CIIL NewsLETTER

CIIL
CENTER FOR INFECTION & IMMUNITY OF LILLE

This year, the CIIL is preparing for its evaluation by the HCERES. After the reorganization of several teams and the pre-evaluation by the international scientific advisory board of the Institut Pasteur de Lille, the document of auto-evaluation was sent last month. We are now beginning to prepare for the on-site HCERES visit which will take place between the 19th and 21st of November this year. In this issue, we continue the presentation of the researchers and engineers who actively participate in the CIIL project. They include Dr Sandrine Belouzard, a CNRS researcher who gained visibility during the COVID-19 crisis, Professor Eric Kipnis, a MD-PhD developing research programs in the field of respiratory diseases at the university hospital of Lille, and Dr Patricia de Nadai, a junior professor focusing her research activities on asthma. Also presented in this Newsletter are Kamel Djaout, a research engineer recently recruited at Inserm in the team of Ruben Hartkoorn, and Céline Wichlacz, recently promoted research engineer at CNRS in the team of Priscille Brodin. On the 16th of April, all the members of the CIIL gathered for the annual retreat of the unit and some pictures of this event are presented in this issue. I would like to take the opportunity of this message to thank the members of the animation team for the organization of this event as well as for their involvement in the organization of the weekly seminars of the CIIL.

Jean DUBUISSON

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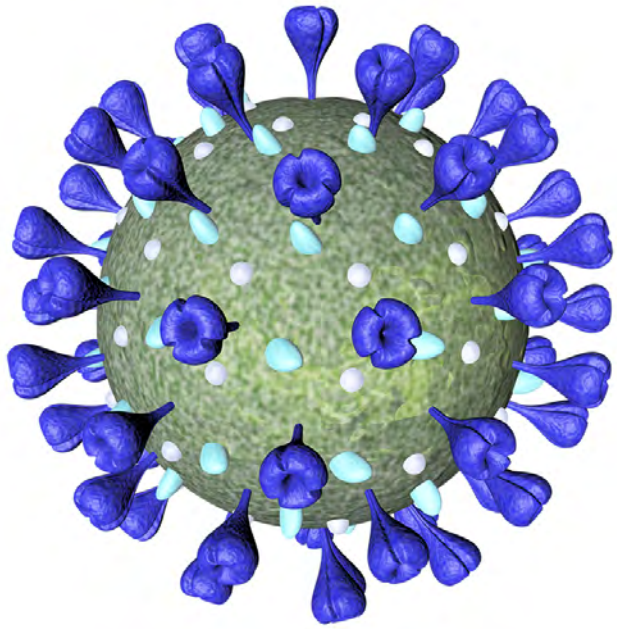
Sandrine BELOUZARD
CNRS Researcher

I'm Sandrine Belouzard, research fellow at the CNRS. After completing my undergraduate studies at the University of Lyon, I moved to Lille to do my DEA.

I did my thesis in cell biology on the endocytosis mechanisms of leptin receptors under the supervision of Yves Rouillé. During my thesis, Yves joined Jean Dubuisson's team, which gave me a foothold in the field of virology, even though I kept my original thesis project. After my thesis, I joined Gary Whittaker's laboratory at Cornell University (Ithaca, NY) to study the endocytosis mechanisms of coronaviruses. In the end, this project was quickly abandoned to study the fusion mechanisms of SARS-CoV (severe acute respiratory syndrome coronavirus). I was fascinated by the ability of coronaviruses to cross species barriers and infect new hosts. The restriction is almost entirely at the level of viral entry into the cell, so if we are to better understand the mechanisms by which these viruses emerge, it is essential to know more about their entry mechanisms. Coronaviruses are enveloped viruses which must fuse their viral envelope with a membrane of the target cell in order to deliver their genome and begin their replication process. This fusion must be finely regulated to ensure successful infection. When I started this project, it had been shown that SARS-CoV fusion was activated by proteases, but the precise mechanisms were not known. The coronavirus spike protein consists of an S1 receptor-binding domain and an S2 fusion domain. During my post-doc, we identified the key cleavage site for fusion activation in S2. While some coronaviruses have a spike protein on their surface that is cleaved between the S1 and S2 domains via a furin cleavage site, the SARS-CoV spike protein is not. We also showed that for SARS-CoV, a first cleavage of these two domains during entry facilitated the second cleavage and fusion. This work was in part misused by conspiracy theorists during the emergence of SARS-CoV-2 to claim that the virus was the result of laboratory manipulation.

In 2009, I was recruited by the CNRS and joined Jean's team. Following the emergence of the coronavirus responsible for Middle East Respiratory Syndrome (MERS-CoV) in 2012, I initiated research projects on coronaviruses. I continued to focus on coronavirus entry mechanisms, first those of HCoV-229E and more recently those of SARS-CoV-2. Coronaviruses are able to use different proteases to enter a cell and propagate, and we are



far from having understood all the mechanisms involved. In addition to the spike protein, two other proteins are present in the coronavirus envelope: the membrane proteins (M) and the small envelope protein (E). The assembly of new viruses is orchestrated by the M protein, which generates interactions with all the other structural proteins of the virus. This assembly step has been little studied, and requires that all virus components be addressed at the assembly site. To better characterize this assembly step, we first looked at the intracellular trafficking of M proteins. We have shown that the last 20 residues of the protein play a central role in intracellular trafficking of the protein and in the morphogenesis process. We are now seeking to better characterize this role and identify the cellular partners of the M protein required for its trafficking and viral assembly. For this project, we are collaborating with Emmanuelle Blanchard-Laumonnier (INSERM U1259, Morphogenesis and Antigenicity of HIV and Hepatitis Viruses (MAVIH), University of Tours) and Xavier Hanoulle (INSERM U1167 - CNRS EMR9002).

Since the SARS-CoV-2 pandemic, I have also been developing tools to screen molecules against coronaviruses with minimal manipulation, and we are now looking to extend our screening capabilities to other viral families. Indeed, the emergence of SARS-CoV-2 has highlighted our lack of preparedness and available treatments to deal with epidemics caused by new viruses.

Eric KIPNIS
Clinician-researcher

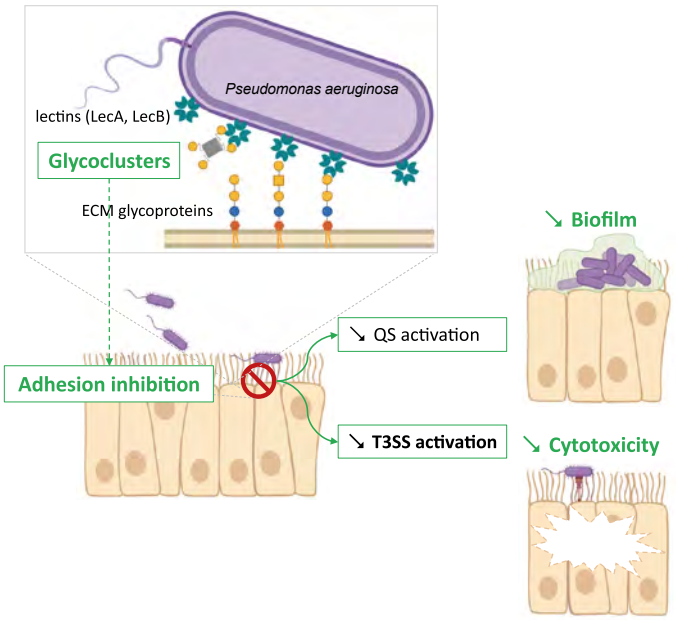
I am Pr. Eric Kipnis, a clinician-researcher dedicated to understanding how a WHO problem pathogen, *Pseudomonas aeruginosa*, leads to severe infections and how to target these mechanisms and modulate host responses to improve outcomes. As an Anesthesiologist and Critical Care physician, I face daily challenges treating patients infected by *P. aeruginosa*, a "problem" pathogen increasingly resistant to antibiotics and highly virulent through an array of virulence factors that injure the lung and elicit uncontrolled host immune responses. My research focuses on targeting virulence factors, such as adhesins (LecA, LecB) that allow *P. aeruginosa* to attach to lung cells and the subsequently activated type 3 secretion system (T3SS) which allows it to "inject" toxins into lung cells.

This journey began during my medical studies with a B.A. in Physiology and a summer of research at Albert Einstein School of Medicine in New York. While completing my Anesthesiology and Critical Care residency at Lille University, I also earned a Masters in Respiratory Biology/Physiology from University Paris XII. My research, under the mentorship of Pr. Benoit Guery (EA 2689, Lille University), focused on lung responses to *P. aeruginosa* infection, particularly the activation of lung coagulation and bacterial virulence factors such as the T3SS. I then spent two years in the Translational Research on Microbial Pathogens Group (Pr. Wiener-Kronish) at University of California San Francisco (UCSF) in a Research Fellowship, metnored by Teiji Sawa, where I developed proteomic analysis of lung epithelial lining fluid and participated in testing humanized anti-PcrV antibodies targeting the T3SS in murine models of *P. aeruginosa* lung infections.

Returning to Lille, I completed a clinical Fellowship in Anesthesiology and Critical Care and continued my research with Benoit Guery on modulating *P. aeruginosa* virulence and host response, culminating in a Ph.D. in Health Biology. I also became Board Certified in Infectious Diseases. As a Critical Care physician, I was an investigator in the randomized controlled study testing the anti-PcrV monoclonal antibody developped at UCSF that I had tested in pre-clinical murine models.

Our team joined the Center for Infection and Immunity (LI3 team led by Francois Trottein and then the Inflammasome team led by Mathias Chamaillard), where I mentored doctoral students and focused on the host response against *P. aeruginosa*. We demonstrated how *P. aeruginosa* exploits T3SS recognition by the NLRC4-inflammasome through IL-18 by dampening IL-17-dependent mucosal antipseudomonal response, and that this is countered by IL-18 binding protein, IL-17 administration or T3SS-targeting molecules.

In 2012, I became Associate Professor, and by 2015, Full Professor, and led the Host-Pathogen Translational Research team (EA 7366, Lille University). We further explored the T3SS/inflammasome pathway, showing that the human NAIP-NLRC4-inflammasome senses T3SS proteins. Building upon earlier results we developed synthetic carbohydrate-based glycoclusters targeting *P. aeruginosa* adhesins (LecA and LecB), that showed significant inhibition of bacterial adhesion and attenuation of lung injury in cellular and murine models. These findings led to a large-scale academic-industrial project, Anti-Pyo, to synthesize and screen glycoclusters for pharmaceutical development.



Reapeated collaboration over the years with Philippe Gosset led us naturally to the successful merging of our teams in 2019 into the Opportunistic Infection Immunity and Environment in Lung Disease (OpInfIELD) lab led by Philippe Gosset at the CIIL where I continued to develop glycoclusters targeting *P. aeruginosa* lectins and participated in our team's developping work on the microbiome in responses against *P. aeruginosa* infection. Recognizing *P. aeruginosa*'s role in cystic fibrosis (CF) infections, we led a collaborative project supported by the French Cystic Fibrosis Fund to synthetise and test newer glycoclusters in relevant models. This was followed by an R&D project supported by SATT-Nord to advance the best compounds towards pharmaceutical development. Pre-clinical development is ongoing in a joint academic/SMB project supported by a BPIFrance grant.

Currently, as Head of the Lille University Hospital Surgical Critical Care Unit, I advocate for collaborative efforts translating research into patient care. My ongoing projects aim to enhance antibiotic efficacy against multidrug-resistant pathogens. By actively engaging in both scientific discovery and patient care, each domain informs and enhances the other, contributing to advancing better patient outcomes.

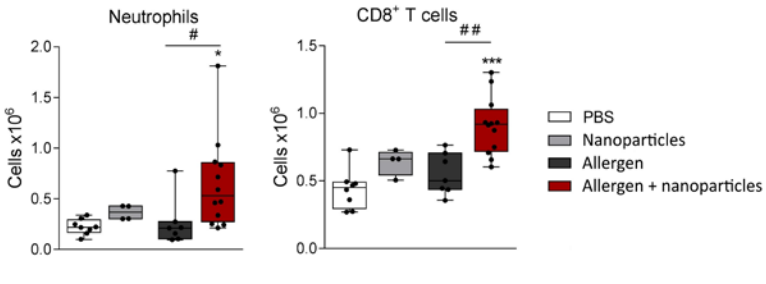
Patricia DE NADAI
Associate Professor
University of Lille

After training at the Paul Sabatier University in Toulouse, I came to the Pasteur Institute in Lille to do my DEA and then my thesis on chronic respiratory pathologies, in the Inserm Unit U416, under the supervision of Dr Anne Tsicopoulos. My thesis project focused on the role of the chemokine CCL18 in pulmonary pathophysiology and particularly in human asthma. The team's projects were very much oriented towards translational research with pulmonologists at Lille University Hospital. This collaboration gave me personal and professional benefits and gave a new perspective to my research.

After my thesis, I joined the Institut de Recherche Interdisciplinaire en Biologie Humaine et Moléculaire (IRIBHM) in Brussels as a post-doctoral fellow under the supervision of Prof. Marc Parmentier, working on G protein-coupled receptors, including chemokine receptors. During my 6 years at the Institute, I developed techniques for purifying proteins from human inflammatory fluids. Thanks to my expertise in immunology and inflammatory lung diseases, we studied the ChemR23 receptor, whose ligand, chemerin, had been discovered in the laboratory. We showed that it was expressed by dendritic cells and macrophages, and that it had an anti-inflammatory role in vivo in mouse models of acute lung injury (LPS) and acute viral pneumonia (PVM). I had the chance to work with a supervisor who was considerate and open to discussion, and I was able to carry out my research freely.

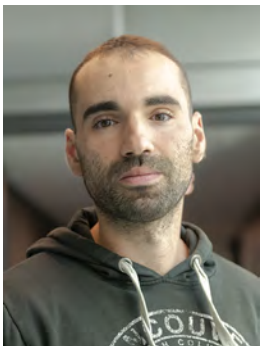
In 2012, I obtained a position as Associate Professor at the University of Lille in the CIIL and the Lung Immunity team led by Dr Anne Tsicopoulos. My duties as Associate Professor are twofold: on the one hand, teaching at the university, which takes up a large part of my time (170 hours/year), and on the other, research in the laboratory. I mainly teach immunology at UFR3S, particularly in medicine and pharmacy, but also in Masters 1 and 2. Recently, with Dr Muriel Pichavant, I created a DU in Pneumology and Translational Research, which is due to open in November 2024. As well as teaching, I'm involved in the university's dynamic by helping with the reform of medical studies by taking part in exam invigilation and examinations from years 1 to 6.

My research projects are focused on asthma and have two main directions: the impact of nanoparticulate pollution on the disease and the identification and development of new therapies. Asthma is a chronic respiratory disease that is strongly influenced by the environment. I have developed several mouse models of exposure to nanoparticles and house dust mite allergens. We have shown that co-exposure to high doses of allergen leads to changes in lung inflammatory infiltrate, with neutrophils and CD8+ T cells (Figure),



two cell types that are more resistant to the usual treatment of asthma with corticosteroids. Pollution could therefore have an impact on the effectiveness of corticosteroids in asthma patients.

All my collaborations have enabled me to develop a cross-disciplinary project on the impact of climate change on the allergenicity of pollen grains, as well as a project on the impact of in utero exposure to ultrafine particles on the development of asthma. These projects are funded by ANR and ANSES. I'm also in charge of a cross-disciplinary project with the Pneumology Department of the Lille University Hospital on severe neutrophil asthma, a type of asthma that is difficult to treat with available therapies and which reduces patients' quality of life. We have developed an original murine model of chronic exposure to dog allergen that reproduces the characteristics of severe human neutrophil asthma and enables us to evaluate new therapeutic targets. The translational part of this project is being carried out in collaboration with Professor Cécile Chenivesse's Respiratory Department at Lille University Hospital, and aims to characterise this particular type of asthma in order to identify the inflammatory mechanisms involved, define clinico-biological markers and develop specific therapies.



Kamel DJAOUT
INSERM research engineer

After obtaining a bachelor's and master's degree in molecular and cellular biology, which I started at the University of Paul Cézanne in Marseille and completed at the University of Pierre and Marie Curie in Paris, I dedicated myself entirely to research and the development of new antibiotics. My career quickly focused on tuberculosis, the disease of poverty, which is particularly close to my heart.

I completed a PhD at the Optics and Biosciences Laboratory of the École Polytechnique (2012-2015, Palaiseau), focusing on ThyX, an essential alternative thymidylate synthase in *Mycobacterium tuberculosis*. There, I characterized the enzymatic mechanism of the mycobacterial enzyme and identified naphthoquinones targeting ThyX, thus inhibiting the growth of the Koch bacillus.

Motivated by the development of anti-tuberculosis drugs, I joined Alain Baulard's team at the CIIL from 2016 to 2023. At the CIIL, and in collaboration with Professor Nicolas Willand's team (University of Lille), I learned to search for original vulnerabilities in *M. tuberculosis* that we could therapeutically exploit with combinations of molecules.

I selected compounds from the norbornene family that enhance the activity of pretomanid, a first-line anti-tuberculosis drug for cases of multidrug-resistant tuberculosis. I led and contributed to all stages of the development of these molecules, from screening to proof of concept in vivo. We identified an intrinsic mechanism of


Image générée par IA (OpenAI)

resistance to pretomanid, an alternative pathway for the synthesis of arabinogalactan, which we inhibit with norbornenes to potentiate the effect of pretomanid. Thus, these norbornenes improve the efficacy of pretomanid by almost 100-fold in a murine model of acute tuberculosis infection.

Simultaneously, I initiated a project aimed at understanding quorum sensing in *M. tuberculosis*. These bacilli coordinate their growth through secreted molecules and proteins. In their absence, replication is not initiated, which is associated with antibiotic tolerance. Our goal is to exploit this regulation for therapeutic purposes to restore the effectiveness of treatments. This project is currently led by Oriane Rivière as part of the Mustart project coordinated by Alain Baulard.

Since January 2024, I have held a research engineer position in Ruben Hartkoorn's CBA team, dedicated to combating antibiotic resistance through the research and development of new antibiotics. I have already launched a new anti-tuberculosis research project and established the CRISPRi library developed by Jeremy Rock, a valuable technology for all mycobacteriologists at the CIIL who are interested.

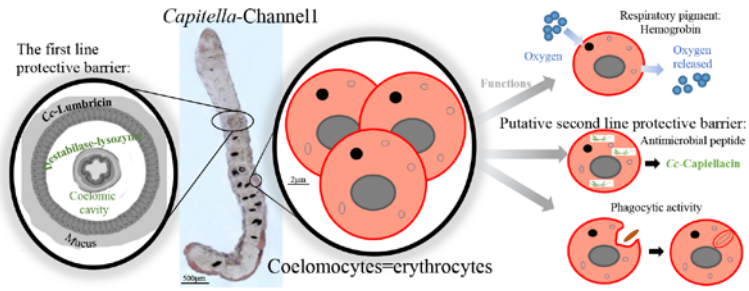
Céline BOIDIN-WICHLACZ

CNRS research engineer

I completed my thesis at the Annelid Neuroimmunology Laboratory (CNRS 2933) directed by Prof. Michel SALZET. My PhD was devoted to the characterization and functional study of the actors of the immune response in the leech, *Hirudo medicinalis*. I focused on the morphological and functional characterization of circulating cells, in particular blood cells, in the medicinal leech. In particular, I focused on the immune effectors that are the antimicrobial peptides produced by blood cells, and their implications in the protection and repair of the leech's central nervous system.

I then joined the Evolution, Ecology and Paleontology unit (UMR 8198), where I set up a biochemistry technical platform and a rearing and experimentation room for a coastal annelid, *Capitella capitata*. I have been involved in projects to assess the effects of stress on immune functions in invertebrates. That's why I've been interested in using hemocytes or coelomocytes as biosensors to study environmental stresses. Indeed, hemocytes or coelomocytes can be affected by a variety of environmental factors, from contaminants to pathogens. I have designed and developed in vitro analyses of immune cells such as coelomocytes/hemocytes, which are effective biomarkers and an obvious link between environment and immunity. Through the various studies I have carried out on cells, I have also become interested in antimicrobial peptides as sensitive markers of animal adaptation to extreme and changing environments.

In 2020, I joined the CIIL in the CGIM team (headed by Priscille Brodin) where, under the direction of Aurélie Tasiemski, head of the Antimicrobial Peptides (PAMs) axis, we are looking at antimicrobial peptides from extremophilic worms as new antibiotics to combat multi-resistant bacteria causing infectious lung diseases. The ever-increasing drug resistance of pathogenic bacteria represents a major challenge for global public health. Against this backdrop, there is an urgent need to identify potential new antibiotics, particularly against WHO-prioritized bacteria such as those responsible for tuberculosis (*Mycobacterium tuberculosis*, M.tb) and pneumonia (Pseudomonas aeruginosa, P.a.). Infectious sites such as the niches of M.tb and P.a. present a wide range of pH, iron and redox potential, requiring drugs that remain stable and active under a wide range of physicochemical conditions. My objective is to generate the relevant *in vitro* and *in vivo* biological data to establish a partnership with technology transfer accelerator companies or an industrial group involved in the pre-clinical and clinical development of new antibiotics. In September 2024, I'll be joining the team headed by Oleg Melnyk,



to continue this work as part of an iterative loop of synthesis-evaluation of analogues produced by our chemists' partner.

Life at the CIIL

Highlights of the IBL building

The major highlight of 2023 is the doubling of the electricity bill, from €208,989 in 2022 to €444,446 in 2023, despite a fall in consumption. Don't forget to turn off the lights when you leave a room.
The motor of one of our lifts has broken down in recent weeks (1st repair estimate: €32,000).

Actions taken since the beginning of 2024:

- Replacement of the hot water tank craned to R+6 (1)
- Ten-year inspection of the Colussi autoclave and qualification of the 121°C solid and liquid programmes
- Renovation of the slab of the laundry storage room on second basement to create a shop (2)
- Change of service provider for the multi-technical contract taken over by Pouchain

- Resumption of L2 cleaning by laundry staff

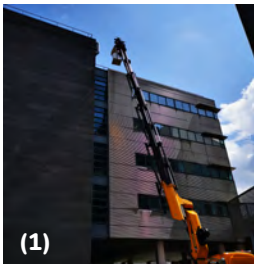
- Cleaning of water treatment tanks before discharge (3)
Future actions:

- Audit of our BMS supervision system
- Checks on electrical installations and fire safety
- Repair of fire door seals
- Call for tenders for HVAC maintenance (Heating/Ventilation/Air Conditioning)

Upcoming actions in 2024, financed by the DR18 :

- Refurbishment of the emergency staircases at the end of teeth 1 and 2.
- LED relamping of basements, emergency staircases and bathrooms.
- Renovation of the Cedilla roof.
- The energy metering plan to target hightly consuming equipment
- Improving central heating by adding thermostatic valves and replacing some of the radiators

Alexis DENHEZ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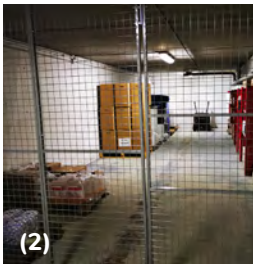
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PVC Bacteria Symposium

The PVC bacteria superphylum is named after its three key phyla: Planctomycetes, Verrucomicrobia, and Chlamydiae. These PVC bacteria are shrouded in mystery. They possess unique characteristics that set them apart from other bacterial groups, including the most developed prokaryotic endomembrane system. Scientists believe they may even have played a part in the evolutionary history of more complex cells. In addition, PVC bacteria exhibit a remarkable diversity covering the entirety of the symbiont-parasite spectrum, with some members forming beneficial partnerships with other organisms, while others have evolved parasitic lifestyles. Chlamydia, perhaps the most familiar member of this group, is a bacterium responsible for the common

sexually transmitted infection of the same name.
A two days and a half conference, just took place at the Institut Pasteur de Lille, on the 13th to 15th of May 2024, where the main actors of the field have presented their recent findings exploring the fascinating biology of these bacteria.

Damien DEVOS

Off-site day 2024

Laureates of the best poster's prize

On Tuesday the 16th April, the CIIL held its traditional off-site day at the Cité des Echanges in Marcq-en-Baroeul. It was a day of conviviality and sharing, and provided an opportunity to listen to presentations by a number of researchers on the progress of their translational projects, as well as on some of their more fundamental programmes. A Posters session provided an opportunity to appreciate the work of our PhD students and post-docs. This year, our guest speaker was Fréderic Batteux, the new Director General of the Institut Pasteur de Lille, who presented his work on systemic scleroderma, from pathophysiology to the clinic. It was also an opportunity to discuss with him the research projects developed within the CIIL. At the end of the day, prizes were awarded to Joan Fine, Elise Delannoy and Lowiese Desmarets, who were chosen by an internal jury for their posters. A double bravo to Joan Fine, who also won the public prize for her poster. The day was a great success, reflecting our commitment to scientific excellence and human interaction.

HCERES Evaluation

On November 19 to 21, our Unit will be evaluated by a committee of the Haut Conseil de l'Evaluation de la Recherche et de l'Enseignement Supérieur (HCERES), whose aim is to give an opinion on the quality of the scientific work produced over the period 2018-2023 and 2024 during the hearings. Other aspects will be considered, such as attractiveness, relations with the academic and economic sectors, and the impact on civil society in general.
As part of this process, discussions will be organised with the Committee for the various categories of staff.
(The research teams will, of course, be presenting their results and their plans for the 2026-2030 term of office. Over the last few months, the teams have been restructured, resulting in a reorganisation into 12 teams, which will submit a dossier for this new mandate to the supervisory bodies, in particular INSERM, by October 1st (with the whole dossier to be defended before INSERM's Scientific Council, scheduled for June 2025).
1-BELOUZARD Sandrine: Molecular & Cellular virology
2-BRODIN Priscille: Chemical Genomics of Intracellular Mycobacteria
3-DEVOS Damien: Evolutionary and Environmental Microbiology
4-GISSOT Mathieu: Biology of Apicomplex Parasites
5-GRASSART Alexandre: Mechano-biology of Host-Microbe Interactions
6-HARTKOORN Ruben: Drugs Discovery & Development
7-MELNYK Oleg: Miniproteins & Therapeutics
8-MIELCAREK Nathalie: Research on Mycobacteria & Bordetella
9-PICHAVANT Muriel: Targeted Immunomodulation for Lung Infections & Diseases
10-REAL Fernando & TROTTEIN François: Viral Infections & Chronicity
11-SEBBANE Florent: Plague & Yersinia pestis
12-SIRARD Jean-Claude & VAN MAELE Laurye: Bacteria, Antibiotics & Immunity.

Frank LAFONT

In brief ...

New recruit

Thierry Razafindratsita

Thierry Razafindratsita, currently account manager at Unit 9198 «Institut de Biologie Intégrative de la cellule» located at Gif-sur-Yvette, will be joining the CIIL's team of administrative managers from July 1st this year. We wish him a warm welcome. He will replace Fabienne Lebleu, who is retiring in September. We would-like to extend our warmest thanks to Fabienne for the professional support she has given our teams, and wish her all the best in her retirement, far from the «Etamine-Notilus-Goelett» trilogy.

Fabienne Lebleu

Arrival of Damien Devos's team

Damien Devos, IPL Research Director, officially took up his post this month. His emerging team on PVC bacteria, supported by IPL, has just moved into the Emile Roux building on the Institut Pasteur campus in Lille.

Thesis Prize

From left to right: Laurence Cocquerel, Martin Ferrié, Yazdan Yazdanpanah (Director of the ANRS-MIE)

Martin Ferrié is one of the 2 winners of the «ANRS-MIE / Société française de virologie» thesis prizes for basic research in viral hepatitis, which were awarded at the 24th AC42 - ANRS-MIE National Viral Hepatitis Network meeting on 11 and 12 March 2024 in Paris. This year's awards recognise 2 young scientists whose research work in the basic sciences of viral hepatitis has left its mark on the field through its innovation, originality and high quality. Martin completed his doctoral thesis entitled «Study of proteolytic maturation and intracellular trafficking of the ORF2 capsid protein of the hepatitis E virus», under the supervision of Laurence Cocquerel (MCV team).

Setting up of a new videoconference system

The CIIL has just installed a new videoconferencing system in the IBL boardroom, with financial support from the CNRS regional delegation.

Contributors to this issue include:

- Sandrine BELOUZARD
- Céline BOIDIN-WICHLACZ
- Eric KIPNIS
- Alexis DENHEZ
- Patricia DE NADAI
- Damien DEVOS
- Kamel DJAOUT
- Frank LAFONT

Director and supervisor of the publication	:	Jean DUBUISSON
Editorial coordination	:	Sabine BLIN
Design	:	Sophana UNG
Proofreading	:	Orane CHEDDAD

CIIL - CNRS UMR9017 - INSERM U1019
1, rue du Professeur Calmette - 59000 Lille

https://www.ciil.fr