Center for Infection & Immunity of Lille

CIIL

NEWSLETTER

#3 - March 202

For more than a year, research on SARS-CoV-2 has been on the frontline of the media. However, despite the COVID-19 crisis, the majority of the teams of our Center have continued to be very active on their own research programs. This is the case of the teams working on parasites. Often neglected, this scientific discipline is particularly well represented at the CIIL. Indeed, four teams develop research programs on parasites, and the models studied include schistosoma, plasmodium, toxoplasma, cryptosporidium, blastocystis et leishmania. The diversity of these models is an asset for the CIIL and for research in parasitology in general. These programs developed by our teams include basic research on parasites and their interaction with their host, innovative research in microfluidics, development of novel anti-parasitic drugs and field research on parasites. Several remarkable papers have recently been published by CIIL teams in this field, highlighting the quality of our research activities on parasites.

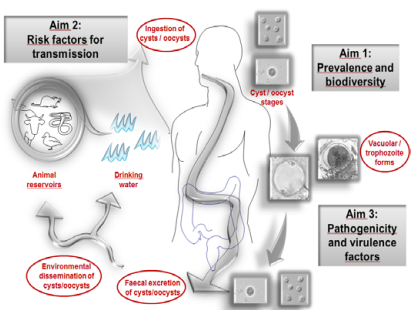
Jean Dubuisson

Ecology and Physiopathology of Intestinal Protozoa (ECOPHIP) : An integrative research approach from the cell to the population

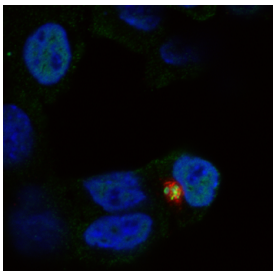
Enteric parasites including protozoa affect hundreds of millions of people every year and remain one of the main causes of morbidity, malnutrition and mortality worldwide, especially in children. Directly related to the faecal peril, the transmission of these parasites is promoted by poor sanitary and hygienic conditions and by a lack of sanitation of drinking water, hence the more significant impact of these parasites in developing countries. Among these microorganisms, two of them, Blastocystis and Cryptosporidium, are the subject of several research projects conducted by the ECOPHIP team led by Eric Viscogliosi (Director of Research at CNRS). These two protozoan parasites represent major socio-economic and public health problems and are responsible for gastrointestinal infections which, in the case of Cryptosporidium, can be serious and even fatal in children and immunocompromised patients. However, these protozoa are still neglected by health authorities and few or no treatments are effective against these parasites. The work of ECOPHIP, which has the particularity of combining «field studies» and «laboratory research», aims at clarifying the molecular epidemiology of these parasites, their circulation in human and animal populations as well as in the environment (risk factors of transmission) and their physiopathology while identifying the proteins and mechanisms involved in the pathogenesis of these parasites. The objective of ECOPHIP is to propose prevention and control measures to reduce the burden of these parasites.

ECOPHIP has international recognition in the field of parasitology and health ecology and has contributed to a better understanding of the epidemiology, transmission and pathogenesis of Blastocystis and Cryptosporidium through a very large network of regional, national and international collaborations. For example, recent or ongoing large-scale surveys conducted in Africa (Senegal, Guinea), the Middle East (Lebanon, Syrian refugees), Asia (Vietnam, Funding: French Embassy in Vietnam) or Europe (France) have highlighted the important circulation of Blastocystis in the human population and have identified the main animal reservoirs of zoonotic transmission. Its pathogenicity and invasive potential were confirmed through clinical case studies and the development of proteomic and genomic approaches have led to the outline of a scheme of the mechanisms involved in its virulence. ECOPHIP is also interested in the antioxidant enzymatic machinery of Blastocystis as a virulence factor and potential therapeutic target. Furthermore, this team has demonstrated the positive impact of this parasite on the human intestinal microbiota. The study of the role of this parasite on human and animal health is currently supported by the Hauts-de-France Region (Funding: STIMulE exploratory project) and by SATT Nord (co-maturation program).

ECOPHIP was also the first team to demonstrate the involvement of Cryptosporidium in the development of digestive cancers in experimental models in vivo and ex vivo. This is also strongly suggested in humans through several epidemiological studies and as a result, the infection of human colonic explants by Cryptosporidium is underway (Funding: Groupement des Hôpitaux de l'Institut Catholique de Lille). These results have led ECOPHIP to focus its research on the identification of the molecular signature of digestive cancer induced by this parasite.



In particular, the role of Cryptosporidium in cancer epigenetics is explored (Funding: Plan Cancer) as well as the signaling pathways potentially involved in the induction of neoplasia (Funding: Bonus H CHU of Lille Coll. D Hot, UMS 2014/US 41) through different approaches such as transcriptomics and comparative genomics. In parallel, different inhibitors potentially targeting Cryptosporidium are currently being tested (Funding: CIIL inter-team program Coll. M Gissot, CIIL).



Cryptosporidium (in red and green) infecting an intestinal cell (nucleus in blue)

Finally, ECOPHIP, through its expertise activities, collaborates on different projects dealing with the molecular identification of trichomonads of veterinary interest (Coll. W Landman, GD Health, The Netherlands) and on fish parasites focusing on their economic impact and their risk in human health (Funding: Région Hauts-de-France).

Team ECOPHIP:
Eric Viscogliosi

Do concomitant multi-species protozoan infections promote the establishment of more effective immunity?

Among the prevalent infectious diseases, multiple concurrent protozoan infections exceed one sixth of the global population. Despite their widespread and great morbidity protozoan multi-infections remain poorly studied. Existing epidemiological data suggest a greater incidence of negative impacts on the pathogen-specific host immune responses toward heterologous pathogens during co-infection resulting in a wide variability in the clinical outcome of the infection, ranging from subclinical (no symptoms or signs) through clinical illness to death. However, the underlying mechanisms remain poorly understood. This scenario could be the case for *Plasmodium falciparum* or *vivax* transmitting malaria and *Toxoplasma gondii* causing Amazonian toxoplasmosis and *Leishmania guyanensis* leading to cutaneous leishmaniosis, three highly prevalent diseases in the Amazonian border of French Guiana.

The "Tropical Biomes and Immunophysiopathology" team directed by Magalie Demar, PU-PH, University of Guyana and Sylviane Pied, DR CNRS, located in Lille and Cayenne, is focused on this issue. The specific objectives of the project aim at :

1) deciphering the complex nature of the immune mechanisms induced during these parasitic (co) infections;

2) define their roles in protection or pathology and

3) assess the impact of environmental factors including deforestation and the host's multi-biome on modulations of the parasitic genome, the infectious process and immune responses. The strategy used is an integrative approach which, thanks to the multidisciplinary expertise of the members of the team, combines clinical studies with parasitology, integrative immunology, molecular epidemiology. As part of the MALTOX project (LABEX CEBA funding), a study is underway in cohorts of patients who are mono or co-infected with *P. falciparum* and / or *T. gondii* showing different disease phenotypes (asymptomatic, uncomplicated, severe), recruited from Camopi, Amazonian region of French Guiana. Parasite genotyping will be done to study the impact of synergistic and / or competitive interactions occurring between *T. gondii* and *P. falciparum* within the host and to evaluate their influence on transmission. The profiling of the repertoires of parasites specific antibodies and autoantibodies, identification of cytokine and chemokine clusters and phenotyping of the T lymphocyte subpopulations are carried out in parallel in order to assess the impact of coinfection on the adaptive immune response. Multivariate statistical approaches and modelling will be implemented on the integrated database for the identification of immunological signatures associating parasite-specific antibodies, autoantibodies, cytokine clusters and clinical phenotypes. Deciphering and analyzing these interactions in a holistic way during co-infections should allow the identification of biomarkers that could be therapeutic targets and / or be used for diagnosis and / or prognosis for improving patient care. In addition, this project will contribute to the establishment of sample banks and biological, immunological and epidemiological data carried out in an Amerindian population exposed to malaria and Amazonian toxoplasmosis.

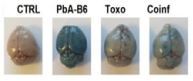


Figure A

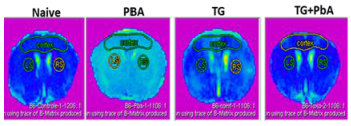
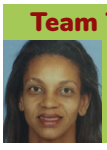


Figure B

In experimental model, coinfection with T. gondi and P.berghei ANKA inhibits cerebral malaria in susceptible mice by preventing blood–brain barrier (BBB) disruption (figure A), brain edema (figure B) and inflammation associated with the neuropathology. Figure A: Evans blue permeability assay for BBB integrity; Figure B: Representative apparent diffusion coefficients (ADC) maps from control (naivel), P. berghei ANKA-infected (PbA) developing cerebral malaria, T. gondi infected (TG) and co-infected mice.

Team Tropical Biomes and Immuno-Physiopathology

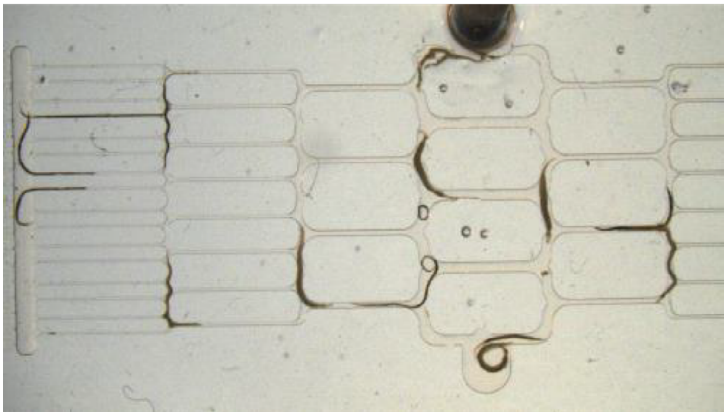


Magalie Demar

Sylviane Pied

Microfluidics : A new playground for the schistosome

Schistosomiasis is a parasitic model that is difficult to study due to the absence of transgenic strains and of systems allowing the cultivation of worms outside their mammalian host. Classical in vitro studies in a Petri dish do not allow the long-term survival of pairs of worms, which rapidly lose their basic biological functions such as mobility and pairing. In collaboration with Vincent Senez from LIMMS (Laboratory for Integrated Micro Mechatronic Systems, CNRS / Univ. Tokyo), we have designed a microfluidic device that permanently lodges pairs of adult worms. Through a design mimicking the mesenteric venous system, we have shown the influence of the composition and physical characteristics of the culture medium on the mobility, pairing and long-term survival of the worms. This system makes it possible to assess the early effects of antiparasitic molecules, which are usually not detected in conventional in vitro systems. It is therefore a new preclinical assessment tool.



Microfluidic system developed by Vincent Girod during his thesis. We can distinguish worms in the canal system.

This work carried out by Vincent Girod as part of his doctorate was awarded the "Oustanding Student Paper award" at the 34th MEMS international meeting, a key event in the field of micro-nanotechnologies.

Promising results in the repositioning of a molecule for the treatment of schistosomiasis

A consortium of Lille teams including the CBF team and the Brain Biology & Chemistry team (Pr P Melnyk, UMR-S-1172) demonstrated that a molecule, currently in clinical development in humans (phase II) for a non-parasitic disease, is active in vitro on different stages of the Schistosoma mansoni parasite, in particular the larval stage corresponding to the entry of the parasite into the skin and the adult stage. This discovery is significant because Praziquantel, the only molecule currently used for the mass treatment of infected populations, is not active on the larval stage. This molecule therefore has a potential interest for the prophylactic and curative treatment of schistosomiasis. In vivo tests in mice will be carried out from the end of February. I-site funding enabled to recruit Julien Lancelot for this project.

Team Chemical Biology of Flatworms

Oleg Melnyk

A promising pathway for anti-malarial and anti-toxoplasmosis drug discovery

Plasmodium sp. and *Toxoplasma gondii* are protozoan pathogens with clinical significance. They cause malaria and toxoplasmosis and share a common evolutionary history (apicomplexan parasites) and susceptibility to common treatments. These parasites possess a substantial repertoire of conserved enzymes including those involved in chromatin remodeling and histone modifications. These enzymes have been described to play vital roles in epigenetic mechanisms for spatio-temporal regulations of gene expression that are crucial for parasite growth and differentiation. For instance, in Plasmodium falciparum, histone deacetylases (HDAC), histone acetyltransferases (HAT) and methyltransferases (HMT) play key roles in cell cycle progression, and particularly in the control of variable surface gene expression involved in immune evasion by the parasite and therefore are valid therapeutic targets. We started testing this hypothesis and reported the development of novel HDAC inhibitors against different parasites including Plasmodium falciparum. Currently, we exploit the basic principles and major results to target not only P. falciparum but also Toxoplasma gondii and develop the inhibitors into potent, selective and in vivo active drug candidates. This will lead to the generation of selective epigenetic antiparasitic compounds with a high potential to delay or circumvent the development of resistance and the ability to provide additional range of treatments with effective combination options. In parallel, we define the mode of action of the most promising compounds that will give rise to new approaches for examining and manipulating biological processes and will enhance the understanding of how these enzymes work. This could be achieved through the chemistry/biology cross fertilization and the generated knowledge will likely continue to improve the quality of treatments against apicomplexans. This research is supported by the CIIL project and the Région Hauts-de-France (Start Airr project) and the SATT Nord is currently investigating the (pre)maturation of this work.

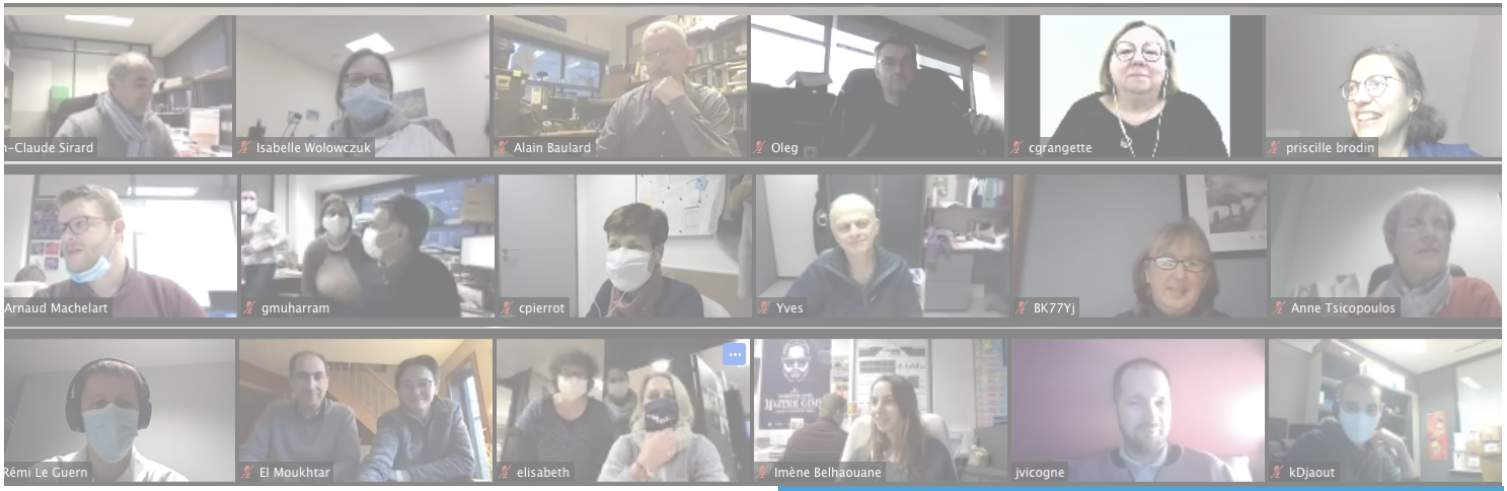
Team Biology of Apicomplexan Parasites

Jamal Khalife

Our thanks to:

Sylviane PIED
Eric VISCOGLIOSI
Oleg MELNYK
Jamal KHALIFE

for their contributions to this issue of the newsletter



Visit of Antoine Arnault (LVMH group)

Antoine Arnault, communication manager of the LVMH group

On February 23th, Antoine Arnault, communication manager of the LVMH group, visited the CIIL teams working on the search for SARS-CoV-2 antivirals. This visit follows the financial support from LVMH for the implementation of a clinical trial in humans, based on the repurposing of a drug whose antiviral activity has been identified by CIIL teams as part of the COVID-19 Task Force set up at the Institut Pasteur de Lille.

Mustart

Multiparametric Strategies against Antibiotic Resistance in Tuberculosis

New recognition for the CIIL teams (CGIM, Priscille BRODIN / CBA, Ruben HARTKOORN / RMB, Nathalie MIELCAREK) who have just obtained funding under the Investments for the Future 2021 program for the project MUSTART, under the scientific responsibility of Alain BAULARD (RMB team). This project involves nine partner (CIIL - Institut Pasteur de Lille, IPBS Toulouse, Sorbonne University Paris, U1177 Lille, IP Paris, TBI Toulouse, LMGM Toulouse, CEA Saclay, CIRI-HCL Lyon) for a total grant of 2.4 M €.

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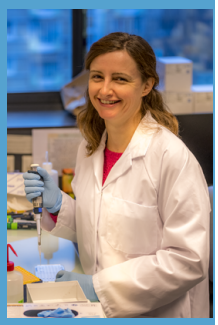
In brief ...

The Hauts-de-France Region honored women scientists



Sandrine BELOUZARD

The International Day of Women and Girls in Science took place on February 11. This initiative aims to promote women through their training and their scientific and technical skills. On this occasion, Sandrine Belouzard was honored by the Hauts-de-France Region. Since the onset of the COVID-19 epidemic, Sandrine has devoted all of her energy to the study of SARS-COV-2 as well as to the identification and characterization of antivirals to fight this new viral infection. After a doctoral thesis in cell biology at the University of Lille and a post-doctorate on SARS-CoV-1 at Cornell University in the United States, she was recruited in 2010 as a CNRS researcher within the Molecular and Cellular Virology team at the CIIL. On her return from the United States, Sandrine developed projects on the hepatitis C virus. She reoriented her research on coronaviruses when the MERS epidemic appeared in 2013. Today, the CIIL is proud to count on young women, like Sandrine, who devote all their energy to scientific research.

Parity and intersectionality : At the CIIL, women scientists are on the spotlight

Interview on parity with Women in Science from CIIL

Welcome to Charlotte MESTDAGH who recently joined the CIIL Management Pole.

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