious origin. Our researchers study the mechanism of the factors’ detrimental actions in an attempt to decode the resilience factors available to the organism so it can put strategies in place for prevention or treatment. Institut Pasteur

de Lille supports the world of medicine as well as citizens and businesses by rising to the challenge of greater life expectancy in good health. And it continues the historic general interest and outreach mission.

Institut Pasteur de Lille actively participates in its academic and economic ecosystem’s value chains. It also has a key role in the management and engineering of national, European, and international research projects.

IN ORDER TO PRESERVE THE QUALITY OF LIFE FOR AS LONG AS POSSIBLE, INSTITUT PASTEUR DE LILLE TEAMS DEVELOP A MECHANISTIC APPROACH TO LONGEVITY.

01 Identify stressors:

■ genetics ■ metabolic ■ diet ■ pollutants ■ behaviour

02 Understand physio-pathological mechanisms, establishment of prodromals and resilience mechanisms in multi-disciplinary studies over long periods.

03 Limit exposure to avoidable stressors and offer innovative preventive strategies and treatment.

Combining research and prevention, Institut Pasteur de Lille relies on its teams’ expertise and complementarity to grow scientific knowledge of diseases associated with ageing and to contribute to development of new preventive health tools and treatments. What’s the objective: extending life in good health after age 60 in order to **live better longer**.

A LONGEVITY EXPERT CENTRE UNITING RESEARCH AND PREVENTION

LONGEVITY RESEARCH CENTRE

Understanding diseases which prevent ageing well in order to slow their development, imagine the treatments of the future, and offer prevention strategies.

PREVENTION IN HEALTH AND LONGEVITY CENTRE

Adopting an innovative approach, unique in France, for prevention and health education associated with research, advice, and support for active and successful ageing based on detection of age-related disease risk factors and supplying advice and tools to limit the consequences and change behaviour.

POLLUTION HEALTH LONGEVITY

Develop a research programme which aims to understand the impact of pollution on health and longevity. Institut Pasteur de Lille offers expertise in the field of environmental pollutants and their toxicity, particularly that of nanoparticles on the respiratory tract.

KEY FIGURES

50,000 m²
campus

800
employees

33
research teams

26
nationalities

4
ERC laureates

342
scientific papers

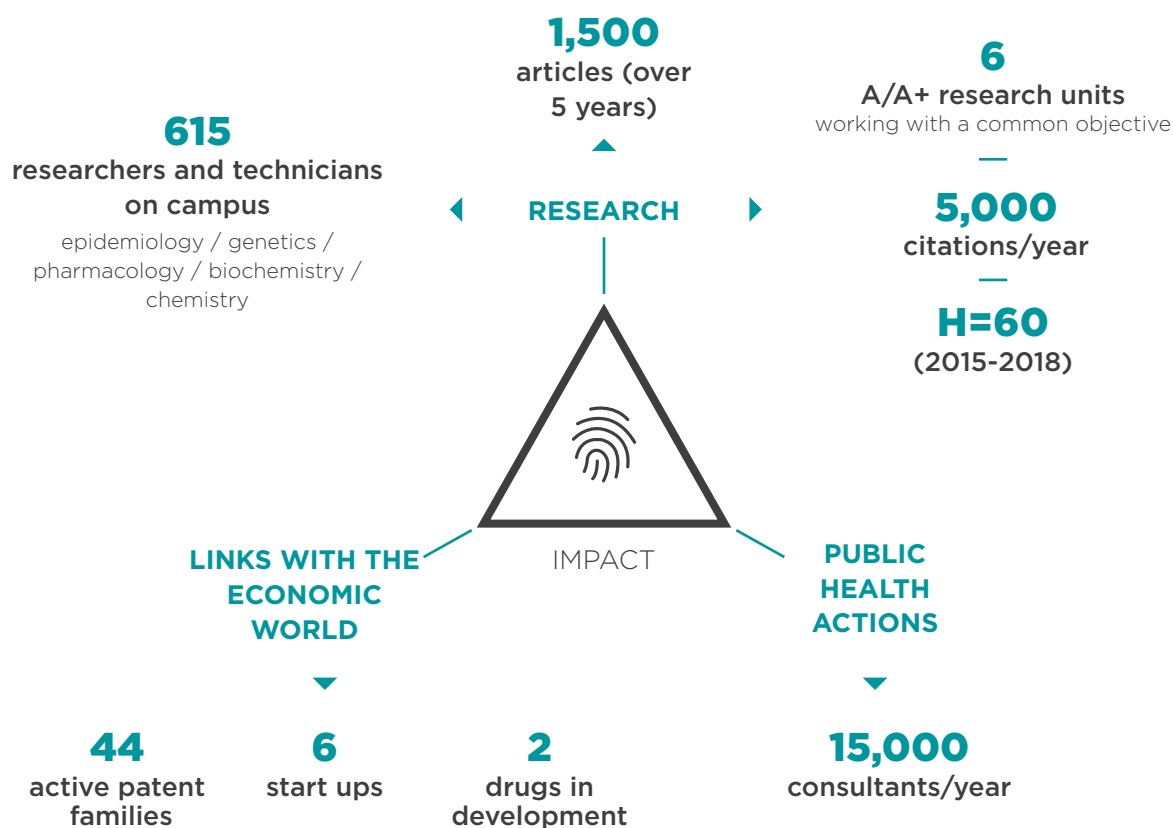
3
LabEx
(Excellence Laboratory)

10
technology platforms
including 2 equipex

15,000
Preventive Health Examinations

26,000
vaccinations per year

INSTITUT PASTEUR DE LILLE'S DNA



INTERNATIONAL SCIENTIFIC COLLABORATIONS

	Imperial College London University of London Harvard University Helmholtz association University of Oxford University of Cambridge Univ Oxford University College London
	National Institutes of Health NIH USA University of California System Boston University VA Boston Healthcare System Washington State University
	Erasmus University Rotterdam
	Karolinska Institutet
	Helmholtz Centre Munich
	Ghent University
	University of Helsinki
	Spain
	Italy
	Japan
	Switzerland
	Estonia

2ND CPER-CTRL CALL FOR PROJECTS (JUNE 2017) RESULTS

To support interdisciplinary projects on longevity, Institut Pasteur de Lille is coordinating the 2016-2020 CPER-CTRL programme (State-Region plan contract - Interdisciplinary Centre for Research on Longevity) funded by the state, the Hauts-de-France Region, the Métropole Européenne de Lille (MEL) and the ERDF. The CPER-CTRL calls for projects aim to promote cooperation between regional teams on new

longevity-related issues as well as the emergence of new teams.

Following the June 2017 launch of 2nd CPER-CTRL call for projects, 8 projects, including 4 exploratory and 4 collaborative projects, 1 emerging team and 1 junior team were selected for funding after evaluation by independent experts and the International Advisory Board (SAB).

EXPLORATORY PROJECTS

PROJECT NAME	APPLICANTS	PROJECT TITLE
NL4TB	Baptiste Villemagne/UMR1177 Alain Baulard/CIIL	Nouvelle génération de leads pour combattre la tuberculose <i>New leads for Tuberculosis</i>
RAGING	Eric Boulanger UMR995 LIRIC Florence Pinet/U1167	Antagonistes du RAGE pour contrôler le vieillissement inflammatoire systémique chronique <i>RAGE Antagonists fighting inflammaging</i>
SALMA-AIEC	Benoît Foligné/UMR995 LIRIC Priscille Brodin/CIIL	Screening Automatisé Longitudinal & Multi-analytique des pathovars Adhérents Invasifs d'E. Coli (AIEC) <i>Automated longitudinal and multianalytic screening of Adherent-Invasive Escherichia Coli (AIEC) strains</i>
ChipsToSoma	Jérôme Vicogne/CIIL Vincent Senez/UMR8520 IEMN	Développement d'une biopuce dédiée à l'étude du parasite Schistosoma mansoni <i>Development of a BioChip for the study of the parasite Schistosoma mansoni</i>

COLLABORATIVE PROJECTS

PROJECT NAME	APPLICANTS	PROJECT TITLE
OutSMART-TB	Alain Baulard/CIIL Nicolas Willand/U1177	Molécules de réversion de la résistance au PZA et au PA824 chez M. Tuberculiss <i>Small molecules aborting resistance to PZA and PA824 in tuberculosis</i>
FISSURE	Olivier Pluquet/UMR8161 Nicolas Pottier/EA4483	Rôle de l'UPR dans la fibrose associée à l'âge <i>Role of the pathway in fibrosis associated to aging</i>
Chol-O-Rev	Philippe Lefebvre/U1011 Tony Lefebvre/UMR8576	Vieillesse et athérosclérose: régulation du transport du cholestérol par le système Rev-Erba/OGT <i>Ageing and atherosclerosis: regulation of cholesterol transport by the ev-Erba/OGT system</i>
INFLAMMAVAX	Stéphane Cauchi/CIIL David Dombrowicz/U1011	Bénéfices anti-inflammatoires et métaboliques d'un vaccin vivant <i>Anti-inflammatory and metabolic benefits of a live vaccine</i>

EMERGING TEAM

CANDIDATE FIRST AND LAST NAME	HOST UNIT	PROJECT TITLE	ARRIVAL DATE
Marcos COSTA	U 1167 Inserm, Lille University, Institut Pasteur de Lille Risk factors and molecular determinants of diseases linked to aging	Sonder la maladie d'Alzheimer en utilisant des CSPi et des organites du cerveau <i>Probing Alzheimer's disease using iPSCs and brain organoids</i>	Dec-2018

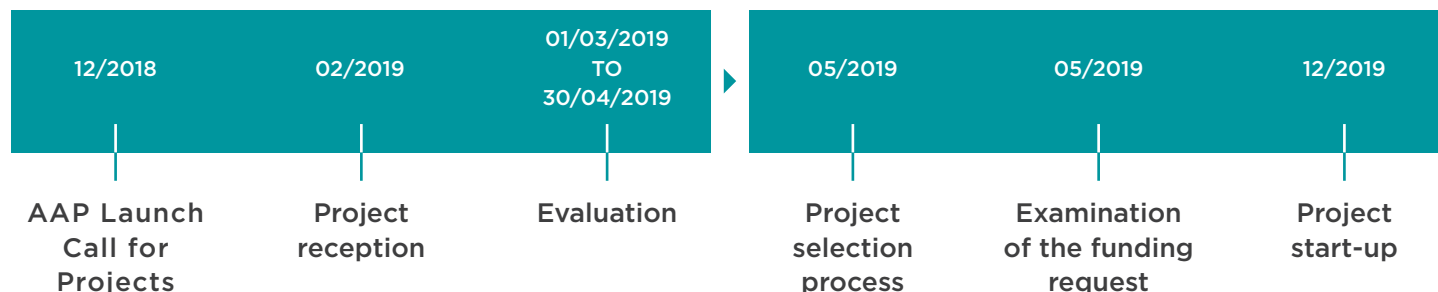
JUNIOR TEAM

CANDIDATE FIRST AND LAST NAME	HOST UNIT	PROJECT TITLE	ARRIVAL DATE
Fabien DELAHAYE	UMR8199 CNRS, Lille University, Institut Pasteur de Lille	Epigenetics in fetal life repertoire	Feb-2019

LAUNCH OF THE 3RD CALL FOR 2018 CPER-CTRL COLLABORATIVE AND EXPLORATORY PROJECTS

In December 2018, Institut Pasteur de Lille launched the **3rd CPER-CTRL call for research projects**. Each submitted project must be proposed by 2 teams from different research units. And each

must project include one of the 2 objectives of the Longevity research project. This call for projects will fund collaborative projects up to €200,000 and exploratory projects up to €50,000.



CPER-CTRL FINANCING



AN INTERNATIONAL SCIENTIFIC ADVISORY BOARD (SAB)

Pr Bernard Thorens

Centre for Integrative Genomics
Lausanne - Switzerland

Pr Gordon Dougan

Wellcome Trust Sanger Institute,
Cambridge - United Kingdom

Pr Folkert Kuipers

Gröningen Longevity Research Centre
Netherlands

Pr Thomas Thum

Hanover Medical School IFB
Germany

Pr Miroslav Radman

Mediterranean Institute for Life
Sciences MedILS, Split - Croatia

Pr Philip Scheltens

Alzheimer Centre
Amsterdam - Netherlands



SUPPORT FOR SHARED TECHNOLOGICAL PLATFORMS

Institut Pasteur Lille is one of three major platform sites in Biology and Health in the Lille greater metropolitan area. The others are the university hospital campus and the Villeneuve d'Ascq Science Centre university campus. These platforms are managed in partnership with Lille University, CNRS, Inserm, and Inria.

The facilities include cellular imaging, transcriptomics, genomics, bioinformatics and bioanalysis, chemistry, pharmacology, proteomics and mass spectrometry, nuclear magnetic resonance, life imaging,

experimental resources, etc. These exceptional tools, some of which are unique in France, attract researchers and industrial collaborations from all over the world. They aim to provide public and private research teams with unique expertise and a complete set of tools and skills that can be used to multiply the opportunities for collaboration.

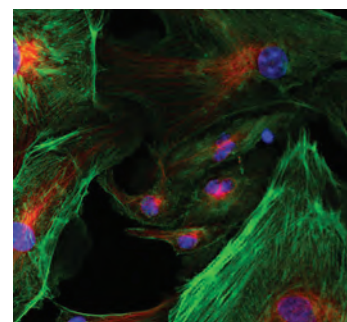
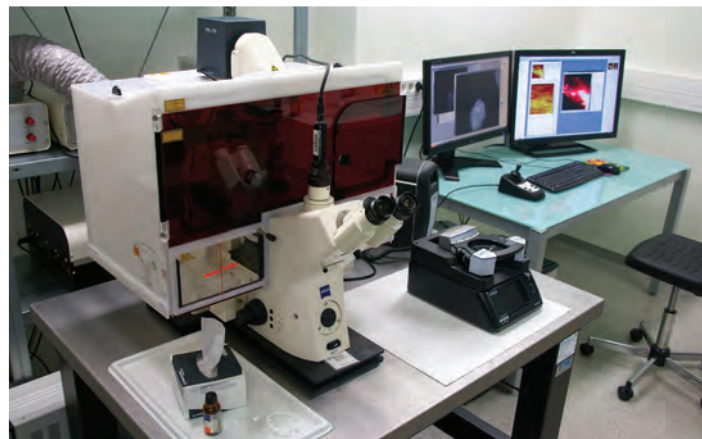
These platforms represent a unique panel in terms of analysis capacity. In 2018, two benefited from new equipment and personnel support from CPERCTRL programmes.



■ BiImaging Centre Lille - North of France (BICeL)

The objective of BICeL is to support the research efforts of the regional, national, and international community with an eye to maintaining a level of excellence in the development of relevant technologies for the service of high-visibility scientific issues. Several research teams in close collaboration with the BICeL develop innovative systems and protocols.

More specifically, with EquipEx ImagInEx BioMed, the BiImaging Centre is a reference platform for a pipeline that goes from high-speed and high-content microscopic screening on through analysis with the highest possible resolution in biophotonic, electronic, and atomic force imaging. And these within the laboratory's different containment safety levels 1, 2, and 3. This effort rests on R&D work of international reputation in atomic force microscopy in the biomedical field and in multi-modal photonic microscopy. This project notably meets important needs in the academic and private sectors specifically in high-content imaging with whom BICeL has a close partnership.



■ LIGAN-PM Lille platform for high-speed sequencing and genotyping

Developments in the LIGAN-PM platform make it possible to increase the number of sequenced genomes and differentiate our applications. The platform should make it possible to identify new genes and variants that play a role in the development of common diseases. Ultimately, the goal is to achieve personalized medicine by sequencing a patient's genome, on demand.

This platform allows researchers to have the most effective tools for sequencing and phenotyping. The LIGAN-PM platform also allows research training at different skill levels (technicians, engineers, students, post-doc).



■ FOCUS ON... MARCOS COSTA, WINNER OF THE CALL FOR PROJECTS "EMERGING TEAM" 2017

Further to the 2nd call for CPER-CTRL projects launched in June 2017, an emerging team joined the Institut Pasteur de Lille campus in December 2018, to strengthen and innovate in the longevity

research projects. Marcos Costa, a researcher specialised in neuroscience, consequently allows the Institut to consolidate its leadership in research linked to Alzheimer's disease.

Dr. Marcos Costa is a Brazilian researcher. After medical studies in Brazil with a specialisation in neuroscience, he became more specifically interested in research concerning brain functions.

"This is an area in health, even in physiology, which is never fully understood. There are still so many things to discover and I think that the brain defines who we are."

Dr. Costa chose to study medicine to understand the functioning of the human body which fascinates

him: "When I had the opportunity to work in a laboratory, I finally discovered that this was the place par excellence to nourish and develop my curiosity. I quickly became passionate about research and understood that was my vocation."

With a doctorate in physiology and a post-doc completed in Germany, Marcos Costa became a neuroscience professor at Rio Grande do Norte Federal University in Brazil. Since 2009, he has paired his passion for teaching with his vocation as a researcher through his work as a professor and his position as director of a laboratory.

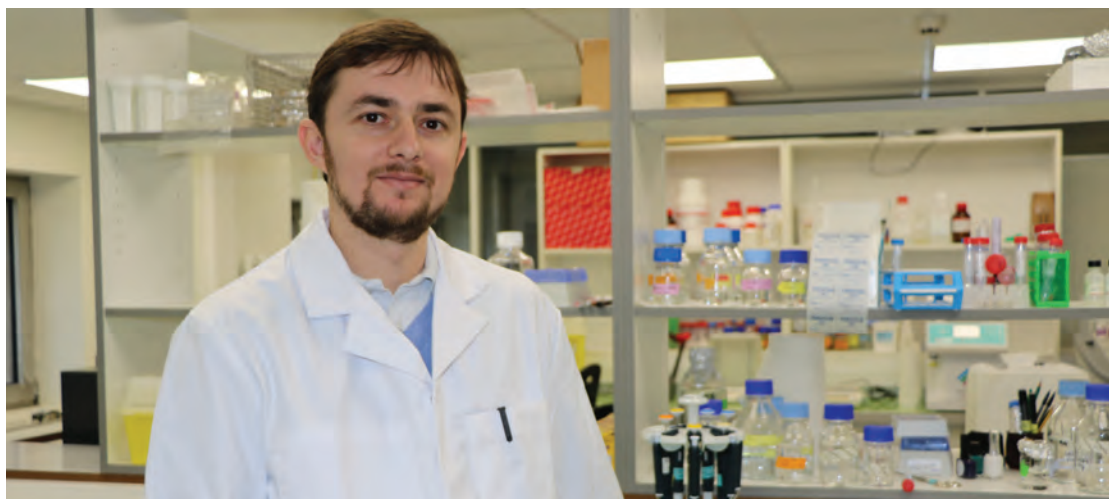
In December 2018, Marcos Costa joined Institut Pasteur de Lille as a researcher in Dr. Jean-Charles Lambert's team. He leads projects on stem cell and organoid models to study the mechanisms of Alzheimer's disease.

Generally, the use of cells is extremely useful making it possible to study diseases' cellular and molecular mechanisms without having to conduct animal testing beforehand.

As a result, stem cells offer the possibility of obtaining all types of human cells. This is a very important component in the research undertaken against pathologies such as Alzheimer's disease as it has particularities unique to humans.

"I am very proud to join this Institut with its rich history and important scientific breakthroughs. It's an honour for me to work here today!"

In addition to his research activities, Marcos Costa is passionate about travelling, which allows him to keep the open-mindedness which is essential for researchers. Arriving in France and Institut Pasteur de Lille are part of his most beautiful experiences.



INTERNATIONAL RELATIONS

The health of populations is a major societal and global issue. The spread of infectious disease and also the development of noncommunicable diseases know no borders. The impact of pollution on public health is a growing problem in industrialised countries. As for extending life expectancy, this is a visible feature on all continents. In order to increase knowledge and provide innovative tools to fight diseases

which affect the quality of life and longevity, the scientists at Institut Pasteur de Lille are developing crossdisciplinary projects between different departments of the institute as well as with the best academic researchers and industrial partners present around the world. European (Horizon H2020, IMI2, etc.) and international (NIH US Foundations and Companies, etc.) funding support these collaborative projects.

INSTITUT PASTEUR DE LILLE: KEY PLAYER IN THE INSTITUTS PASTEURS INTERNATIONAL NETWORK

Institut Pasteur de Lille is particularly involved in the Instituts Pasteurs International network (IPIN) where it has the vocation of developing a longevity programme. During the network's last general assembly in November 2018, Institut Pasteur de Lille was elected for a 3-year term to represent and coordinate the Europe region within the IPIN..

MORE THAN 110 MASTER AND PHD STUDENTS, OF WHICH ABOUT 22% ARE FOREIGN STUDENTS (2017), ARE TRAINED EACH YEAR IN THE LABORATORIES ON THE INSTITUT PASTEUR DE LILLE CAMPUS.



Within the network, Institut Pasteur de Lille has also created privileged links with the FIOCRUZ Foundation (Brazil) for the evaluation of a candidate-vaccine against schistosomiasis with the NGO "Espoir Pour La Santé" (Senegal) and for the development of joint projects in the field of neuroscience.

More recently, Institut Pasteur de Lille strengthened its strategic collaboration with Belgian colleagues from Sciensano. (www.sciensano.be) an entity born of the fusion of the Centre d'Étude et de Recherches Vétérinaires et Agrochimiques (CERVA) and the former Scientific Institute for Public Health (ISP). The goal is to strengthen

our partnership in 2 areas of joint interest: antimicrobials resistance and the impact of air pollution on health.

Institut Pasteur de Lille regularly hosts students and trainees from other network institutes in its laboratories to share knowledge, provide network members access to the high-tech equipment present on campus, and to advance joint projects.

Institut Pasteur de Lille studies all partnership proposals with universities and institutions seeking to establish scientific collaborations which share the same values and missions.

In 2019, Institut Pasteur de Lille will organise the 3rd edition of the International Symposium on Longevity Symposium which will take place

DECEMBER 11-12, 2019.

AN INTERNATIONAL DEVELOPMENT STRATEGY

- Provide international leadership in longevity research
- Collaborate with the best scientists around the world
- Explore strategic funding sources around the world
- Increase its visibility and attractiveness

Le Réseau International des Instituts Pasteur

Une communauté humaine et scientifique mondiale unie par des valeurs et des missions communes au service de la santé.



32
INSTITUTS MEMBRES

25
PAYS

23 000
PERSONNES



AMÉRIQUE

Fiocruz (Rio de Janeiro)
INRS-Institut Armand-Frappier (Laval)
Institut Pasteur de la Guadeloupe (Pointe-à-Pitre)
Institut Pasteur de la Guyane (Cayenne)
Institut Pasteur de Montevideo

EUROPE

Institut Pasteur d'Italie - Fondation Cenci Bolognietti (Rome)
Institut Pasteur hellénique (Athènes)

Institut Pasteur de Lille
Institut Pasteur (Paris)
Institut Pasteur de Saint-Petersbourg
Sciensano (Bruxelles)
Institut Stepan Angeloff (Sofia)

MAGHREB-IRAN

Institut Pasteur d'Algérie (Alger)
Institut Pasteur d'Iran (Téhéran)
Institut Pasteur du Maroc (Casablanca)
Institut Pasteur de Tunis

AFRIQUE

Centre Pasteur du Cameroun (Yaoundé)
Cermes Niger (Niamey)
Institut Pasteur de Bangui
Institut Pasteur de Côte d'Ivoire (Abidjan)
Institut Pasteur de Dakar
Institut Pasteur de Guinée (Conakry)
Institut Pasteur de Madagascar (Antananarivo)

ASIE - PACIFIQUE

Institut National d'Hygiène et d'Epidémiologie (Hanoi)
Institut Pasteur du Cambodge (Phnom Penh)
Institut Pasteur de Corée (Séoul)
Institut Pasteur d'Hô Chi Minh Ville
Institut Pasteur du Laos (Vientiane)
Institut Pasteur de Nha Trang
Institut Pasteur de Nouvelle-Calédonie (Nouméa)
Institut Pasteur de Shanghai, Académie chinoise des Sciences
Pôle de recherche Université de Hong Kong - Pasteur

Present in 25 countries across all the continents, the Instituts Pasteurs International Network (IPIN) brings together 32 institutions united by common missions and values for the benefit of the general public. Located at the heart of numerous endemic zones, the IPIN has, on multiple occasions, demonstrated its major role as a sentinel in response to infectious emergencies.

Driven by ethics and the respect of Pasteurian values, the Instituts Pasteurs International Network strives to improve human health.

■
ACCELERATING RESEARCH AND
ACTING ON TOMORROW'S HEALTH



LONGEVITY: INTERDISCIPLINARY TEAMS FOR EXCELLENCE IN RESEARCH

Institut Pasteur de Lille hosts a longevity research centre divided into six units, with multidisciplinary, cross-cutting skills. This interdisciplinary research programme which mobilises all Institut Pasteur de Lille teams aims to identify and characterise the genetic, environmental, metabolic, and infectious factors which contribute to lowering the cells' and the organisms functional performance. We call this ageing. With better knowledge of these mechanisms, exposure to these factors can be prevented and their impact reduced by stimulating the cells' and organism's resilience using innovative prevention strategies or treatment.

It is organized around the following research areas:

- 01** NEURODEGENERATIVE DISEASES
- 02** CARDIOVASCULAR DISEASES
- 03** INFECTIOUS AND INFLAMMATORY DISEASES
- 04** RESEARCH FOR NEW PRESCRIPTION DRUGS
- 05** METABOLIC DISEASES, DIABETES, OBESITY
- 06** CANCERS

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:

Institut Pasteur de Lille's campus boasts an exceptional concentration of high level facilities and technology platforms to serve all the

- A LABEX DEDICATED TO ALZHEIMER DISEASE (DISTALZ)
- A LABEX DEDICATED TO STUDYING DIABETES (EGID)
- A RESEARCH CENTRE ON INFECTION AND IMMUNITY (CIIL) INVOLVED IN THE PARAFRAP LABEX
- AN EQUIPEX DEDICATED TO CELLULAR IMAGING PHARMACOLOGICAL SCREENING (IMAGINEX BIOMED)
- AN EQUIPEX DEDICATED TO GENOMICS (LIGAN-PM)

researchers in the regional scientific community. It also has the largest molecule library in Europe – the chemical library – where thousands of tests are conducted every year, helping in the discovery of new drugs.

RISK FACTORS AND MOLECULAR DETERMINANTS OF DISEASES LINKED TO AGING

This unit focuses on the fight against age-related diseases, especially cardiovascular and neurodegenerative diseases. Prof Philippe Amouyel coordinates Distalz laboratory of excellence (LabEx), dedicated to Alzheimer's disease. Three teams interact within UMR1167 on the "epidemiology and public health of cardio and cerebrovascular diseases", the "molecular determinants of heart failure and ventricular remodelling", as well as on the "molecular determinants of Alzheimer's disease and cognitive disorders".



Pr Philippe Amouyel

PU-PH, University, Lille
University Hospital, U1167 -
Labex Distalz, Inserm, Institut
Pasteur de Lille, Lille University
Hospital, Medical School, Lille
University

Analysis of the risk factors to improve the prevention of cardiovascular disease

This team led by Dr Aline Meirhaeghe analyses the role of cardiovascular risk factors (genetics, excess weight, obesity, type 2 diabetes, high blood pressure, cholesterol, smoking, etc.) in the emergence and progress of myocardial infarction and strokes. Their work is based on Lille's morbidity register of ischemic heart disease and stroke, which continuously inventories all cases of these diseases occurring within the Metropolitan Community of Lille. The purpose of these studies is:

- to understand the evolution of the vascular pathology in terms of classification, management and prevention,
- to analyze the role of genetic and environmental determinants of cardiovascular diseases.

Detection of cardiac ageing in order to anticipate it more effectively

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. Dr Florence Pinet, who leads this team, is looking for the early markers of heart failure. Specialising in proteomics, a science that studies proteins

and their functions and interactions within cells, it has developed protocols for clinical research at the patient's bedside that have made it possible to discover early biological markers of the remodelling of the left ventricle associated with heart failure. Since then, it has developed a dosage that can be used in clinical routines and help prevent the accelerated ageing of the heart.

Understanding genetic susceptibility to Alzheimer's disease in order to combat it more effectively

Alzheimer's disease is a neurodegenerative disorder of the brain that develops over several decades. So when the clinical signs appear, the disease has already done irreparable damage. The team led by Dr Jean-Charles Lambert is interested in the study of individual susceptibility to Alzheimer's disease and was able to identify the majority of the genes involved in the occurrence of this disease. This research should help to gain a better understanding of the causes in order to propose new treatment and prevention options.

HIGHLIGHTS

01

The existence of a register of cerebral vascular accidents (CVA) since 2008 in Lille, has made it possible to compare differences in the risk of CVA in men and women. While the number of total CVA is higher for women than for men, the risk of women developing this disease is 30% lower than in men, regardless of the cause of the CVA. This can be explained as women's life expectancy is 8 years longer than men's, and suggests that CVA prevention must be undertaken with the same intensity for men and women (Meirhaeghe et al., Journal of Stroke and Cerebrovascular Disease 2018).

02

We studied associations between long-term exposure to pollution and diabetes markers in the ELISABET survey established by a representative sample of the Lille and Dunkirk populations. With the Hauts-de-France ATMO, we evaluated annual exposure to three pollutants: micro-particles (PM10), NO2, and sulphur dioxide (SO2) in the survey participants' place of residence. We were able to demonstrate that an increase in PM10 and NO2 was associated with an increase in glycated haemoglobin known to be a long-term diabetes marker. Therefore, our study established an epidemiological link between pollution and glycaemic balance (Riant et al. Environment International, 2018)

03

After their first myocardial infarction, a certain number of patients develop modifications in their cardiac muscle in the shape of a ventricular remodelling. This ventricular remodelling is observed in 31% to 38% of patients in the REVE and REVE2 studies. After 11 years and 7.8 years of monitoring of these two studies, we demonstrated that patients presenting this ventricular remodelling had increased risk of death or hospitalisation for heart failure despite proper therapeutic treatment (Bauters et al, 2017). Consequently, one of the major challenges for this team is to identify predictive markers of this remodelling which will enable prevention of the long-term risk of complications.

04

We brought to light an increase in blood rates for a protein known as clusterin in the REVE patients presenting cardiac remodelling. The clusterin rates in the heart were correlated to remodelling parameters. We also identified the pro-hypertrophic role of clusterin in cardiomyocytes and we confirmed a significant increase in clusterin in biopsies of human hearts with heart failure. Our results show, for the first time, that the plasmatic rates of clusterin are associated with post-infarction cardiac remodelling and that they are predictors of premature death in patients suffering from heart failure (Turkieh et al, 2018).

05

Within the scope of the international IGAP consortium, coordinated by the unit, we were able to identify new susceptibility genes associated with the risk of Alzheimer's disease. This study covered a total of 90,836 individuals. Consequently, we were able to confirm 20 of the previous genes associated with the risk of Alzheimer's disease and to identify five new genes of interest. The biological pathways involving these new genes has oriented our research to the immune system, lipid metabolism, as well as, for the first time, towards binding proteins to tau and APP proteins which are the two major proteins implicated in Alzheimer's disease. (Kunkle*, Grenier-Boley*, et al, Nat Genet, in press).

06

No medical treatment has yet been found to fight Alzheimer's disease. However, in the more developed countries such as France, it has been observed that the first signs are delayed suggesting that prevention is possible. Consequently, we analysed all modifiable factors associated with the disease's later start and grouped them in the form of prevention rituals in a book intended for the general public. This is truly an everyday practical guide for the prevention of Alzheimer's disease founded on the most recent scientific and medical data. ("Le guide anti-Alzheimer, les secrets d'un cerveau en pleine forme", Philippe Amouyel, Le Cherche-Midi, in French only)



NUCLEAR RECEPTORS, CARDIOVASCULAR DISEASES AND DIABETES

UMR1011 studies the physio-pathological mechanisms at the molecular, cellular level, in preclinical models and in humans, at the origin of obesity, type-2 diabetes, and its cardiovascular (atherosclerosis, heart failure, valvular diseases) and hepatic complications. The impact on the immune system of circadian and epigenetic alterations. Therapeutic approaches centred on nuclear receptors are implemented.

Pr Bart STAELS

PU-PH - Lille University, Lille University Hospital, U1011, Inserm, Lille University, Institut Pasteur de Lille, Lille University Hospital

Metabolic pathologies such as obesity and type-2 diabetes and their cardiovascular complications are the primary cause of death not only in industrialised countries but also in developing countries. Using fundamental and translational approaches, UMR1011 studies the physio-pathological processes at the origin of these pathologies with a particular interest for the nuclear receptors which represent choice therapeutic targets.

Over the course of 2018, **major breakthroughs touched on the role of the Rev-erba** nuclear receptor, a major regulator of the circadian clock in controlling acute inflammatory reactions in mice (hepatitis) and **cardiovascular complications further to**

myocardial surgery in humans. The receptor's molecular action mechanism at the hepatic level was also specified.

The contribution of other nuclear receptors, and more generally transcription factors, to hepatic functions was also highlighted (PPARα in septic shock, FXR, bile acid receptor, in the control of neoglucogenesis).

Unit 1011 published **43 scientific and clinical publications** over the course of 2018.



01

Daytime variation of perioperative myocardial injury in cardiac surgery and its prevention by Rev-Erba antagonism: a single-centre propensity-matched cohort study and a randomised study.

Cardiac complications are less frequent and less severe when valvular surgery is performed in the afternoon rather than in the morning. The issue under consideration here is a modulation of the ischemia lesion by the molecular actors of the biological clock present in each of the cells of the heart. The shift of this internal clock by the suppression of the activity of one of its actors, the nuclear receptor, Rev-erba, reduces the significant susceptibility of the heart to ischemia observed in rodents in the waking period. These findings point to new therapeutic approaches in cardiac pathology, especially in the context of myocardial ischemia.

03

Hepatic PPARα is critical in the metabolic adaptation to sepsis.

Septicaemia is the primary cause of death in critically ill patients. Although literature suggests inflammation's important role in this pathology, we demonstrated that the absence of hepatic expression in nuclear receptor PPARα reduces survival in the case of septic shock in mice. This diminished survival is associated with an alteration in the metabolic response with greater hypoglycaemia and steatosis and a deficit in the production of ketone bodies. The hepatic expression of PPARA is lower in critically ill patients and correlates positively with the expression of genes in lipidic metabolism. Metabolic interventions could therefore represent a viable strategy for diminishing mortality due to septicaemia.

05

Nuclear Receptor Subfamily 1 Group D Member 1 Regulates Circadian Activity of NLRP3 Inflammasome to Reduce the Severity of Fulminant Hepatitis in Mice.

Fulminant hepatitis (FH) is a serious disease which provokes rapid degradation of the liver, haematite coagulation difficulties, and incurable cerebral damage. Until the present, no specific treatment of FH exists and the only solution remains a liver transplant within 24 hours after the appearance of symptoms. From the observation that immune functions vary over the day, we studied a biological clock protein, Rev-erba, and its implication in regulation of inflammation during FH. Our work on mice and human cells of the immune system, allowed us to highlight that the inflammatory phenomena follows a circadian rhythm. We demonstrated that injection of a molecule increasing the action of REV-ERBa reduces the inflammatory reaction responsible for the death of liver cells during FH.

HIGHLIGHTS

02

Arterial Pulsatility and Circulating von Willebrand Factor in Patients on Mechanical Circulatory Support.

Highlighting the role of pulsatility in maintaining circulatory concentrations of the von Willebrand factor (VWF) and haemorrhagic risks due to absence of pulsatility and shearing forces in circulatory support mechanisms. An original animal model developed to explore the endothelial response to hemodynamic variations, made it possible to establish for the first time that acute variations in arterial pulsatility are able to stimulate VWF secretion and angiogenic factors from Weibel-Palade bodies. As a result, the size and distribution of VWF multimers circulating in this model reflect the residual arterial pulsatility level and the shear stress provoked by the pump. Subjecting this observation to different assistant sequences enabled us to confirm the relevance of the model. This work established for the first time the causal relation between arterial pulsatility and VWF, and could thus explain the differences in bleeding frequency between cardiac assistance pumps with pulsated flow and continuous flow.

04

Combinatorial regulation of hepatic cytoplasmic signalling and nuclear transcriptional events by the OGT/REV-ERBa complex.

The REV-ERBa nuclear receptor interacts with O-GlcNAc transferase and regulates its activity and stability. OGT modifies numerous proteins including certain implicated in the insulin signalisation pathway or in the epigenomic regulation process. Cyclic regulation of OGT by REV-ERBa in the liver impacts in a sequential manner on the sensitivity to insulin and the expression of lipogenic genes in the liver.

The activity period for REV-ERBa is sensitive to meal times at the level of liver. Currently, no pharmacological approach allows for resynchronising sensitivity to insulin over the course of the day. Consequently, it is recommended that meal times coincide with everyone's social activity in order to limit the desynchronization between the biological clock, metabolic needs, and our daily activities.

INFECTION AND IMMUNITY CENTRE OF LILLE

Microbial and parasitic infections as well as inflammatory diseases are major causes of mortality and morbidity. Their long-term impact on other conditions, such as cancer, cardiovascular, metabolic and neurodegenerative diseases, is considerable. In order to understand infection and immunity, including their deregulation, integrated multi-disciplinary approaches are required. These are developed among the 14 complementary teams of the Centre for Infection and Immunity of Lille (CIIL).

Dr Camille Locht

Inserm research director
UMR 8204 - U1019, CNRS,
Inserm, Lille University, Institut
Pasteur de Lille

The **14 teams from CIIL** and its related platforms bring together **more than 14 researchers, engineers, and technicians** with complementary expertise covering a wide range of disciplines, from molecular epidemiology, virology, bacteriology and molecular and cellular parasitology, to the immunological bases of infectious and non-infectious diseases and the development of clinical applications. More precisely, the scientists search for **treatments against respiratory infections** (tuberculosis, pertussis, influenza, MERS, pneumococcus infections), **hepatitis C and E, the plague, bilharzia, toxoplasmosis, Blastocysts and Cryptosporidium infections**, (ii) and **inflammatory diseases**, whether intestinal or pulmonary (asthma, respiratory allergies, chronic bronchitis, chronic obstructive bronchopneumonia). The 14 teams are divided in three major fields: **parasitology, molecular and cellular microbiology, immunity and inflammation**.

2018 saw **the identification and definition of new active anti-viral compounds' mode of action on the hepatitis C virus**; other new compounds proved to be active against *Mycobacterium tuberculosis*, and yet others against the *Plasmodium* and *Schistosoma*

parasites. In addition, a powerful molecular system was developed and validated in the cohorts. It permits identification of *M. Tuberculosis* clinical isolates which are resistant to first line anti-tuberculosis treatments.

The role of the ArfGAP1 protein in restricting entry of *M. tuberculosis* into the pulmonary epithelium was determined. This protein regulates the rearrangement of cytoskeletons composed of actin.

The action mechanism of flavone apigenin which is found in plant-based foods, in protection against colitis was determined. It is a mechanism which implicates the NLRP6 protein yet is independent of inflammasome activation.

The importance of signalisation by means of cytokines in the interleukin 20 family was determined in infection by *Streptococcus pneumoniae* and pulmonary inflammation.





HIGHLIGHTS

01

The deterioration of NOD2 by NLRP12 in monocytes increases bacterial tolerance. The Nods-like receptors in infection and inflammation team, *Dir. Mathias Chamaillard*. Mutations in the NLRP12 protein are responsible for a familiar form of the auto-inflammation syndrome induced by cold and characterised by recurring episodes of fever and digestive problems. Recent data from Dr. Chamaillard's laboratory has made it possible to question a hyper-activation of the major NOD2 gene for predisposition to Crohn's disease which could enable taking into account the North-South gradient in the incidence of this digestive tract inflammation which affects millions. The results were published in Nature Communications.

02

Development of new combinations of compounds for treatment of multi-resistant tuberculosis. Bacterial respiratory infection: pertussis & tuberculosis team, *Dir. Camille Locht*. The WHO recently stated that the rapid rise in cases of antibiotic-resistant tuberculosis imperils the global programme to fight this pandemic which destroys more lives than any other infectious disease. The CIIL BRIPT team and U1177 developed a candidate-drug which restores ethionamide sensitivity in tuberculous bacillus resistant to this antibiotic. This drug may be compared to an "information virus" which reprogrammes the bacteria forcing it to circumvent resistance mechanisms which it established. This work which was published in the scientific magazine, Science, has just received the support of a European IMI programme to execute the clinical human innocuousness phase under the aegis of the Bioversys and GSK laboratories.

03

The importance of ApiAP2 cooperative binding for expression of *Toxoplasma gondii* gene virulence. Biology of apicomplexan parasites: factors regulating growth, differentiation and virulence team, *Dir. Jamal Khalife*. *Toxoplasma gondii* is a single-cell eukaryote of medical importance. *T. gondii* has a very complex life cycle. The crucial phase for this parasite's pathogenesis in humans consists in the proliferation of the tachyzoite stage. This form of the parasite expresses virulence and invasion factors which are indispensable for its survival in a human host. These factors' expression profile is strictly regulated while the implicated factors are unknown. We have identified a couple transcription factors able to regulate the parasite's virulence gene expression. We thus demonstrated for the first time that these two factors' cooperation is a key event in controlling virulence. Discovery of these regulators is a crucial step in understanding the molecular mechanisms which govern the parasite's virulence.

04

Chemical ligation to difficult amino acids for the synthesis of cyclic peptides. Chemical biology of flatworms: identifying the molecular determinants of *Schistosoma mansoni* reproduction team, *Dir. Oleg Melnyk*. The pharmaceutical industry is increasingly turning to development of peptide drugs in addition to classic approaches based on small organic molecules. Production means have evolved as has the emergence of real-time synthesis procedures which offer numerous advantages such as precision control of thermal exchange and reaction times. Their development raises however numerous methodological challenges. The article published in Nature Communications by the Chemical Biology of Flatworms team describes a microfluidic system which enables real-time synthesis of anti-microbial cyclic peptides thus opening the way to new means of producing biologically active peptides.

05

Start of the clinical 2 phase with BPZE1, the live nasal vaccine for the prevention of whooping cough. Bacterial respiratory infection: pertussis & tuberculosis team, *Dir. Camille Locht*. After two clinical trials in phase 1 which demonstrated its safety and provided the first data on immunogenicity in humans, the BPZE1 live nasal vaccine for the prevention of pertussis has now entered phase 2 in collaboration with the company ILiAD Biotechnologies and the American NIH. The data obtained in primates has shown that this vaccine protects against both the disease and against infection by *Bordetella pertussis*, the causal agent in whooping cough, which is crucial to avoid carriage and spread of the bacillus. The team demonstrated that protection from infection depends on the vaccine's capacity to induce secretory IgA-type antibodies in the nose which current vaccines are not capable of doing.

MEDICINES AND MOLECULES FOR ACTING ON LIVING SYSTEMS

The laboratory's mission is to design and synthesise drug prototypes with an innovative mode of action. This interdisciplinary molecular invention work is inspired by the most recent discoveries made on infectious diseases, metabolic diseases and cancer. This work proposes areas in the body to be targeted with new active ingredients.

Pr Benoît Déprez

PU - Lille University, U1177, Inserm, Institut Pasteur de Lille, Lille University, (Pharmacy faculty)

The design and optimisation of new drugs requires interdisciplinary expertise covering chemistry, physics, biology and in silico modelling. Indeed, the active ingredient of modern drugs, whether they are synthetic or biological in origin, is always defined at the molecular, or even the atomic, level. This particular molecular structure - perfected by the researchers of the unit - is the key to all the properties of the drug. It conditions its ability to cross the physical and chemical barriers between the different biophases (intestine, blood tissues, brain, etc.) of the body and reach the intended target. It is also key to its

interaction with the intended target and the achievement of the desired effect. Beyond the therapeutic goal, molecules also serve as valuable tools that help biologists better understand how the cell and living organisms work and verify that the proposed targets for treating diseases are relevant. Researchers are working on **antibiotic resistance**, **type 2 diabetes**, certain forms of **cancer**, the **recognition of intracellular antigens by the immune system** and **pain**.





HIGHLIGHTS

01

A passage in regulatory preclinic development of candidate-drugs for treatment of multi-resistant tuberculosis in collaboration with Bioversys and GSK. Industrial synthesis is finalised, phase 1 testing (first administration to humans) is scheduled for 2020.

02

Creation of a common laboratory financed in part by the Hauts-de-France Region, between U1177 and the Swiss Bioversys company which installed its subsidiary in Lille. The objective is to develop new strategies to fight the resistance of bacteria to antimicrobials.

03

The laboratory was incorporated into LabEx Egid2 which was just approved by Agence Nationale de la Recherche (ANR), the French national research agency. This inclusion brings LabEx, centred on diabetes, recognised expertise in the field of new drug discovery and strengthens the impact of the work of the 4 other LabEx partners.

04

The discovery of unknown functions of the Insulin-Degrading-Enzyme protein outside of the field of diabetes. Thanks to chemical modulators that we have designed for several years, we can study the functions of this poorly known enzyme but its unique three-dimensional structure and the preservation in all eucaryote organisms suggest a central role in cellular life. The chemical modulators that we designed could have several therapeutic applications which are studied in several preclinic models.

05

Hosted by Dr. Bruno Villoutreix's unit, Director of Research at Inserm. Bruno is specialised in development of in silico models. He directs the unit's "dry lab" which in addition to experimental sciences, helps scientists in their selections, guides their hypotheses, and accelerated discovery and optimisation of candidate-drugs. Conversely, the experimental results in the "wet lab" participate in validation of models.

2018 KEY FIGURES FOR THE DRUG DISCOVERY CENTRE:

50

research contracts awarded

10

articles published in international peer-review magazines

1

patent submitted

2

patents licensed

1

patent awarded

INTEGRATIVE GENOMICS AND MODELING OF METABOLIC DISEASES

UMR8199 included two teams:

1 | “Genetic and Epigenetic of diabetes and obesity” co-directed by **Philippe Froguel** and **Amélie Bonnefond**, and **2 |** “Molecular bases and modelisation of metabolic diseases” directed by **Jean-Sébastien Annicotte**. It counts 63 individuals, researchers, teachers, docs/post-docs, engineers, and technicians. The unit is at the origin of LabEx-EGID and of EquipEx-LIGAN-PM, the genomic platform for personalised medicine.

Pr Philippe Froguel

PU -PH - Lille University, Lille University Hospital, LabEx, UMR8199, EGID, CNRS, Institut Pasteur de Lille, Lille University

The unit's research objectives are **to identify new genes implicated in diabetes and obesity, and to better diagnose forms of diabetes and obesity of genetic origin** which thus allows **personalised medicine** according to genetic sub-type. All projects also have as an objective to better stratify genetic and environmental risk factors, and the primary genetic causes, of metabolic diseases at different ages in life. Different “multi-omic” approaches were taken by means of our genomic platform which is unique in France (high-speed DNA and RNA sequencing, genotyping, and transcriptomic analysis by DNA chips, digital molecular counting using NanoString technology). Opening the LIGAN-PM platform to outside teams makes it possible to initiate collaborative research projects on other genetic diseases such as intellectual deficiencies associated, or not, with obesity, Crohn's disease, breast and ovarian cancers (using exome sequencing). The unit is a partner to several EU-H2020 Innovative Medicines Initiative programmes: IMIDIA (Improving beta-cell function and identification of diagnostic biomarkers for treatment monitoring in Diabetes), DIRECT (Diabetes research on patient stratification) and RHAPSODY (Risk assessment and progression of diabetes); as well as with R.H.U. PreciNASH (PIA-ANR, coordinated by François Patou, UMR1190). In these projects,

our teams have a key role in producing and analysing (epi)genomic, transcriptomic data, or derivative microbiomes, starting with large European cohorts of diabetic and/or obese patients and control populations (including human samples selected from pancreatic, hepatic, or muscular tissues). The environment's epigenetic effects (which modify genetic activity) on the metabolism and hepatic and renal complications of diabetes are studied, consequently epigenetic variations in pre-diabetic conditions such as gestational or premature diabetes (EPx-GDM and EPIPRETERM projects). Thanks to the UMR8199's organisation, which is divided up between two teams, **new pathways can be identified leading to metabolic diseases**, after which cellular or animal models can be established in order to conduct in-depth studies leading to the development **of new diagnostic and therapeutic strategies**. Beyond that, the goal of the European Genomic Institute for Diabetes (EGID) is to offer optimal conditions for translational research on diabetes to truly ameliorate treatment of diabetics and their life.





HIGHLIGHTS

01

CoDE-seq, an optimised exome sequencing for detecting isolated mutations and variants of the genome structure. We developed a new sequencing method of the human genome which optimises, in terms of time and cost, determination of causal mutations of genetic diseases. Tested successfully in children with extreme obesity paired with intellectual deficiencies, this new methodology called CoDE-seq makes it possible, in one step, to sequence isolated mutations of all types, and the very precise detection of chromosomal deletions and duplications (known as CNV). These results were published in *Molecular Metabolism* (Montagne L, Derhourhi M, et al. *Mol Metab.* 2018 Jul;13:1-9).

02

Genetic diagnosis of monogenic diabetes and severe infantile obesity.

The etiologic diagnosis of precocious non-immune diabetes and severe infantile obesity was conducted by complete exome sequencing and the analysis of gene panels and regions screened for the genome. Several collaborations were initiated with the Mediterranean Group for the Study of Diabetes (MGSD) which counts 37 centres in 11 countries, and the paediatric endocrinology departments in France and abroad (Pakistan, Israel, Georgia, Guadeloupe, and Reunion). A genetic diagnostic rate of 40%-60% was obtained depending on the centres and pathologies studied; specifically, 48% of obese children diagnosed in consanguineous populations in Pakistan, and the detection of new mutations of genes GCK, HNF1A, HNF4A, LEP, and ADCY3. These results enable implementation of precision medicine from an early age.

04

The browning of fatty tissue: a new treatment which could cure obesity-related diabetes.

In a study published in the journal "*Molecular Metabolism*" in December 2017, we demonstrated in mice and in human stem cells that invalidation of CDKN2A gene, a major cellular cycle regulator, increases the expression of specific markers in abdominal brown fatty tissue cells; this leads to its general browning and better adaptation to metabolic stress with a resistance to obesity induced by a high-fat diet. These results suggest that blocking this gene in humans may be a new opportunity for treating obesity and related diabetes.

03

Genetic loci and gene expression (eQTLs) in human samples of pancreatic clusters.

The combination of GWAS and transcriptomic studies makes it possible to identify eQTLs which may shed light on gene regulation mechanisms in conjunction with genetic associations. In the IMIDIA project, the gene expression of human pancreatic clusters starting with 203 pancreas samples of deceased subjects or partial pancreatectomies (PPP) highlighted that cis-eQTLs localised in open chromatin regions (active enhancers) close to RPH3AL genes implicated GSTT1 et UHRF1BP1, two loci associated with type-2 diabetes in insulin secretion; and eQTLs paired with the Hba1c values of PPP patients for 2 other genes. Identification of genes of interest in the biology of beta cells opens new fields of investigation. These results were submitted to *Molecular Metabolism* (Khamis A et al.) for publication.

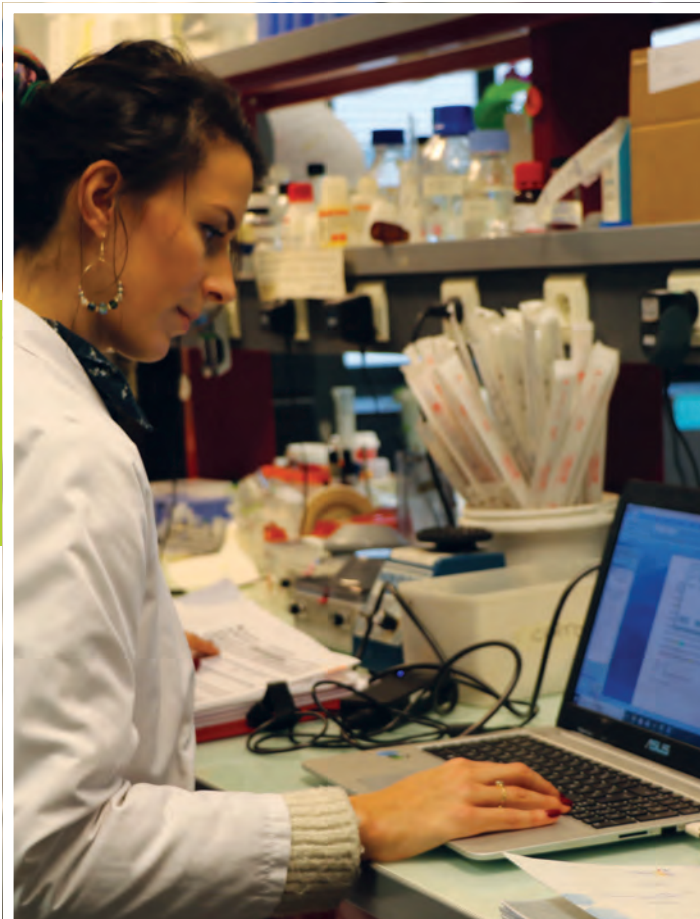
05

BETA, a maturation project upheld by SATT-Nord aims to identify new anti-diabetic drugs.

After having identified a target as a function regulator for beta pancreatic cells and insulin secretion, we used a pharmacological approach in order to identify new original molecules modulating this target. In collaboration with Pr. Benoît D  prez's team (U1177), and thanks to the support of SATT-Nord, our encouraging results opened new therapeutic paths for treatment of diabetes.

INSULIN TUMORIGENESIS MECHANISMS AND TARGETED THERAPY

Despite major progress in their detection and treatment, cancers are still a feared disease, a major cause of morbidity and mortality. Scientific research in cancerology at Institut Pasteur de Lille is part of a long tradition since the discovery of the first cancer genes, the oncogenes, in the aughts. Today, sixty-some researchers, engineers, technicians, and thesis students organised in 6 research teams continue to decrypt the very complex mechanisms by which a normal cell becomes tumoral and finally metastatic.



Pr Corinne Abbadie
PU - Lille University, UMR 8161,
CNRS, Inserm, Lille University,
Institut Pasteur de Lille

These six research teams' primary mission is to advance knowledge of the precise molecular mechanisms which are disrupted in cancerous cells and which are responsible for the initial formation of a tumour, its growth, and its escape from anti-tumoral immune defences, and then the dissemination of tumoral cells, their attraction to certain organs, and their metastatic installation. Beyond this fundamental research mission, the challenges are obviously therapeutic: each piece of new knowledge makes it possible to propose a new therapeutic lead or to modify a treatment protocol.

For example, **Professor Corinne Abbadie's team** works on understanding why cancers develop preferentially at an advanced age. The hypothesis is that certain molecular mechanisms which lead to cellular senescence could favour tumoral transformation. Supporting this idea, numerous senescent cells are found in pre-cancerous lesions. Consequently, the pharmacological inhibitors of certain proteins implicated in cellular senescence mechanisms could allow the elimination of these senescent cells and thus prevent the malign evolution of pre-cancerous lesions.

For several years, Dr. David Tulasne's team has endeavoured to comprehend how the MET receptor functions. Today, it is known that this receptor mutates in certain lung cancers.

As a result, targeted anti-MET therapies have been developed. Unfortunately, resistance to these therapies can develop. The team is concentrating on understanding these resistance mechanisms.

As for Dr. Martine Dutерque's team, it is interested in understanding why prostate cancer preferentially develops bone metastases. The TMPRSS2-ERG oncogene it is working on appears to be a major actor in regulating the gene's expression conferring a bone tropism to prostate cancer cells.

The cancerous cells present mutations which distinguishes them from others. As a result, they can be recognised by the immune system and eliminated. Nonetheless, during this malignant evolution, cancerous cells acquire the capacity to negatively regulate the immune response. These are the mechanisms studied by **Professor Nadira Delhem's team** with an aim to finding therapeutic targets which would allow the restoration or amplification of natural anti-tumoral immune responses.

01

Senescent cells develop endoplasmic reticulum stress.

Dr. Olivier Pluquet, a researcher in Pr. Corinne Abbadie's team and teacher at Lille University Medical School has completed and published work showing that senescent cells develop stress in the endoplasmic reticulum, the cell organelles implicated in the secretion of proteins, as for example, inflammatory cytokines. This reticulum stress contributes to stabilising the senescent phenotype and opposes the malignant evolution of senescent cells. Consequently, this mechanism has the properties of a tumour suppressing mechanism. *Drullion et coll (2018). Pre-malignant transformation by senescence evasion is prevented by the PERK and ATF6alpha branches of the Unfolded Protein Response. Cancer Lett 438, 187-196*

03

MET mutations revealed.

In close collaboration with the Lille University Hospital, Dr. David Tulasne's team optimised molecular diagnostics allowing the detection of Tyro Kinase MET receptor mutations in lung cancer. These diagnostic solutions are now used routinely at the Lille University Hospital. *Descarpentries et coll (2018). Optimization of routine testing for MET exon 14 splice site mutations in non-small cell lung cancer patients. Journal of Thoracic Oncology, 1, 33038-7.* The team also demonstrated that lack of oxygen (hypoxia), often observed in tumours, induced a decrease in MET phosphorylation and a resistance to targeted therapies. *Mekki et coll (2018). Hypoxia leads to decreased autophosphorylation of the MET receptor and promotes its resistance to tyrosine kinase inhibitors. Oncotarget. 9, 27039-27058.*

05

The gamma-synuclein is responsible for breast cancer cells' resistance to radiotherapy.

Lu Thia, a student in Dr. Roland Bourrette's teams, upheld his thesis at end 2018. His work of 3 years covered cancerous stem cells (CSC) in breast cancers. These CSC play a central role in tumour growth, the formation of metastases, and above all acquisition of resistance to treatment. Lu Thian isolated a CSC population from the mammary tumours of genetically modified mice. Analysis of these CSC's transcriptome made it possible to identify disruptions in the Notch pathway as well as the genes responsible for resistance to chemo- and radiotherapy such as gamma-synuclein. *Tian et coll. (2018). Synuclein gamma enhances radiation resistance of breast cancer cells. Oncotarget 9, 27435-27447.*

07

A new photosensitiser to treat ovarian peritoneal carcinosis.

Pr. Nadira Delhem's team, in collaboration with Pr. Serge Mordon (Unité OncoThAI), filed an invention patent for a new photosensitiser drug useable in Photodynamic Therapy. This photosensitiser coupled with Folate is specific to ovarian peritoneal carcinosis. The ancillary biological study lead by the team validates the hypothesis according to which this new treatment could generate an "abscopal effect" favourable to activation of anti-tumoral immune response. This project was financed by SATT Nord and SATT Nord Est and was awarded the Prix des Translationnelles in November 2018 by the BMS Foundation under the aegis of the Cancerpole Nord-Ouest.

HIGHLIGHTS

02

A mushroom with anti-cancer powers.

Approximately 10% of genetic diseases including cancers and rare pathologies such as cystic fibrosis, implicate a nonsense mutation which prematurely stops protein synthesis. By screening the Extract Library of the National Museum of Natural History, Dr. Fabrice Lejeune (Dr. David Tulasne's team) demonstrated that the extract of the *Lepista inversa* mushroom can correct the consequences of a nonsense mutation by allowing the reexpression of tumour-suppressing genes in cancerous cells. This discovery carries hope as this mushroom is edible and quite common. *Benhabiles et coll (2017) Optimized approach for the identification of highly efficient correctors of nonsense mutations in human diseases. PLoS One. 12, e0187930. Patents PCT/EP2017/076848 and PCT/EP2017/076846*

04

The ERG oncogene confers osteo-mimicry to prostate cancer cells.

Dr. Martine Dutertre's team demonstrated that the ERG transcription factor which is abnormally expressed in more than half of prostate cancers, favours the formation of metastases and their localisation in bones. Expression of the ERG factor as a consequence of genomic rearrangement participates in the acquisition of tumoral cells in a phenotype related to bone cells by directly regulating the genes essential for bone physiology. This osteo-mimicry contributes to the survival and proliferation of tumoral cells in bones and the formation of osteoblastic metastases in prostate cancer. *Delliaux et coll (2018). TMPRSS2:ERG gene fusion expression regulates bone markers and enhances the osteoblastic phenotype of prostate cancer bone metastases. Cancer Letters. 438:32-43.*

06

Spotlight on Yvan de Launoit.

Yvan de Launoit, CNRS Research Director, Professor at Université Libre de Bruxelles (ULB) and Director of UMR8161 until September 30, 2018, was twice honoured this year. In November 2018, the Royal Academy of Medicine of Belgium elected him "Virology and Viral Oncogenesis" Chair further to his research work in the field of cancer and more specifically of genes implicated in metastatic dissemination in breast and prostate cancer. In addition, he was promoted to the position of CNRS Associate Scientific Director responsible for the cancer research laboratories. He was replaced by Professor Corinne Abbadie at the head of UMR8161.

THE CAMPUS RESEARCH TEAMS



U1011 | Director: Bart Staels

NUCLEAR RECEPTORS, CARDIOVASCULAR DISEASES AND DIABETES

Inserm - Lille University - Institut Pasteur de Lille

- Team 1** ■ Nuclear receptors in the metabolic syndrome / **Group Leader: Bart Staels**
- Team 2** ■ Molecular control of monocyte/macrophage functions in the cardiometabolic syndrome | **Group Leaders: Sophie Susen / Eric Van Belle**
- Team 3** ■ Nuclear receptors, immuno-inflammation and cardiometabolic pathologies
Group Leader: David Dombrowicz
- Team 4** ■ Molecular analysis of gene regulation in the cardiometabolic syndrome
Group Leader: Philippe Lefebvre



U1167 | Director: Philippe Amouyel

RISK FACTORS AND MOLECULAR DETERMINANTS OF DISEASES LINKED TO AGING

Inserm - Lille University - Institut Pasteur de Lille

- Team 1** ■ Public health and molecular epidemiology of cardiovascular diseases
Group Leader: Aline Meirhaeghe
- Team 2** ■ Molecular determinants of heart failure and ventricular remodelling
Group Leader: Florence Pinet
- Team 3** ■ Molecular determinants of Alzheimer's disease and cognitive disorders
Group Leader: Jean-Charles Lambert



U1177 | Director: Benoît Déprez

M2SV: MEDICINES AND MOLECULES FOR ACTING ON LIVING SYSTEMS

Inserm - Lille University - Institut Pasteur de Lille



UMR8199 | Director: Philippe Froguel

INTEGRATIVE GENOMICS AND MODELING OF METABOLIC DISEASES

CNRS - Lille University - Institut Pasteur de Lille

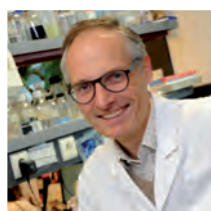
- Team 1** ■ Genomics and epigenomics of metabolic diseases / **Group Leader: Philippe Froguel**
- Team 2** ■ Molecular bases and modelling of diabetes and obesity / **Group Leader: Jean-Sébastien Annicotte**
- CS** ■ Joint Research Department / **Group Leader: Philippe Froguel**



U1019 - UMR8204 | Director: Camille Locht

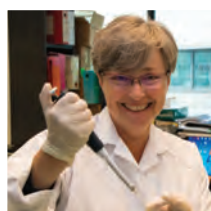
INFECTION AND IMMUNITY CENTRE OF LILLE Inserm - CNRS - Lille University - Institut Pasteur de Lille

- Team 1** ■ Biology and chemistry of Platyhelminthes | **Group Leader: Oleg Melnyk**
- Team 2** ■ Biology of Apicomplexa parasites: factors regulating growth, differentiation and virulence / **Group Leader: Jamal Khalife**
- Team 3** ■ Biology and Diversity of Emerging Eukaryotic Pathogens (BDPEE) / **Group Leader: Eric Viscogliosi**
- Team 4** ■ Basic and clinical immunology of parasitic diseases / **Group Leader: Sylviane Pied**
- Team 5** ■ Molecular and cellular virology | **Group Leader: Jean Dubuisson**
- Team 6** ■ Plague and Yersinia pestis | **Group Leader: Florent Sebbane**
- Team 7** ■ Chemogenomic of Intracellular Mycobacterium | **Group Leader: Priscille Brodin**
- Team 8** ■ Bacterial respiratory infections: Pertussis and Tuberculosis / **Group Leader: Camille Locht**
- Team 9** ■ Microbiology and cellular physics of infection / **Group Leader: Frank Lafont**
- Team 10** ■ Lactic bacteria and mucosal immunity / **Group Leader: Corinne Grangette**
- Team 11** ■ NODS-like receptors in infection and immunity / **Group Leader: Mathias Chamailard**
- Team 12** ■ Pulmonary infection and innate immunity | **Group Leader: François Trottein**
- Team 13** ■ Pulmonary immunity | **Group Leader: Anne Tsicopoulos**
- Echo-endoscopy** ■ Chemical Biology of Antibiotics / **Group Leader: Ruben Hartkoorn**
- CS** ■ Common service and scientific management / **Group Leader: Zarifé Hanna-Abboud**
- Platform** ■ Laboratory of applied transcriptomics and genomics studies / **Group Leader: David Hot**
- Platform** ■ BICeL | **Group Leader: Frank Lafont**
- Platform** ■ P3M | **Group Leader: Jean-Michel Saliou**
- Platform** ■ ARIADNE | **Group Leader: Priscille Brodin**
- Platform** ■ EPLS | **Group Leader: Gilles Riveau**



UMR8161 | Director: Yvan de Launoit beginning October 1, 2018: Corinne Abbadie

MECHANISM OF TUMORIGENESIS AND TARGETED THERAPIES (M3T) CNRS - Lille University - Institut Pasteur de Lille



- Team 1** ■ Initiation of epithelial cancers | **Group Leader: Corinne Abbadie**
- Team 2** ■ Functional studies of the tumour suppressor gene H1C1 (H1C1) | **Group Leader: Dominique Leprince**
- Team 3** ■ Activation of angiogenesis endothelium and cancer / **Group Leader: Fabrice Soncin**
- Team 4** ■ Signalling, apoptosis and cancer (SIGNAL) | **Group Leader: David Tulasne**
- Team 5** ■ Immunoregulation of virus-induced cancers | **Group Leader: Nadira Delhem**
- Team 6** ■ Proteins and associated diseases | **Group Leader: Martine Duterque**
- SPES (ESSONNE SUD** ■ Studies of prostate stem cells | **Group Leader: Roland Bourette**
- PALLIATIVE CARE)** ■ Joint service unit Lille Institute of Biology (general secretariat of the IBL and human resources, IBL management teams and IBL teams, IT team of the IBL) / **Director: Philippe Boutin**
- UMS 3702**

TECHNOLOGY PLATFORMS



TRANSCRIPTOMICS AND APPLIED GENOMICS

Transcriptomics and Applied Genomics Group (TAG)

U1019, UMR8204, Inserm, CNRS, Institut Pasteur de Lille

Group Leader: **David Hot**

High-throughput genomics platform specialised in microbial genomics. Since 2012, TAG has been a member of the Genes Diffusion Genomic Platform for the implementation of a common structure called PEGASE, in order to offer cooperation and services pooling the skills of each of the entities.



HIGH-THROUGHPUT SCREENING (HTS) AND HIGH CONTENT SCREENING (HCS)

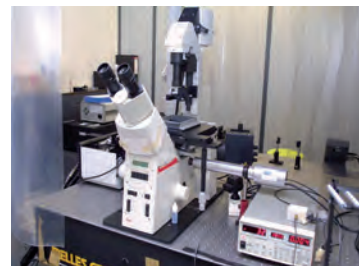
U1177, Inserm, Institut Pasteur de Lille, Lille University

Group Leader: **Benoît Déprez**

Platform that combines a chemical library and all the high-throughput screening tools (except for the techniques based on high-throughput confocal imaging which are available on the microscopic imaging platform).

Website: www.deprezlab.fr

TISSUE AND CELL IMAGERY- CYTOMETRY



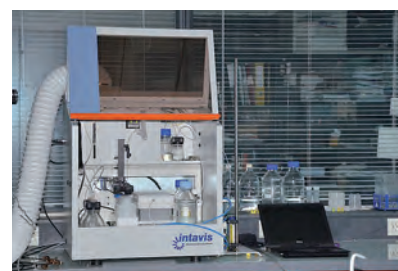
U1177, Inserm U1019, UMR 8204, Inserm, CNRS, Institut Pasteur de Lille, Lille University

Group Leader: **Frank Lafont**

The BioImaging Centre Lille-Nord de France (BICeL), represents the most important part of EquipEx ImaginEx BioMed.

Website: www.bicel.org

PEPTIDE CHEMISTRY



Peptide Chemistry, Systems, Biology

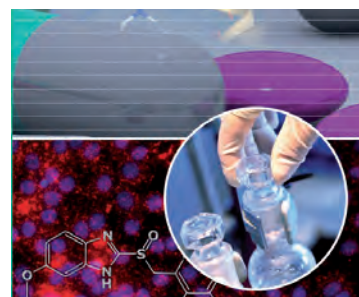
UMR 8204 - U1019 CIIL, Inserm, CNRS, Institut Pasteur de Lille, Lille University

Group Leader: **Oleg Melnyk**

Peptide chemistry and protein chemical synthesis

Website: www.csb.cnrs.fr

HTS & PHARMA- COKINETICS STUDIES AND ADME-PK DISTRIBUTION SCREENING LAB



U1177, Inserm, Institut Pasteur de Lille, Lille University

Group Leader: **Benoît Déprez**

Platform to characterise the qualitative and quantitative future of experimental active principles in cells and the organism.

Website: www.deprezlab.fr



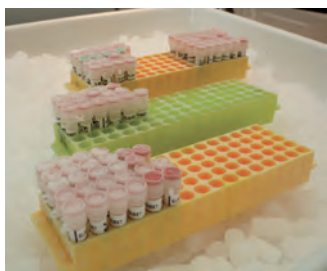
NUCLEAR MAGNETIC RESONANCE (NMR)

Nuclear Magnetic Resonance

UMR8576, CNRS, Institut Pasteur de Lille, Lille University

Group Leader: **Isabelle Landrieu**

Nuclear magnetic resonance (NMR) spectroscopy helps probe the molecular structure by making the natural magnetization of nuclei interact with a magnetic field.



LABORATORY FOR THE STUDY OF THE GENOME

Genomic Analysis Laboratory

U1167, Inserm, Institut Pasteur de Lille, Lille University

Group Leaders: **Philippe Amouyel** and **Nathalie Fievet-Verrecas**

Logistics and oversight of large collections of human biological samples with patients recruited mainly from epidemiological studies based on the cardiovascular, metabolic, and neuro-degenerative disease themes.



PROTEOMICS AND MODIFIED PEPTIDES PLATFORM (P3M)

LabEx ParaFrap, Institut Pasteur de Lille, CNRS, Lille University

Group Leader: **Jean Michel Saliou**

Platform dedicated to proteomic analysis and the characterisation of proteins and peptides.

PLEHTA PLATFORM



Institut Pasteur de Lille

Group Leaders:

• **Fabrice Infanti**

Laboratory for research and experimentation

• **Michèle Vialette**

High Security Laboratory.

GENOMICS AND METABOLIC DISEASES



EquipEx LIGAND-PM (Lille Integrated Genomics Advanced Network for Personalized Medicine)

Group Leader: **Philippe Froguel**

The Lille Ligan-PM platform for genome sequencing can establish the list of mutations likely to explain the clinical signs of each patient, predict the possible evolution of his/her disease, and predict the efficacy or side-effects of existing drugs.

Website: <http://ligan.good.cnrs.fr>

BIOTECHS

DRAW THE ACADEMIC AND INDUSTRIAL SECTORS CLOSER TOGETHER TO ACCELERATE VALIDATION OF DISCOVERIES

At the heart of the campus, Institut Pasteur de Lille supports the development of projects, start-ups and biotechnology and health innovation companies. The aim is to bring new services and analysis or diagnosis products to the fore which stem directly from the fundamental research carried out in Lille. Institut Pasteur de Lille relies on the proximity of its research teams and their equipment (laboratories and technological platforms) to facilitate collaboration

with the entrepreneurs and start-ups of the sector, whether they be in the experimental or developmental phase. The Institute is also committed to fostering synergies and expertise in order to allow biotechs to move more easily into the maturation phase of their projects.

These biotechs, located on the Pasteur Lille Campus, benefit from the available premises, equipment and skills.



Created on the campus of Pasteur Lille in January of 2001, Genoscreen offers 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 now has about thirty employees. 80% of its turnover is generated outside of Metropolitan Lille, of which 30% is exported. Over the past few years, research programs in themselves, conducted in partnership with research units from Institut Pasteur de Lille, INSERM and the INRA have contributed to the development of some very competitive applications in areas such as the genetics of Alzheimer's disease, microbial molecular typing and monitoring of biodiversity.

www.genoscreen.fr



Set up on the Lille Pasteur campus, the company X'ProChem markets proteins synthesized using a chemical method, an innovative technology stemming directly from the academic research of the laboratory of Oleg Melnyck. These 100% chemical proteins are custom-made to meet requirements that classic methods of recombinant biology are unable to synthesize, such as toxic, membrane proteins or proteins equipped with a probe so they may 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 end of the first decade of this century before a cost-effective, easily replicable method was developed at Institut Pasteur de Lille.

www.xprochem.com/fr



Strengthened by its collaborations with the Pasteur Lille campus, 4 P-Pharma develops innovative molecules at an early stage of pre-clinical development and brings them to the preliminary phases of clinical trials. The company is positioned as an intermediary between entities that have developed high-potential early biomedical projects and the pharmaceutical companies.

Since September of 2016, 4 P-Pharma has also been financially supported by the mutual company "M comme Mutuelle" with an eye to conducting the first phase I clinical trial on one of its products possessing properties that constitute a deterrent to psycho-stimulant abuse. R&D's activities focus on inflammatory diseases, oncology and the central nervous system. Around ten drug candidates are currently being developed in the molecule portfolio.

The ongoing projects of 4 P-Pharma have benefited from several collaborations with the teams of Institut Pasteur de Lille, especially with the Pharmacokinetics/ADME platform directed by Prof. Benoît Déprez, the Transcriptomics and Applied Genomics platform directed by Dr. David Hot, and the Genetic Toxicology Laboratory directed by Dr. Fabrice Nesslany.

www.4p-pharma.com



APTEEUS

engaging patients in discovery

Created in 2013 by Terence Beghyn, pharmacist and researcher, along with Prof. Benoit Deprez, Director of the Drug Discovery Centre of Institut Pasteur de Lille, APTEEUS is an innovative company in the field of individualized medicine for patients with rare and orphan diseases. Thanks to their expertise acquired in the U1177 Research Unit (Inserm - Institut Pasteur de Lille - Lille University), their mission is to bring the miniaturized techniques of drug discovery to the bedside of patients suffering from orphan diseases.

The APTEEUS approach combines in vitro cell screening with drug repositioning. The team's savoir-faire, with the assistance of doctors and scientific experts in disease, have made it possible to develop a screening test for any new disease sufficiently characterized from a functional point of view. The test systematically uses cells taken from the patient to guarantee the link between the molecular cause of the disease that is specific to the patient with its symptomatic manifestations. Thus the idea is to measure the effect of each of the active ingredients of the medications from the global materia medica on the altered function at the root of the symptoms. It is the exhaustiveness of the collection of active ingredients, the relevance of the tests developed, and the environment of scientific excellence that constitute the strengths of APTEEUS today.

The company is currently evaluating the clinical benefit of two drug candidates in several rare and orphan pathologies. Drug repositioning is a means of quickly responding to the medical need of small populations of patients by mastering both the risks and costs of development.

The patient's involvement in the discovery process earned APTEEUS the prize in the category of Individualized Medicine of the Concours Mondial d'Innovation 2030. Today, several partnerships with teams from Institut Pasteur de Lille, various hospitals and pharmacy actors, are making it possible to broaden the scope of the technology.

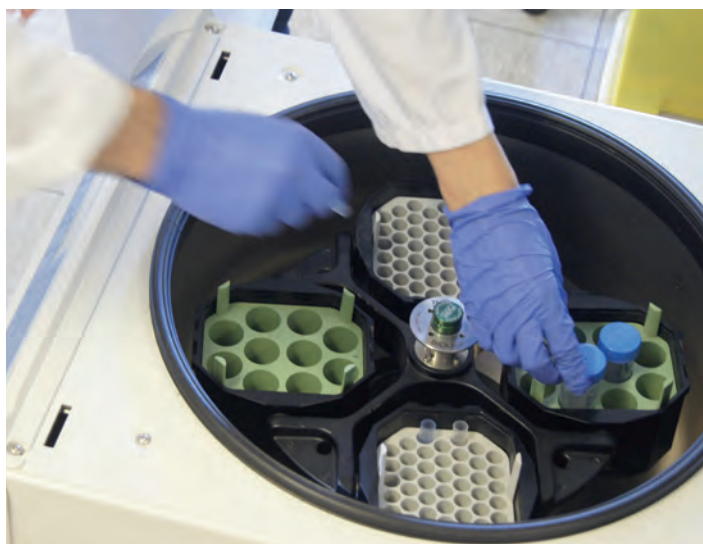
<http://apteeus.fr>



Immune insight
Save the balance.

Led by the doctors Nadira Delhem and Olivier Moralès and directed by Hamza Aboussemdai, this biotech officially commenced in July of 2016 on the premises of the Lille Institut de Biologie (CNRS) on the Institut Pasteur de Lille Campus. Immune Insight offers an unprecedented and effective method of validating the safety of new drug candidates prior to the launch of clinical trials. A method directly stemming from Pasteurian research. It offers unique services internationally making it possible to validate, in a preclinical phase, the safety of a drug candidate with regard to immune cells, and T regulatory lymphocytes in particular. Balance of the immune system Regulatory T lymphocytes (Tregs) are a particular population of white blood cells that maintain the proper balance of the immune system so that it can protect the organism from aggression. Some diseases deregulate the function of the Tregs. Thus, in cancers, Tregs are abnormally activated, which weakens the immune response directed against the tumor and facilitates its progression. Conversely, in the case of allergies, chronic inflammatory diseases or organ transplants, the Tregs underfunction and the immune response is excessive.

www.immune-insight.com



Lunginnov

In close collaboration with the research teams of the Pasteur Lille campus, Lunginnov develops and markets innovative solutions targeting respiratory diseases that facilitate earlier therapeutic decision-making in the interest of the patient. Lunginnov is a platform for developing new theranostic concepts for respiratory diseases.

In addition, a close collaboration between Inserm, Institut Pasteur de Lille and the Lille University Hospital has been established in order to develop new diagnostic concepts and new pulmonary tropism biomolecules, two of which are already at the clinical stage.

www.lunginnov.com/fr

PREVENTION

RESEARCH

HEALTH

LONGEVITY



1899 > 2019

| Institut Pasteur de Lille créé en 1894 - Reconnu fondation d'utilité publique en 1898 - Bâtiment Calmette inauguré en 1899 |

120 ANS

1899-2019

DE RECHERCHE ET D'INNOVATION



DE L'INAUGURATION À AUJOURD'HUI

■

PREVENT TODAY IN ORDER
TO AGE WELL TOMORROW



PREVENTION IN HEALTH AND LONGEVITY CENTRE: INNOVATION FOR AGING IN GOOD HEALTH

The Preventive Health and Longevity Centre is a place for prevention, research, expertise, innovation, and teaching in public health. It groups historical Institut Pasteur de Lille and new activities based around "aging well": the CPAM prevention health examinations, the "company" health check-ups, the international vaccination centre, the nutrition and physical activity department, and research unit.

In March 2018, a development unit composed of a 3-person team was created within the centre. This new department has a cross-disciplinary role with different hubs within the centre. It supports them to develop and to value their prevention expertise to cell. The development unit is also responsible for relations with the centre's partners (institutions, associations, private businesses, etc.) and participates in building collaborative projects in connection with the experts. It is also charged with organising conventions and specific theme days on prevention: Innovation in Public Health Day, Nutrition Workshops, Nutrition Interviews, etc.

The Longevity Pathway, a new Institut activity created in 2017 in partnership with the Lille University Hospital welcomed its first consultants. Its objective is to identify and then reverse fragility to achieve successful aging. This pathway, composed of a check-up, monitoring, and coaching, is designed to spread across France. The goal is to develop preventive health for the largest number, making data for robust and frail individuals available to research.

Positioned in the Hauts-de-France area, as a key player in prevention, the Prevention in Health and Longevity Centre intends to become a reference centre at the heart of a longevity network.

Numerous local actors already support this approach: ARS, the regional health agency - within the scope of a 5-year *Multi-Annual Means and Objectives Contract (CPOM)* - CARSAT Hauts-de-France, AG2R La Mondiale, Adix, Macif Foundation, and others, are some of our privileged partners.



PREVENTION



RESEARCH



ASSESSMENTS



INNOVATION



TEACHING

HEALTH CHECK-UPS DEPARTMENT

The Health Check-Ups Department is a space for prevention, health promotion, and aging well. It presents three prevention pathways, each one adapted to the populations targeted, and relying on the most recent medical recommendations in terms of prevention. These pathways complete the actions

of treating physicians, occupational physicians, or specialised doctors. They should be considered a response to the current primary challenges faced in health matters: social inequality, longer working hours, and an ageing population.

3 PREVENTION PATHWAYS

- 01 The Preventive Health Check-Up** concerns priority individuals who are the furthest removed from the health system and in precarious situations. It can be adapted to age, gender, risks, and also the insured individuals' usual medical care. It takes into account the difficulty of access to care and prevention by including information on health rights and measures that assist in acquiring supplemental health insurance.
- 02 The Company Health Check-Up** concerns employees exposed to specific risks over the course of their career. This check-up is also adaptive to be as aligned as possible with the specifics of each.
- 03 The Longevity Pathway** incorporates examinations and specialised interviews which aim to identify risks linked to ageing and concentrates on cognitive, osteo-muscular, and sensorial declines. Upon completion of the initial check-ups, individuals receive detailed information of their risk factors, the means of reducing them, and personal preventive actions to implement within the scope of personalised monitoring and collective coaching.

FROM HOME



Scheduling appointment
(Internet / Phone)



Questionnaire
(online)



Health examination
(1/2 day)



Choice of suitable orientation



Motivational interview & coaching



Evaluation

AT INSTITUT PASTEUR DE LILLE OR PARTNER SITES



The Health Examinations Department is also a **research facility**. It deliberately participates in research projects such as the "Cohorte Constances" study. Since its restructuring, it aims to strengthen and develop research projects in the area of prevention, essentially the identification of risk factors which lead to weaknesses and frailty which leads to a loss of autonomy.

To meet this ambition, an **information system** dedicated to the "Longevity Pathway" and the "Company Check-Ups" **was designed and will be put into production starting April 2019**. It will make it possible to:

- Collect a person's individual data (in keeping with the General Data Protection Regulation - GDPR)
- Extract epidemiological data, with an aim to studies on targeted subjects
- Produce dashboards and statistics
- Steer the Longevity Pathway and Company Check-Up activities: management of consultant appointments and practitioners' schedules

PREVENTIVE HEALTH EXAMINATIONS (PHE) AND EDUCATIONAL ACTIVITIES

In 2018, **14,847** individuals insured by the CPAM of Lille-Douai, Artois, Flandres, Roubaix-Tourcoing, and Côte d'Opale, had the benefit of a Preventive Health Examination (PHE) in one of the Lille and Tourcoing health examination centres as well as on delocalised sites (Nord and Pas-de-Calais). The PHEs were implemented within the scope of conventions established between the Caisse Primaires and Institut Pasteur de Lille. The PHE is part of a care pathway in line with the general practitioner. More specifically, health insurance intends these examinations for the most vulnerable individuals (social precarity, isolation, lack of follow-up by a general practitioner, lack of enrolment in organised

tracking schemes, of screening, or vaccination, etc.) **These said vulnerable populations, represented over 56% of the centres' consultants in 2018.**

The PHE is part of the scope of a national renovation of the examinations offered as a function of consultants' personal or family risk factors and their clinical symptomology. The educational approach is reinforced by interviews with professionals encountered during the PHE (nurses, dentists, dieticians, doctors). After an examination, consultants may be directed, depending on need, to structures adapted to their situation and state of health.



14,847

CPAM-INSURED INDIVIDUALS BENEFITED
FROM A PREVENTIVE HEALTH EXAMINATION



FURTHER TO AN INSTITUT PASTEUR DE LILLE, THE FOLLOWING ARE POSSIBLE:



Therapeutic education sessions for
type-2 diabetic patients



Health education workshops on
"Nutrition, physical activity, and dental
hygiene" for overweight consultants



Individual consultations on tobacco
addiction and group awareness
sessions
to stop smoking

IN 2018, HEALTH EVENTS WERE ALSO ORGANISED:



Awareness-raising booths at "Tabac Parlons-En" (Let's Talk about Smoking) in the Health Examinations Centre hall and participation in "A Month without Smoking" (Mois sans Tabac). in November



Group events for 16 to 25 year-olds within the scope of PHEs on the subject of "pleasure and addiction", "Emotional and sex life", "Nutrition, Physical Activity, and Dental Hygiene"

RESEARCH WITHIN THE PREVENTION IN HEALTH AND LONGEVITY CENTRE



Given its unique position, as an interface for care actors, clinical research, or fundamental research, and even the type of research undertaken at the Prevention in Health and Longevity Centre (CPSL) which requires the participation of experts in various fields, research projects are undertaken in close collaboration with Lille University Hospital health professionals as well as with Institut Pasteur de Lille research teams, in particular, UMR 1167 "Public Health and molecular epidemiology of age-related disease" led by Pr. Philippe Ayoumel.

The Prevention in Health and Longevity Centre pursues the following objectives:

- Development of epidemiological research to identify and understand the influence of factors which determine successful aging
- Contribution to development of scientific prevention based on development of interventional research and evaluation of actions under-taken;
- Proposing interventions based on scientific proof in order to improve health and well-being and to reduce inequality in health.

In order to successfully lead and implement this work, the Prevention in Health and Longevity Centre aims to:

- Develop interactions between actors in prevention, care, and research, notably using its unique situation at the interface of Institut Pasteur de Lille research teams and its partner, the Lille University Hospital;
- Facilitate use of its work results to help in decision-making for health policy actors and group leaders.

CONSTANCES HEALTH CHECK-UPS

The Institut Pasteur de Lille Health Examinations Centre welcomes over 1800 Constances volunteers per year since 2012 (a total of 12,700 exams conducted). Constances is a "generalist" epidemiological cohort composed of a representative sample of 200,000 adults aged 19 to 69 included, organised around certain subjects: professional and social health determinants, ageing and chronic diseases, women's health, genetic and biological factors, and interaction with the environment.



Source: Constances - Credit: ©Gabs

COMPANY CHECK-UPS

Capitalising on over 30 years' experience acquired through the Preventive Health Examination and relying on the innovation of the Longevity Pathway, the Prevention in Health and Longevity Centre sought to rethink the "customisable health examinations".

Consequently renamed, the "Company Check-Ups" are a collection of preventive and screening examinations designed with company management and medical services. These Check-Ups are intended for employees exposed to particular risks over the course of their career with an aim to staying in better health at work. The Prevention in Health and Longevity Centre's goal is to adapt to company needs, to better meet expectations by offering

adjustable examinations. Also, close ties between Institut Pasteur de Lille vaccination centre and external partners are established to meet needs within the scope of specific procedures linked to travel or expatriation. This activity fits fully within the objective of allowing everyone to live better longer.

The number of check-ups between 2017 and 2018 remains stable. The "Company Check-Ups" activity has shown positive development. The goal is to make the Prevention in Health and Longevity Centre a reference centre in this domain.

ISO 9001 certification version 2015 for preventive health examinations and company check-ups.



LONGEVITY PATHWAY

The Longevity Pathway, created in collaboration with the Lille University Hospital welcomed its first consultants on April 19, 2018, in a fully-renovated and equipped building.

As a result, **100 individuals qualified as Care-Givers** for a dependent family member (disease or handicap) and **120 retired individuals** were able to take advantage of this innovative preventive medicine pathway.

After their health examination which addressed medico-psycho-social aspects, consultants qualified as "robust" were comforted

that their lifestyle is favourable for active and successful ageing. The consultants screened for a pathology were directed to their general practitioners for follow-up and treatment. Support for subjects considered "fragile" will be offered in the first semester of 2019. This approach is intended to support consultants and build their awareness of the concept of reversible fragility by making them aware of health determinants. It will include an awareness-building session on "ageing well" and thematic workshops in nutrition, physical activity, stress management, sleep hygiene, and preserving cognitive reserve as well as yearly follow-ups. At the end of the follow-up, there will be an evaluation.

220
LONGEVITY
PATHWAY

120
RETIRED
INDIVIDUALS

100
CARE-TAKERS



STUDY OF THE FIRST 220 LONGEVITY PATHWAY CONSULTANT CHARACTERISTICS

The first study covered statistic use of data from the first 220 Longevity Pathway consultants in 2018. The sample's general population characteristics (socio-demographic and lifestyles) as well as the determinants which play an important role in successful ageing such as living standards, social integration, and activity level are described next to the results from the screening examinations conducted.

HEALTH TRAINING

The health examinations department is a validating internship field for medical students (externs and interns in general medicine and in public health in conjunction with Lille University and the Lille University Hospital). In 2018, two interns in general medicine and two externs took part in the health education activities offered by the different units of the Prevention in Health and Longevity Centre (nutrition department, vaccination

department, Therapeutic Education programme). They performed the clinical examinations for the health check-ups (CPAM and longevity) and drafted the medical summary under the supervision of senior doctors. The public health intern also participated in developing the Longevity Pathway on the epidemiological side. The Prevention in Health and Longevity Centre also welcomes nursing students.



NUTRITION AND PHYSICAL ACTIVITY DEPARTMENT

Bringing the activities of the Nutrition Department in line with physical activity, the Nutrition & Physical Activity Department now counts 17 individuals with multi-disciplinary skills: doctors, scientific engineers, dieticians, sports medicine trainers.

AT THE HEART OF THIS DEPARTMENT, TWO HUBS:

- The “**Expertise, Health Education and Training**” Department organised around the Nutrition and Physical Activity duo.
- The **NUTRINVEST** centre which conducts clinical **studies in nutrition** to evaluate a product’s nutritional health benefits.



These missions’ renown increases yearly with partners in both the public and private sectors.

The Nutrition and Physical Activity Department is fully complementary with all the activities within the Prevention in Health and Longevity Centre as much on the nutrition side as on

the physical activity side as both are pillars in prevention at all ages. Consequently, the department addresses hundreds of professionals through events such as Nutrition Interviews (Les Entretiens de Nutrition) and Nutrition Workshops (Ateliers de Nutrition) organised by Institut Pasteur de Lille.

“EXPERTISE, HEALTH EDUCATION AND TRAINING” DEPARTMENT

With a cross-disciplinary team (nutrition engineers, educational dietitians, sports-medicine trainers, project assistants, etc.) the “Expertise, Health Education, and Training” department deals with three complementary activities.

■ ASSESSMENTS:

14 ASSESSMENTS COMPLETED

This year, our expertise missions are directed towards drafting articles, bibliographic research, scientific monitoring, and content creation for educational purposes and digital health education materials and support for company health projects.

For example: In 2018, our teams worked with a company in the modelling of its digital nutritional education platform (eat/move): development of questionnaires, design of activities concerning nutrition, physical activity and the fight against sedentary lifestyles, and content design adapted to targeted pathologies (hypertension, hyperglycaemia, etc.)

■ HEALTH EDUCATION:

PROJECTS were supported as a support operator in the Hauts-de-France region for matters of “nutrition, overall health, and vaccination”. These projects were undertaken with the support of ARS, the Conseil Départemental du Nord, AG2R, the BEL Foundation, the AUCHAN Foundation, and the City of Lille.

Professionals and the general public for structures such as EHPADs (assisted living facilities), local missions, local and regional authorities, care-taker homes, and social centres were able to benefit from our actions in health education.

Our missions:

- Ensure project engineering as a support operator, specifically in its field of competency in matters of nutrition - physical activity and vaccinations.
- Contribute to increasing competency of those offering prevention
- Participate in the Longevity Pathway experiments
- Ensure that educational and support actions on the subjects of “Physical Suffering and Well-being”, “Ageing Better”, “Care-giver and receiver well-being”, “Cooking and Cancer”, “Junior Nutrissimo Programme”, “Therapeutic Education for Type-2 Diabetics”, “Health education for overweight and insufficiently active consultants”, etc.

For example:

Project support for EHPADs in the region

AXIS 1.

Professionals and family members/care-givers

Working from a common “nutrition, physical activity, and dental hygiene” base, it’s a matter of promoting an original offer for support to professionals and care-givers.

AXIS 2.

Residents

Promote maintaining optimal autonomy in secondary preventive care of EHPAD residents.



■ TRAINING:

21 TRAINING SESSIONS LED BY PROFESSIONALS

- Prevention and treatment of denutrition of institutionalised seniors
- Nutrition adapted to handicap
- Hand-held foods and suitable enriched bites
- Overall treatment of obesity and excessive weight
- Balanced diet: passing along the right nutrition messages
- How to help smokers understand and stop their consumption



CLINICAL STUDIES DEPARTMENT

The “clinical studies” department has for several years supported numerous agro-food companies (ingredients, nutriments, foods, diets, dietary supplements) in evaluating their products’ health benefits. It also meets calls for projects to undertake “research-action” type studies aimed at public health (Prev’HoDE project). As a result, it has gained solid expertise in the management of clinical studies in nutrition from proposals of pertinent study design on through submission of final reports.

The Clinical Studies Department and its investigation centre, NutrInvest, managed six clinical nutrition studies in 2018 or close to 574 visits.

01

HONEY STUDY

which evaluates the effect of a dietary supplement consisting of a probiotic yeast on LDL cholesterol levels in volunteers with **moderate hypercholesterolemia**.

02

BABYMILK STUDY

analyses the effect of the consumption of a first-age infant formula on **infant growth from 0 to 6 months**.

03

IBS-GO STUDY

studies the effect of a probiotic yeast on improvements in gastrointestinal disorders associated with **irritable bowel syndrome** with predominant constipation.

04

TOTUM-63 STUDY

determines the effect of a food supplement based on a mixture of plant extracts on carbohydrate and lipid homeostasis in people with **Type 2 diabetes** or a **glucose intolerance** associated with hypertriglyceridemia.

05

TRUEGREEN STUDY

looked at the effect of innovative infant formulae on **tolerance and growth of nursing babies from 0 to 6 months** in comparison to **breast feeding**.

06

OBEMINALE-2

looked at the effect of a **dietary supplement** in weight management of **overweight** or **obese individuals**.

The clinical studies department has implemented an active approach for the recruitment of voluntary participants in nutrition clinical trials:

- In agreement with CPAM, consultants who present themselves to Institut Pasteur de Lille for a health examination (and having given their consent) have the possibility of being re-contacted to participate in studies offered by the clinical studies department.
- Thanks to the partnership between Institut Pasteur de Lille and Synlab Laboratories, volunteers (with their agreement) may be selected on the basis of their biological parameters.

The NutrInvest clinical investigation centre has access to a medical analysis laboratory located on the Institut Pasteur de Lille campus (SYNLAB/EURABIO), and has available high-performance tools (appointment management software, biological and nutritional data) and high-tech equipment (DEXA imaging - *Dual-Energy X-Ray Absorptiometry*).

Thanks to the competency developed by the members of the clinical studies department, the equipment available on the Institut Pasteur de Lille campus, and the elevated capacity for recruitment of volunteers, NutrInvest is a high-performance clinical studies centre with an ever-growing reputation. Four new projects could see the light of day in 2019.

APRIL 5, 2018

**The ISO 9001 certification -
2015 version of the Clinical
Studies pole is renewed**

THE INTERNATIONAL VACCINATION CENTRE

The mission of the Institut's WHO certified (World Health Organisation) international vaccination centre, is essentially aimed to travellers who are leaving for or returning from exotic regions.

In 2018, **close to 26,000 vaccines** were injected including **6,500 vaccines against yellow fever**. These figures have increased constantly for several years (+3.5% in relation to 2017). Since 2017, the wait for a consultation decreased to under one week and in the event of an imminent departure, the appointment can be scheduled the same day. Several hundred specialised consultations were administered for pre-travel as well as for advice on preventing malaria and rabies, or for check-ups of pregnant women departing to or returning from an endemic zone hit by the ZIKA virus.

The **METIS** Internet site is regularly updated with health

recommendations as a function of diseases which rage around the world. As a result, the international vaccination centre meets the expectations of clients looking for information and advice in preparation of their trip: Vaccinations (mandatory or recommended), risks entailed, miscellaneous medical advice.

Every day, **over 3,000 consultations are made on our METIS web site**: an answer is given to travellers within 24 to 48 hours.

Further, as every year, events are organised within the region's companies to vaccinate their employees against the flu. In 2018, **over 4,000 flu vaccinations** were administered.



THE TEAMS

Administrative Director: Cathy Brassart

NUTRITION AND PHYSICAL ACTIVITY DEPARTMENT

Medical officer: Jean-Michel Lecerf

- NutrInvest Clinical Studies Department
Group Leader: Coralie Berthier
- Expertise, Health Education, and Training
Group Leader: Eric Guiot

MEDICAL EXAMINATION DEPARTMENT

CPAM | Medical officer: Gwenaëlle Floch

- Associate: Florence Lejeune

Customised Check-Ups | Medical officer: Sophie Lahousse

Longevity Pathway | Medical officer: Pascaline Cassagnaud

THE INTERNATIONAL VACCINATION CENTRE

Medical officer: Emmanuel Dutoit

RESEARCH UNIT

Medical officer: Maël Barthoulot

ADMINISTRATIVE UNIT

Administrative Manager: Isabelle Dumon

DEVELOPMENT UNIT

Development Manager: Julie Padol



TOWARD A BETTER UNDERSTANDING OF THE IMPACT OF POLLUTION



POLLUTION HEALTH LONGEVITY: MOVING TOWARDS COLLECTIVE AWARENESS

In Europe, it is estimated that air pollution causes 600,000 deaths a year: 482,000 for outdoor air and 117,200 for indoor air. In France, fine particle pollution discharged by human activities is responsible for at least 48,000 premature deaths every year which corresponds to 9% of mortality. When one knows that every day, there are approximately 15,000 litres of air which pass through our bronchial tree and that we breathe in between 150 and 750 billion nanoparticles, the question of air pollution takes on its full meaning.

Institut Pasteur de Lille is committed to **understanding the harmful effects of pollution**, specifically through certain research teams from the Lille Infection and Immunity Centre, the genotoxicity laboratory, and the microbiological safety laboratory.

Conscious of the rise in this public health challenge, in 2017, Institut Pasteur de Lille created the Regional **"Pollution, Health, and Longevity"** Hub. Bringing together numerous regional institutions, makes possible undertaking multi-disciplinary cooperation on the impact of pollution on health and longevity, of informing the public, and raising its awareness. Further, it raises awareness of deciders to the **necessity of efficiently fighting pollution**: outdoor pollution, indoor pollution, physical-chemical characterisation of aerosols, impact of pollution and nanoparticles on health, transgenerational effects.

2ND REGIONAL MEETING ON "POLLUTION, HEALTH, LONGEVITY" SEPTEMBER 19, 2018

"Nanoparticles and Ultrafine Particles in the atmosphere (UFP): impacts on human health".

Presentations by experts on the correlation between UFP (Ultrafine Particles) and nanoparticles issues, on physical-chemical characteristics and the metrology of particles, and on their impact on human health.

MICROBIOLOGICAL SAFETY UNIT



The Microbiological Safety Unit (MSU) examines the behavior of pathogenic micro-organisms in the environment, and in particular, the response of bacteria and viruses to the means of control used to combat them. The Unit gathers together a set of skills and organisations specialised in managing infectious risks in the following fields: water, air, surfaces, cosmetics, health products, hospital environments.

Dr Michèle Vialette

Unit Manager
Institut Pasteur de Lille

The axis of research revolve 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 knowledge on the impact of a type of environment on the spread or destruction of micro-organisms has proven to be a major asset in the management of microbiological risks. The objective consists in **evaluating and controlling the risks associated with the milieux, such as indoor air or hospital environments** (combating hospital-acquired infections).

The team's expertise is nationally renowned for the study of bacteria and viruses that are

highly pathogenic to human beings. Dr. Michèle Vialette is a microbiology expert for Anses (the national agency for food, environmental and occupational health & safety), serving on the committee of experts specialized in water.

The MSU also conducts specific studies for several industries in which there is some awareness of the management of contamination, such as the hospital sector or the cosmetics industry. Very involved with health actors, be they industrial, hospitals, or public authorities, the MSU contributes to the **creation and evaluation of tools (products and processes) for the control of environmental contamination**.

01

Close ties with the hospital were created. MSU has collaborated with the Lille Catholic University Hospital Group (GHICL) for the past 2 years within a Research and Development project. This project aims to develop textiles with an antiviral contact activity making it possible to contribute in the fight against nosocomial infections. This collaboration is also translated by the constitution within MSU of a bank of bacteria resistant to antibiotics isolated from GHICL patients. The aim of a heightened scientific collaboration between these two institutions is becoming a reality as well as the Applied Research actions.

HIGHLIGHTS

02

In 2018, USM extended a partnership with Dyson France. After a first collaboration in 2017 on an air humidifier, a study on an air purifier developed by Dyson allowed MSU to demonstrate that this appliance could eliminate 99% of viruses potentially present in the air (test conducted on the H1N1 Influenza virus). Dyson France asserts these findings with the mention "Tested by Institut Pasteur de Lille". This partnership is destined to continue over the coming years.

03

MSU implemented a rigorous quality approach which makes it possible to guarantee the reliability of its measures, the traceability of its actions, and documentation on its methods and results. This approach was taken in order to offer expertise that's always in line with industrial needs through constant performance improvement. The laboratory's management system is part of a process approach geared toward continuous improvement and relies on demanding documentation management. The precision of these measures and the repeatability of the analyses are both guaranteed by the equipment's metrological verification as by the team's knowledge and technical experience. These actions are validated by internal audits and participation in inter-laboratory tests.

GENETIC TOXICOLOGY LABORATORY

The genetic toxicology laboratory directed by Dr Fabrice Nesslany, research director at Institut Pasteur de Lille, has been studying the mutagenic, i.e. potentially carcinogenic, activity of substances present in our environment.

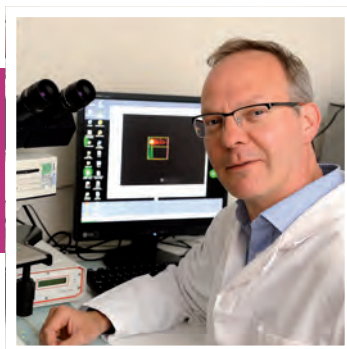
Dr Fabrice Nesslany
Research Director
Institut Pasteur de Lille

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 also participates in **research programmes at a national and European level** aimed at evaluating the genotoxic potential of atmospheric particles, manufactured nanoparticles, heavy metals, mycotoxins...

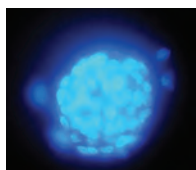


HIGHLIGHTS

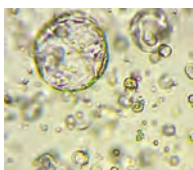
01

Spheroids: 3D models of cellular cultures

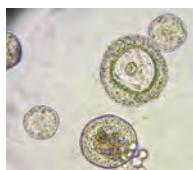
Dr. Fabrice Nesslany's team undertook the development of cellular cultures in 3 dimensions (3D). The goal of this type of culture is to supply cells with an environment that allows them to create structures known as spheroids where the cells can interact with one another. A spheroid has an organ's functions within the same cell type.



Hepatic spheroid



Hepatic spheroids



Intestinal spheroids

This technique makes it possible to recreate a normal physiological micro-environment and to attain more realistic exposure of cells such as subjected to in the organism. In a more general manner, the principal advantage arising from 3D cell cultures is the reduction in the use of laboratory animals which remains an ethical and financial issue.

02

Application to the study of embryotoxic activity

The toxicology laboratory being specialised in all alternative methods to animal testing recently developed an in vitro method which makes it possible to predict a substance's embryotoxic activity. This method was published and validated by the European Centre for Validation of Alternative Methods (ECVAM).

This test was conducted on multipotent embryonic stem cells (mESC) cultivated in 3D so their differentiation in beating cardiomyocytes was possible and in parallel, on BALB fibroblasts / c 3T3.

Differences in the sensitivity of these 2 cell types make it possible to characterise the embryotoxic effect by calculating the inhibition and differentiation values at 50% and the cell growth inhibition values at 50% (IC50).

KEY FIGURES

3

Scientific articles

In 2018, publication of 3 scientific articles in international peer-review magazines

■
SUPPORT THE FOUNDATION,
ADVANCE TOGETHER!



**THANK
YOU!**

DONATIONS AND BEQUESTS | FUNDRAISING

The public's generosity was of capital importance in 2018, a year with a historical drop in charitable giving in France⁽¹⁾. We must commend the commitment of loyal and new donors who supported Institut Pasteur de Lille projects in this context and made it possible to raise **2.2 million euros from the public** with **donations, events, solidarity races**, and **online fund raising**. To which we can add **3.8 million euros in contributions** from bequests and insurance.

In 2018, volunteers and fund raisers committed to promotion and fund raising activities, strengthening support for the Institut teams. Each donation allows the Institut to constantly reinvent itself to preserve its autonomy, its freedom in research, and its reactivity.

In 2018, the public's generosity made it possible to collect **6 million euros** to accelerate discoveries which will save lives.

**6
million euros**

TOTAL COLLECTED IN 2018



**2.2
million euros**
PUBLIC DONATIONS

**3.8
million euros**
LIBERALITIES

(1)According to France Générosités, charitable gifts decreased strongly in 2018 due to a difficult economic context notably in the research sector.



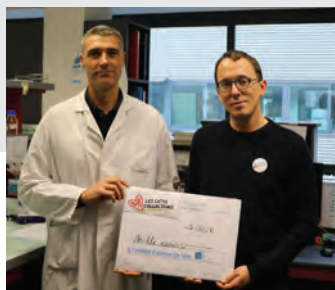
Thanks to you, scientific and medical research is progressing and accelerating:

SEVERAL SCIENTIFIC BREAKTHROUGHS IN 2018:

- Development of a candidate-drug which restores ethionamide sensitivity for tuberculous bacillus resistant to this antibiotic.
- Start of the clinical 2 phase with BPZE1, the live nasal vaccine for the prevention of whooping cough.
- Genetic diagnoses of monogenic diabetes and severe infantile obesity in order to put precision medicine in place starting at a young age.
- Identification and definition of the action mode for active anti-viral compounds on the hepatitis C virus.
- Discovery of a mushroom with anti-cancer abilities.
- Development of therapies which target anti-MET, a receptor implicated in certain lung cancers.
- Gamma-synuclein is responsible for the resistance of cancerous breast cells to radiotherapy.
- Establishment of an epidemiological link between pollution and glycaemic balance.
- Patients presenting ventricular remodelling further to a first myocardial infarction present an increased risk of death or hospitalization for heart failure.
- Plasmatic rates of clusterin are associated with post-infarction cardiac remodelling and they are predictors of premature death in patients suffering from heart failure.
- Identification of new susceptibility genes associated with the risk of Alzheimer's disease.
- Cardiac complications are less frequent and less severe when valvular surgery is performed in the afternoon rather than in the morning.
- The anti-inflammatory action of a biological clock protein makes it possible to prevent the appearance of fulminant hepatitis, to attenuate symptoms, and increase survival rates.
- Discovery of unknown functions of the Insulin-Degrading-Enzyme protein beyond the field of diabetes.
- BETA, a maturation project which aims to identify new anti-diabetic drugs.

Fund raising from individuals is done through different campaigns making it possible to present the Institut's different research projects, its progress, researchers, etc.

In 2018:



And:

19

CAMPAIGNS

3

EDITIONS OF THE MAGAZINE
Living better for longer

2

ISSUES OF JOURNAL
DES LEGS

HEALTH CONFERENCES
AND LABORATORY
VISITS

If a large number of calls for donations was made by mail, the Sponsors Office offers more and more actions online or digital tools to reduce paper consumption and its costs but also to communicate more rapidly on progress and current affairs.

As a result, today it's possible to support Institut Pasteur de Lille by way of different tools: online donations, donations by SMS, or even contactless donations (terminal at the Institut museum or during certain events). Numerous tools make it

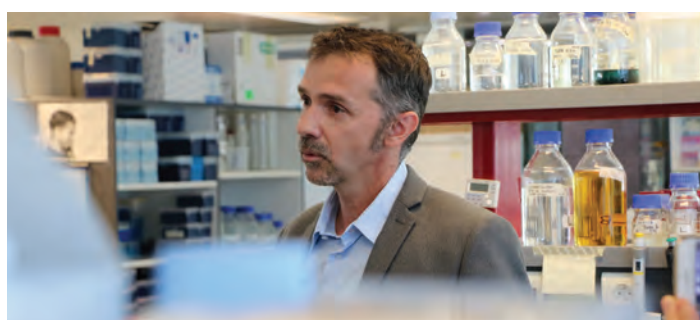
possible to organise fund raising for the Institut simply and safely using online platforms (HelloAsso, Alvarum or Facebook) during different events: races, challenges, drawings, concerts, weddings, birthdays, anniversaries, deaths, etc.

The commitment and creativity of volunteers, schools, and sponsors have made numerous events possible for the benefit of the foundation in 2018.

THE SPONSORS

Two personalities, **Franck Thilliez**, writer and **Jean-Claude Casadesus**, conductor, as sponsors, are raising appeals on behalf of Institut Pasteur de Lille.

The **Together Challenge** launched by our sponsor **Frank Thilliez** in May 2018, for the publication of his new book "**Le Manuscrit Inachevé**" raised over €5,000 in support of research.



BUSINESS PATRONAGE

Developing relationships with the economic and industrial worlds through scientific collaboration, expertise, general interest missions, and sponsorship is essential for making research and prevention available for everyone's good health. With the international reach of its research and its local actions, Institut Pasteur de Lille contributes to the region's attractiveness and it wholeheartedly plays its role as an economic and social actor. In 2018, business sponsorship brought funds of €0.8 million to the Foundation.



THE SPONSORS:

- | | |
|------------------------|------------------------|
| ■ ADIX | ■ ENTREPRISES ET CITES |
| ■ AG2R LA MONDIALE | ■ EURABIO |
| ■ ANIOS | ■ BEL FOUNDATION |
| ■ API RESTAURATION | ■ MACIF FOUNDATION |
| ■ AUCHAN RETAIL FRANCE | ■ LACTALIS |
| ■ BASF | ■ M COMME MUTUELLE |
| ■ BRUNEAU | ■ VERSPIEREN |



API RESTAURATION

"Fully aware of the importance of supporting the populations over the course of their lives and convinced of the importance of eating well for living better longer, API Restauration is proud to support the longevity research conducted by Institut Pasteur de Lille."

Damien Debosque,

Chief Executive Officer of the institutional catering company
Api Restauration



M COMME MUTUELLE

"As an actor in prevention, M Comme Mutuelle wanted to renew its commitment alongside Institut Pasteur de Lille. This year again, we call on support for the foundation in its research projects and on sharing solidarity values which M Comme Mutuelle holds dear."

Jérôme Rehlinger,

General Director, M comme Mutuelle



ENTREPRISES ET CITÉS

"Institut Pasteur de Lille is a place of regional scientific excellence which endeavours to further knowledge, treatment, and prevention of disease. The quality of its research and its commitment to public and business service in our region merits the recognition and the support of the region's economic and industrial sector. That's why we choose to work alongside Institut Pasteur de Lille."

Pascal Boulanger,

President, Entreprises & Cités



SPONSOR EVENTS

The year 2018 was punctuated by many events and achievements. Each partnership led by Institut Pasteur de Lille seeks to be unique.

■ AG2R La Mondiale / Institut Pasteur de Lille: a model partnership with multiple dimensions

The Nutrition Department conducts food education actions in public health. It acts on behalf of private and public actors and participates fully in the regional implementation of public policies in the field of food and health.

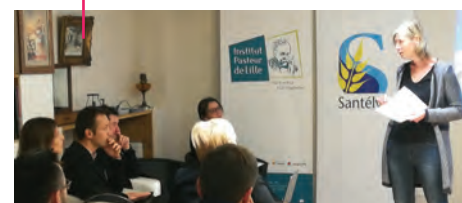


■ Participation in the 2018 Route du Louvre thanks to the partnership with AG2R La Mondiale

For more than 10 years already, AG2R La Mondiale has partnered with Institut Pasteur de Lille to build public awareness of health issues and insist on the importance of prevention. This year, €15,000 was collected with the support of the company's employees who transformed their kilometres into euros.



■ Club Partenaires Santelys round table



■ Gala event for Bruneau key accounts



SOLIDARITY FUNDRAISERS

KIABI

400 employees of KIABI and Institut Pasteur de Lille took part in the "Smart Mobility, let's do it!" challenge! What's the objective? Promoting regular physical activity and fund raising to finance research projects on Longevity. A total of €3,000 was collected!



WEEMBI

SOLID'AIR weekend is a unique collective action that revolves around a new challenge involving the world of wind tunnels: 24 hours of consecutive flight to profit scientific research. With each booked initiation flight, Weembi donated €15 to the foundation. The second edition of SOLID'AIR made it possible to raise €3,000.



BRADERY

Adix, a management consulting firm, organised an inter-company challenge on the occasion of the 2018 "Courses de la Brader'y" races to raise funds for the fight against disease. Forty-some runners crossed the finish line with solidarity colours! Partner businesses: Anios Laboratories, Lutti, and Diagast. The event raised close to €6,000.



LILLE METROPOLE BASKET

During the Derby against Denain, the Metropole club supported Institut Pasteur de Lille by calling on donations by SMS.



INSTITUT PASTEUR DE LILLE AND COMPANY NETWORKS

CLUBSTER SANTÉ (HEALTH CLUBSTER)

Institut Pasteur de Lille joined Clubster Santé, a network of health companies in Hauts-de-France.



CLUB GAGNANTS (THE WINNERS CLUB)

Institut Pasteur de Lille is a member of Club Gagnants. Their goal is to call attention to the economic dynamics and potential of Hauts-de-France.



PASTEUR AWARD AT THE INDUSTRY TROPHIES

On the occasion of the Industry Trophies (Trophées de l'Industrie), Institut Pasteur de Lille which is committed to relations with industry, awarded the Pasteur Lille prize to Anios Laboratoires for their historic commitment to innovation in the fight against infectious disease.



FORCE AWARDS: INSTITUT PASTEUR DE LILLE ALONGSIDE RESEARCHERS-ENTREPRENEURS

A partner to Force Awards 2018, Institut Pasteur de Lille presented the Force Partner award which rewards a partnership project between academic research and the world of business.



THE INSTITUT PASTEUR DE LILLE MUSEUM

Musée de l'Institut Pasteur de Lille

A NEW WAY TO DISCOVER HISTORY AND SCIENCE

Fully financed by the Anios Laboratories sponsorship and inaugurated in September 2017, the Institut Pasteur de Lille Museum reflects not only Institut Pasteur de Lille's history and its founders but also today's dynamic: many future projects on the topic of longevity as well as new collaborations with the business world, as demonstrated by the patronage of Laboratoires Anios.

Lodged in Albert Calmette's former apartment - it's within these walls that Dr. Calmette and the veterinarian Camille Guérin discovered *Bacillus Calmette-Guérin* (BCG), a vaccine against tuberculosis. The original stem cells are presented in the museum. Louis Pasteur and Lille are also linked with the history of alcoholic fermentation, which the scientist discovered at the Faculty of Sciences of Lille when he was the dean in 1854.

Since its creation, Institut Pasteur de Lille, a private state-recognised public-interest foundation, has sought to help local populations by putting science at the service of health.

At the time, certain private individuals, local communities and industrialists came together to create the institute which, in addition to creating serums, educated the population about the rules of hygiene.

Although the health research and risk management objectives have shifted towards the diseases associated with ageing (cancer, cardiovascular diseases, infectious and parasitic diseases, Alzheimer's disease, diabetes, etc...), Institut Pasteur de Lille remains very attached to its roots and history.

"AROUSING INTEREST IN SCIENCE,
RESEARCH AND HEALTH IS A MAJOR
CONCERN FOR INSTITUT PASTEUR DE
LILLE."

The museum is a mix between a cabinet of curiosities, a period laboratory and digital installations, revealing the mysteries of Institut Pasteur de Lille and its founders. This contemporary layout provides a tool that is undeniably suited to communicating science to all audiences. Arousing interest in science, research and health is a major concern for Institut Pasteur de Lille.



Visitors immerse themselves in a fantasy world where scientific research is poetically showcased in every corner of the museum. Installed on everyday furniture, they discover vials brought to life with video, a letter that writes itself by magic, a little mouse that crisscrosses the room, scales that wobble from left to right, etc. This contemporary exhibition has a very particular resonance in this location steeped in history.

4 REALMS:

Room A: Institut Pasteur de Lille

Room B: Louis Pasteur

Room C: Albert Calmette and Camille Guérin

Room D: Institut Pasteur de Lille today

Open to the public: Saturday and Sunday: 10:00am to 12:00pm / 2:00pm to 5:00pm

Private events and guided tours.

Contact: +33 (0)3 20 87 72 42 - musee@pasteur-lille.fr



BUILD TOMORROW'S FOUNDATION



RESEARCH, PREVENTION, HEALTH, AND LONGEVITY: A FOUNDATION ON THE MOVE

The Foundation project is structured on the subject of longevity with the Centre for Longevity Research, the Prevention in Health and Longevity Centre, and the Pollution, Health, and Longevity Hub. These 3 strategic areas (**Research, Prevention, Pollution**) are complementary and nourished by shared knowledge and strong interaction among the campus teams. Institut Pasteur de Lille has consolidated its strategic positioning as a leading centre addressing the issue of longevity and age-related diseases.

Naturally, this development of the Foundation's missions to respond to the challenges of society involves changes to its organisation and governance and the optimisation of resources (financial, material and human).

COLLABORATIONS WITH THE BUSINESS AND INDUSTRIAL WORLD

Institut Pasteur de Lille develops its relations with the business and industrial worlds through scientific collaborations, specialist services, general-interest activities and corporate sponsorship. This relationship, which is faithful to the origins of the institute, is necessary for the Foundation to fulfil its missions of research, specialist services and disease prevention in healthcare. Thanks to the permanent guest seats on the Board of Directors, business and industrial players can find out about and be involved in the management of the Foundation.

Further, to fully play its role as an Hauts-de-France scientific and economic actor, Institut Pasteur de Lille participates in different company networks such as Club Gagnants, FBC, and Club des Entreprises Centenaires. Institut Pasteur de Lille participated in the promotion of Hauts-de-France activities and scientific excellence.

THE BOARD OF DIRECTORS AT MARCH 15, 2018

■ College of founders:

- **Jacques Richir**, Deputy mayor of Lille. *President of the Board of Directors (*)*
- **Marc Bodirot**, Deputy mayor of Lille
- **Dominique Picault**, Deputy mayor of Lille
- **Jérémy Crepel**, Deputy mayor of Lille
- **Isabelle Mahieu**, Advisor City Council of Lille

■ College of institutional partners:

- **François Kinget**, City Councillor, representative of Métropole Européenne de Lille (MEL) *Secretary (*)*
- **Nicolas Lebas**, Vice-Chairman of Higher Education, research and universities, representative of the Hauts de France region. *Vice-Chairman (*)*
- **Nicolas Siegler**, Departmental Advisor, representative of the County Council of the Nord
- **Stewart Cole**, General Manager of Institut Pasteur
- **Yves Lévy**, Chairman and Managing Director of the National Institute of Health and Medical Research (Inserm)
- **Françoise Paillous**, Regional Delegate for the Nord-Pas-de-Calais, representing the Chairman of the National Centre for Research (CNRS)
- **Jean-Christophe Camart**, Chairman of the Lille University

■ College of qualified personalities:

- **Prof François-René Pruvot**, Chairman of the Medical Commission Establishment of Lille University Hospital
- **Patrick Vacossin**, Chamber of Notaries of the Nord. *Treasurer (*)*

■ College of Friends of the Foundation:

- **Thierry Letartre**, Managing director of ANIOS. *Member of the office (*)*

■ Permanent guest members:

- **Pierre-René Tchoukriel**, Auchan
- **Brigitte Villette**, AG2R LA MONDIALE
- **Thierry Mathieu**, Eurabio/Synlab

(*) member of the office

A FOUNDATION THAT ADAPTS

Like all organisations, Institut Pasteur de Lille is developing within a changing environment and must adjust its positioning, strategy and organisation to optimise its activities, ensure the long-term viability of its resources and meet the challenges of tomorrow in terms of health. For this reason, the Foundation strives to support these changes internally as much as possible.

The management of Institut Pasteur de Lille also develops its management tools. This includes a multi-year plan composed of objectives, new tools for managing activities or even the optimisation of the available space in order to group together activities to make work easier for everyone.

■ At the forefront of this change, there have been the following important framework projects for the Foundation:

- appropriate **statuts**
- 3**CPER-CTRL calls for projects** on Longevity
- evolution of **Prevention in Health and Longevity Centre**
- **cross-disciplinary research** which for the 1st time called on all the Institut teams
- a renovation programme for the facilities and equipment

■ But also, the organisational and operational projects, namely:

- voluntary commitment to the regulations **applicable to public contracts**
- creation of an IT continuity plan (backup, archiving and redundancy)
- constitution of the Finance Hub grouping treasury, accounting, and management control
- application of GDPR and naming of a DPO (Data Protection Officer)
- review of projects in relation to the **audit on governance** and **conflicts of interest**

■ To accompany these changes, the management, in association with the Board and the authorities, has set up a number of tools:

- a **training policy** that includes sessions on management and support for change
- **internal events** for employees and internal visits of departments
- **bi-annual staff meetings, an annual event**, regular discussion times with staff
- **welcome sessions** every month and a booklet for new recruits
- **staff reviews**
- **annual reviews** and follow-up
- an **Ecocampus approach** with workshops for staff
- a **CSR approach**

■ In addition, working conditions are taken into consideration with the following:

- modernisation of **technical resources**
- an **all-day** company restaurant
- **sports facilities**
- **renovated premises** and in the process of being renovated
- **wi-fi** on campus
- right to **disconnect**

KEY FIGURES



10

TECHNOLOGY
PLATFORMS



50,000 M²

OF LABORATORIES



14,847

HEALTH
CHECK-UPS



342

SCIENTIFIC
PAPERS



26,000

VACCINATIONS
CONDUCTED

OUR CSR COMMITMENTS



ORGANIZATION

- **Board composition:** a mix of representatives from local authorities, the scientific community, and industrial partners
- **Audit of our CSR approach with skills-based sponsorship**



EQUAL OPPORTUNITIES

- **6% of our staff is disabled** and may be considered for reorganisation of their work stations and working conditions.



LOCAL PLAYER

- **Responsible collective catering** with our contractor, Envies de Saison
- **Personalised medical check-ups** and recommendations (60% of participants in precarious situations)
- Research Education with **Kid Campus**: 450 children took part in Kid Campus in 2018
- Weekly vegetable baskets available with Destinations Légumes
- **Participation in the cultural and tourist heritage** of the city of Lille thanks to the Institut Pasteur de Lille Museum: Over 3,000 visitors to the museum in 2018
- **Job creation:** welcoming foreign researchers, emerging teams, sandwich course students



WELL BEING AT WORK

- **Training:** a budget that is twice that of the legal requirement
- **Labour relations:** regular and transparent dialogue during the bi-annual meetings with personnel
- **Protection of pregnant women** for positions exposed to chemical and biological risks
- **Housing and mobility assistance** for employees with Action Logement
- **Flexible hours**
- Subsidy for **collective catering**



ENVIRONMENT

- **Management of hazardous waste**
- **Sorting and recycling of ordinary waste**
- **"Eco-Campus"** participatory approach
- **Definition of a Company Green Transport Plan**
- **Winner of the 2018 Mobility Challenge - Best participation rate category** (establishment of more than 500 employees)

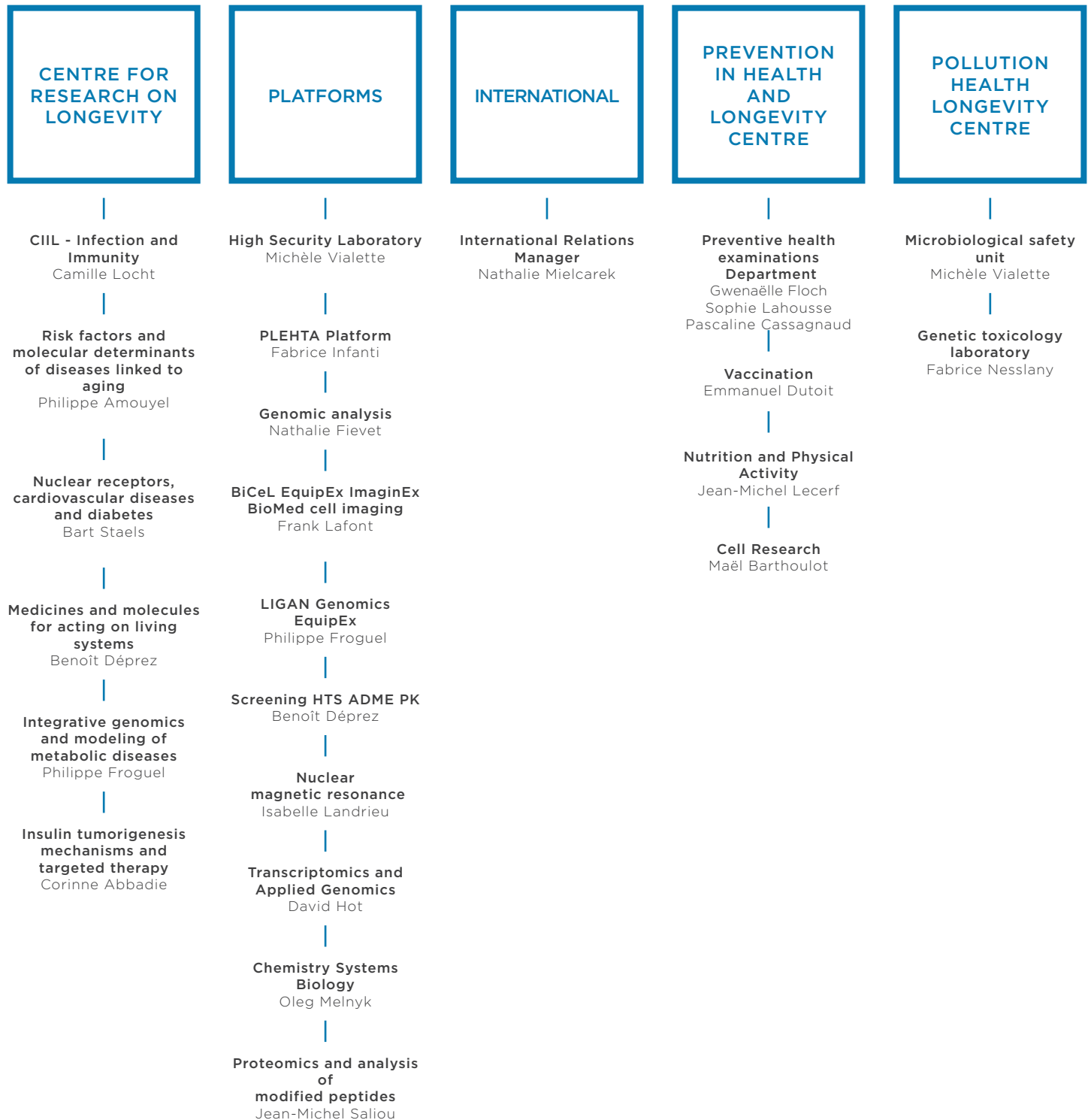
SCIENTIFIC AND ADMINISTRATIVE

GENERAL

Managing director
Recruitment in process

Assistant manager >

Scientific Director > Benoît Déprez

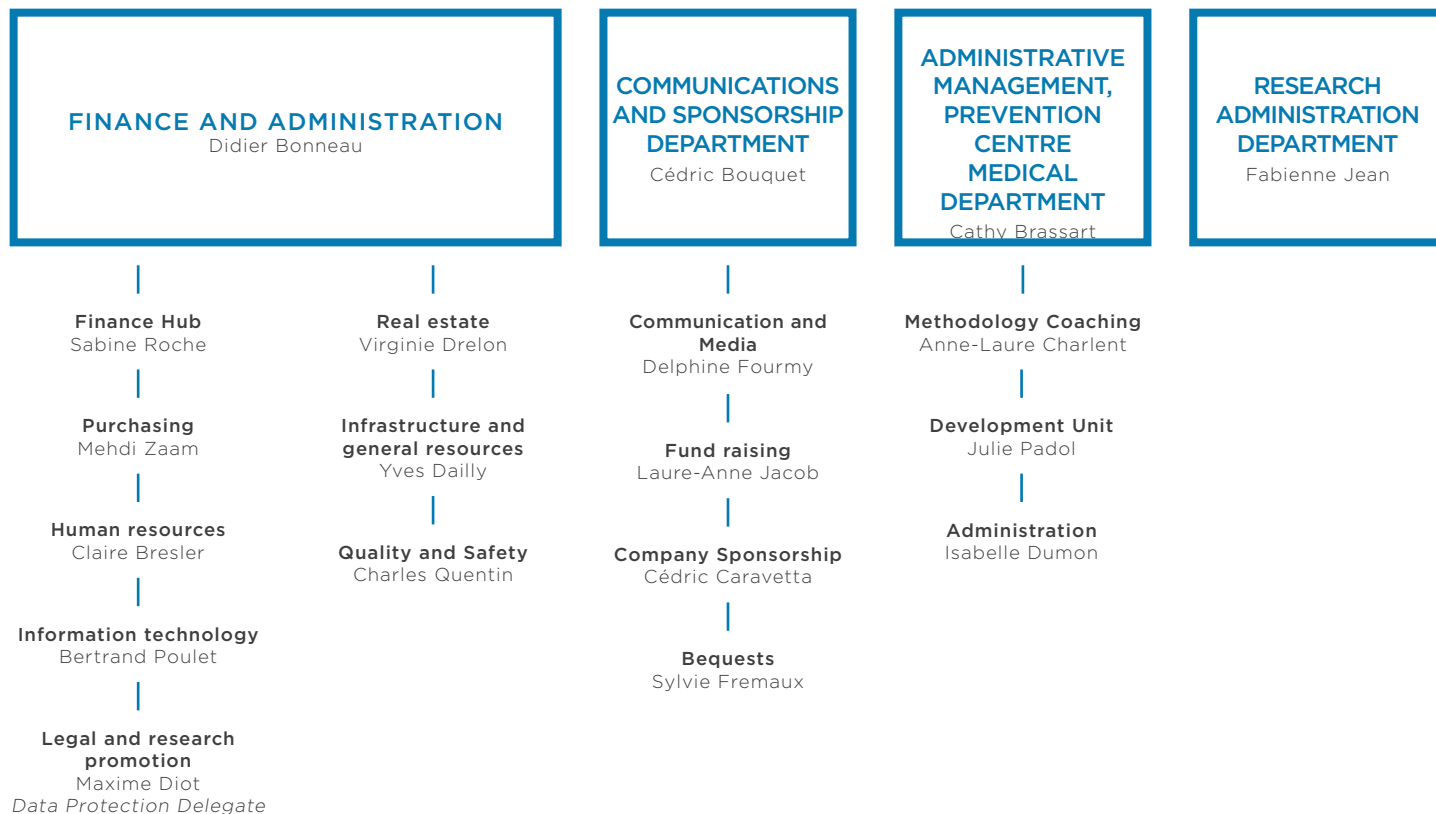


ORGANISATIONAL CHART

MANAGEMENT

Deputy managing director
Didier Bonneau

Sylvie Amoravain



794 EMPLOYEES ON CAMPUS



331 EMPLOYEES
INSTITUT PASTEUR
DE LILLE



102
MEN



229
WOMEN



**463 EMPLOYEES
AND INTERNS**
OTHER
INSTITUTIONS*

* INSERM, CNRS,
LILLE UNIVERSITY,
LILLE UNIVERSITY HOSPI-
TAL, STARTUPS...



26
NATIONALITIES

EMPLOYMENT/RESOURCES

16.3 million euros

DEDICATED TO RESEARCH IN 2018

Financing for Institut Pasteur de Lille's missions comes from a variety of private and public sources.

In 2018, Institut Pasteur de Lille spent €27.9 million on its principal missions of research (€16.3 million), prevention and public information (€9.3 million).

THE €16.3 MILLION FOR RESEARCH BREAKS DOWN INTO:



FOR INFECTIOUS AND INFLAMMATORY DISEASES



FOR THE RUNNING OF TECHNOLOGICAL PLATFORMS



FOR CANCER RESEARCH



FOR THE DISCOVERY OF MEDICINES



FOR RESEARCH ON CARDIOVASCULAR AND METABOLIC DISEASES



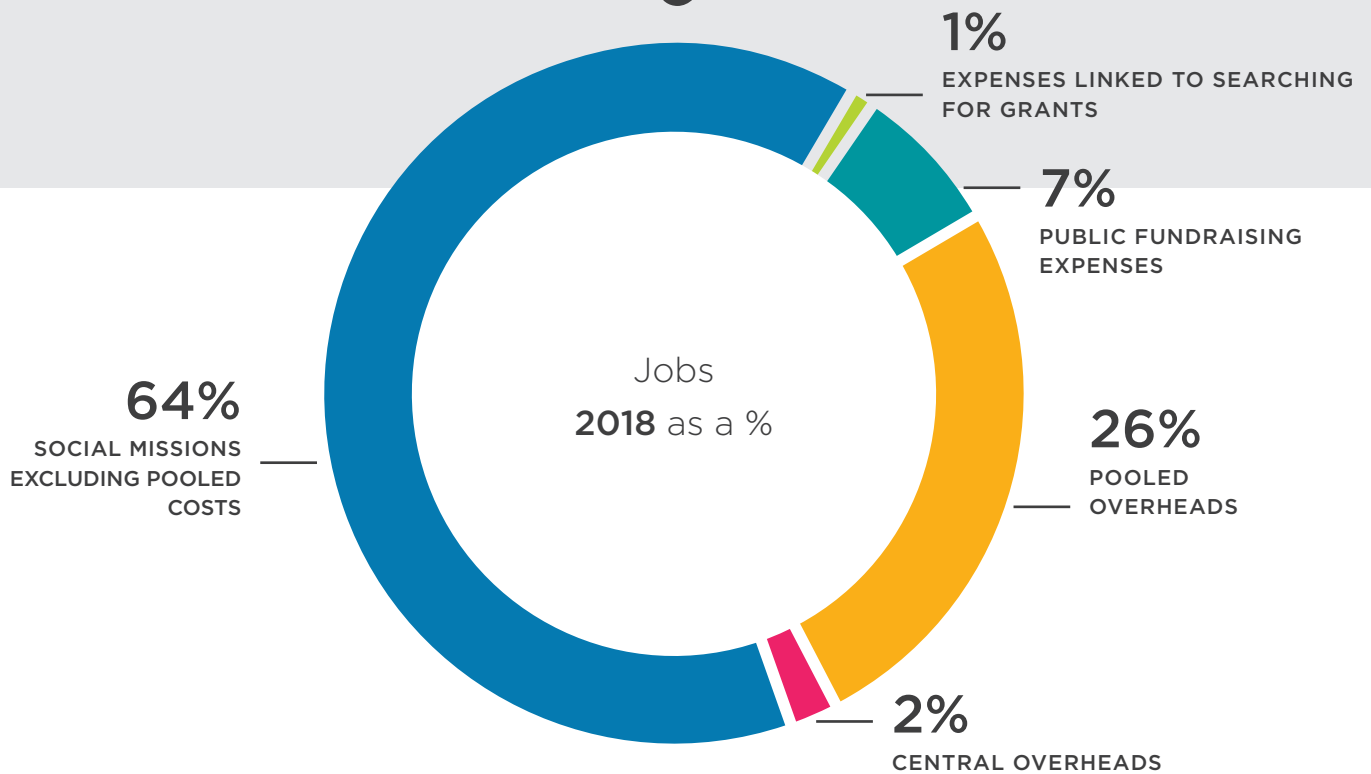
FOR CARDIOVASCULAR AND NEURODEGENERATIVE DISEASES



FOR GENETIC AND METABOLIC DISEASES

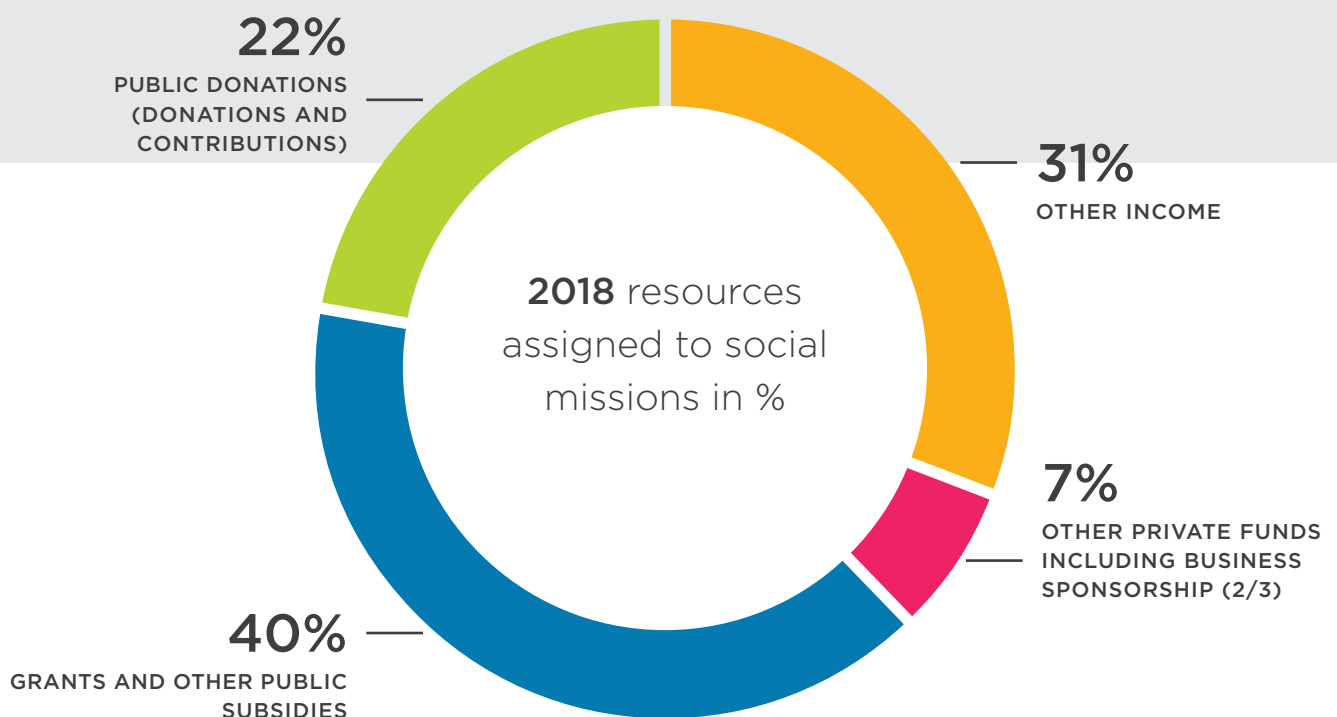
JOBS

€



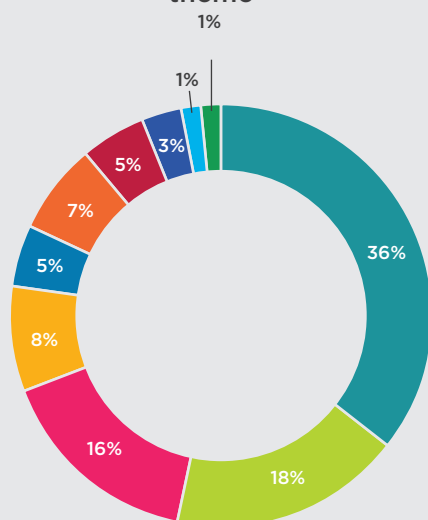
RESOURCES

€

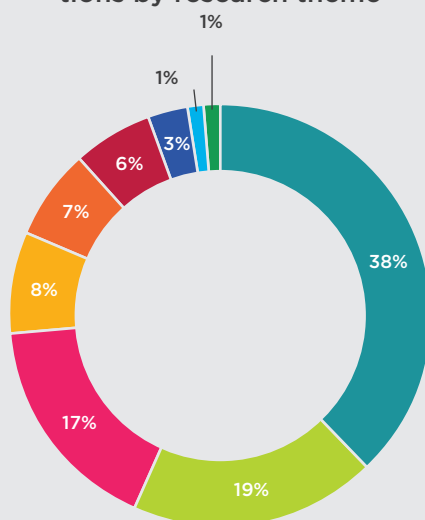


SCIENTIFIC PAPERS

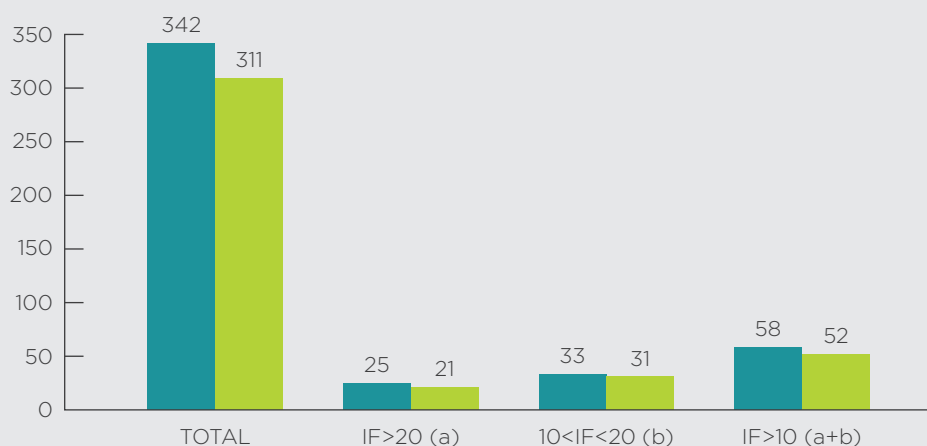
2018 Distribution by research theme



2018 English-language scientific publications by research theme



- CIIL
- Public health
- Cardiovascular disease and diabetes
- Cancer
- Metabolic diseases
- Technology platforms
- Discovery of prescription drugs
- Genetic toxicology
- Preventive Health
- Nutrition



- with epub
- without epub

2018	with epub	without epub
Total	342	311
if >= 20 (a)	25	21
20 > if >= 10 (b)	33	31
if >= 10 (a) + (b)	58	52

Is Institut Pasteur de Lille the leader (1st or 2nd or last author)?	YES	NO	All publications
2013	157	156	313
2014	181	146	327
2015	189	157	346
2016	162	174	336
2017	181	162	343
2018	181	161	342

	2013	2014	2015	2016	2017	2018
Number of publications (with epub)	313	327	346	337	343	342
Number of publications with IF ≥ 20	14	6	14	17	7	25
Number of publications with 10 > IF ≥ 20	31	38	35	29	35	33
Number of publications, led by Pasteur Lille (1st, 2nd or last writer)	157	181	189	162	181	181

IMPACT FACTOR BETWEEN 10 AND 20

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IMPACT FACTOR GREATER THAN 20

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