Center for Infection & Immunity of Lille

CIIL

NEWSLETTER

#4 | July 2021

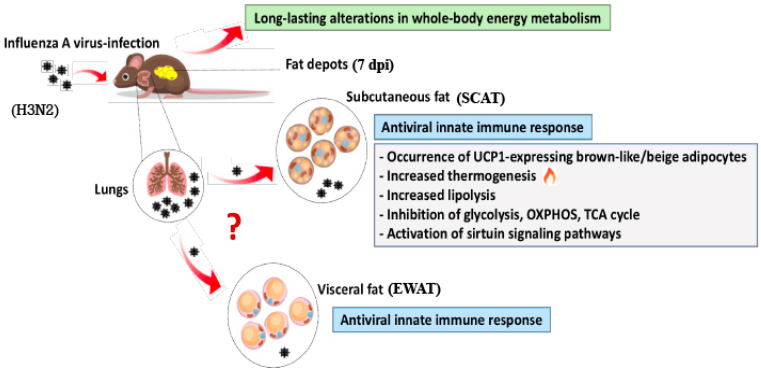
One of the major research themes of the CIIL is dedicated to respiratory diseases. In addition to the study of infectious agents, the CIIL investigates immune responses against these pathogens. This is the case of the team of François Trottein which studies the immune response in the context of flu and COVID-19. The team of Anne Tsicopoulos and Cécile Chenivesse studies immune dysfunctions in the context of asthma and it develops novel therapeutic approaches to treat severe form of this disease. The team of Philippe Gosset develops a program on chronic obstructive pulmonary disease (COPD) and asthma by studying the impact of opportunistic infections on these diseases. In the context of respiratory diseases, our center has recently teamed up with other research groups from Amiens, Caen and Rouen in the context of a Fédération Hospitalo-Universitaire (FHU) coordinated by Claire Andréjak from the University Hospital of Amiens. The objective of this program is to improve respiratory health. Finally, our center is also integrated in the federative structure of research on Infection and Inflammation (SF2i) in the context of the structuration of the axis on infection, inflammation and immunity at the University of Lille. The SF2i, directed by Benoît Foligné, has the objective of promoting collaborations between the units INFINITY and CIIL.

Jean Dubuisson

Respiratory infections in the age of time

Viral respiratory tract infections represent a major burden for the society. Ageing and co-morbidities including chronic metabolic disorders (obesity, diabetes) are the main risk factors of morbi-mortality associated with respiratory infections. The objectives of the team « Influenza, Immunity and Metabolism » (I2M, head : François TROTTEIN) are to better understand the pathophysiological consequences of viral respiratory infections. We focus on influenza A virus and, more recently, on SARS-CoV-2, the aetiologic agent of COVID-19.

We aim to study early immunological events developing in the lung tissue, and also outside the lungs. Our objectives are (i) to identify host defense mechanisms against these infections, (ii) to define ageing and co-morbidity factors associated with the severity of the disease, and (iii) to develop novel anti-infectious therapies. To this end, our research team develops relevant experimental models. We integrate the impact of ageing and co-morbidities (dyslipidemia) in the host response to infection. This research recently led us to identify the gut-lung axis, and particularly the gut microbiota, as an important player of the host response. For instance, we showed that gut dysbiosis due to influenza is in part responsible for secondary enteric and pulmonary bacterial infections (Cell Rep. 2020, Mucosal Immunol. 2021, Infect. Immun. 2021). This may lead to the discovery of new therapeutic options to treat bacterial superinfection, a major cause of death during severe viral respiratory infection (ANR ACROBAT, Région Hauts-de-France). Indeed, we showed that treatment with short chain fatty acids (SCFAs) major metabolic products of the gut microbiota, reduces the severity and secondary effects of flu. Pharmacological approaches and the use of probiotics and prebiotics are being developed. For instance, we selected bacterial strains according to their anti-inflammatory potential or their capacity to produce SCFAs in the presence of fibers (Corinne GRANGETTE). This strategy might have positive application during COVID-19.



Influenza A virus infection leads to changes in systemic glucose metabolism that last up to infection resolution (green frame). Unexpectedly, viral RNA is detected in adipose tissues (both the subcutaneous and visceral depots), and this associated with the development of antiviral innate immunity (blue frames). However, metabolic reprogramming – characterized by the occurrence of brown-like thermogenic adipocytes expressing the mitochondrial uncoupling protein 1 (UCP1)– is observed only in the subcutaneous fat depot (orange frame). From: BARTHELEMY J & WOLOWCZUK I, Let's chew the fat about influenza A virus and adipose tissue, Behind the paper Nature Microbiology Community

Obesity, which corresponds to an excess of adipose tissue, is a critical risk factor linked to severe viral respiratory infections, thus questioning about the precise role of the adipose tissue in the pathophysiology of the disease. Our recent work demonstrated that, indeed, the adipose tissue is solicited during influenza (Isabelle WOLOWCZUK). The inflammatory and metabolic activities of the adipose tissue are altered during infection leading to long-lasting

change of glucose metabolism in the infected host (Commun. Biol. 2020). Surprisingly, we showed that influenza infection also associates with the browing of the subcutaneous adipose tissue depot (Figure). We currently try to identify mechanisms leading to browing and its consequences on disease outcomes (CPER CTRL 19 FEDER DESTRESS-Flu). Altogether, we expect that a better understandingof the gut/lung/adipose tissue axis will be instrumental in conceiving novel treatment options for patients.

We are also studying the impact of ageing on respiratory infections. We are interested in cellular senescence and viral respiratory infections (ANR INFLUENZAGEING et SENOCOVID). Our data suggested a link between the alteration of the circadian rythm and the defects of pulmonary defense mechanisms (collaboration with Inserm U1011). Our hypothesis is that the uncontrolled expression of certain clock genes perturbates the efficacy of the innate immune response, thus favoring infection (CPER CTRL 19 FEDER et ANR DREAM).

Team :
Influenza, Immunity & Metabolism
François TROTTEIN

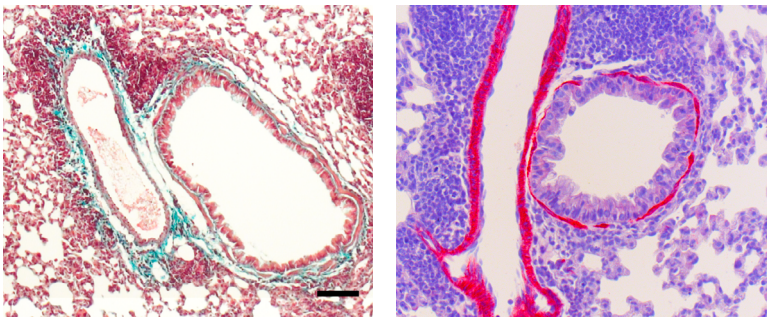
Towards new therapeutic approaches in severe asthma

Chronic respiratory diseases are a major cause of mortality and morbidity. The respiratory tree is located at the interface between environment and host, and as such plays a critical role in the development of the host immune response that can be either beneficial or deleterious. This immune response is one pathway to target, to modify the natural evolution of respiratory diseases. Among them, severe asthma is a major challenge because of the diversity of its clinical phenotypes and biological mechanisms. Severe asthma concerns 5 to 10% of total asthmatics (more than 300 millions people in the world), but generates almost the totality of health costs devoted to this disease. Severe asthma is divided schematically in T2 asthma (with an eosinophilic profile) and non T2 asthma (with a neutrophilic or mixed profiles). These patients have frequent exacerbations that can be triggered by infections, allergen exposure or pollutants. In this context, the pulmonary immunity team headed by Anne Tsicopoulos (Director of Research Inserm) and Cécile Chenivesse (PU-PH), decipher the immunobiological mechanisms involved in asthma, to propose novel therapeutic targets, by using original animal models of asthma, and cohorts of asthma patients.

We have set up a T2 eosinophilic animal model induced by house dust mite (HDM), an allergen involved in 50% of allergic asthma. This model induces a Th2 response and allowed us to evaluate the role of the innate receptor NOD1 (collaboration M Chamaillard, Lille, and Ivo Boneca, Paris) in the aggravation of HDM- induced asthma. Asthma severity was found to depend upon some bacteria recognized by NOD1, a receptor that has been associated with asthma. We evaluated if host and/or HDM microbiota may influence the severity of asthma through the NOD1 receptor. It was shown that inhibition of NOD1 or of its signalling pathway was able to decrease the parameters of HDM-induced asthma, independently of host microbiota. In contrast, peptidoglycans derived from HDM microbiota and belonging to the Bartonellaceae family, activate NOD1 signalling pathway in epithelial cells. Accordingly, when HDM extracts were depleted in peptidoglycans, they showed diminished ability to induce asthma (Ait Yahia S et al, JACI 2021). These results suggest that sensing by NOD1 of some bacteria associated to HDM aggravates the severity of asthma in vivo, and that inhibiting this pathway may be a therapeutic approach for asthma. This approach is being currently evaluated in our models and in cohorts of asthmatic patients. (ANR Innovasthma).

We also set up a non-T2 neutrophilic model induced by dog allergen. This model induces a mixed Th2/Th17 profile, as well a strong bronchial remodelling, which contributes to airways obstruction in humans. These parameters are correlated with the induction of IL-22, and the inhibition of a pathway leading to its synthesis, leads to decreased neutrophilia, bronchial remodelling and airway resistances. (Bouté et al, Allergy, 2021). As there is currently no biotherapy targeting non T2 asthma, these results are very promising and proof of concepts studies are planned (START AIRR, Hauts de France) to evaluate this target in genetically modified mice as well as in asthma patients.

These results have highlighted different pathways that may provide the biotherapies of the future in severe asthma.



Bronchial remodelling in a mixed T2/non T2 model: A) Collagen fibers are stained in green (Masson's Trichrome), and B) Bronchial smooth muscle cells in red are hypertrophic (immunohistochemistry with an anti-smooth muscle actin antibody). Scale : 100 µm.

Team :
Pulmonary Immunity
Anne Tsicopoulos

Bronchial diseases and opportunistic infections

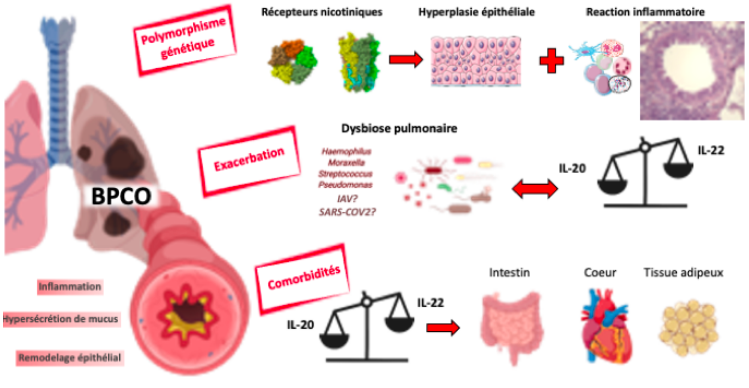
Most of the chronic respiratory diseases, chronic obstructive pulmonary disease (COPD), asthma and cystic fibrosis (CF, the most frequent genetic disease) are associated with opportunistic bacterial, viral and/or fungal infections. These infections favor the development of the disease but also markedly amplify lung inflammation, resulting in tissue damage and disease progression. These bacterial as well as viral infections are also very frequent in newborn leading to bronchopathies which can progress towards severe forms of asthma or juvenile forms of COPD. This process is also associated with the development of comorbidities including cardiovascular, metabolic and intestinal disorders. Many environmental factors such as airway pollutants, nutrition, therapeutics including glucocorticoids and antibiotics might alter the homeostasis between microbiota and the mucosal immune response. Genetic factors can also alter the response to these environmental factors as revealed as the association between polymorphisms in nicotinic receptors (nAChR) and lung dysfunction.

Our overall aim is to understand how environmental factors can facilitate infections in patients suffering from chronic pulmonary diseases and how they can accelerate the progression of these diseases. Several projects have recently emerged focusing on opportunistic infections in the context of young children asthma, the implication of nAChR during COPD and their exacerbations, as well as the comorbidities associated with COPD and malnutrition. These projects rely on clinical studies associated with mechanistic approaches using pertinent and original cellular and experimental models.

The roots of severe asthma in children and of COPD in young adult.

Some factors among environmental factors, nutrition, antibiotherapy and respiratory infections are able to favor development of chronic lung diseases in newborns. All these factors have been associated with COPD in young adults whereas respiratory viral infections are involved in the development of asthma in prescholar children and their exacerbations. However, the mechanism responsible for these diseases are not well identified and medicine doctors needs predictive and prognosis markers associated with the different profiles of disease natural history.

With the immunoallergic pediatric department of the Lille CHU, we have included 2 cohorts of children asthmatics among scholar (Virasthma) and prescholar (Virasthma2) children. The analysis of the clinical, immunological and microbiologic profiles had allowed to precise the environmental factors and the characteristics of inflammatory response associated with the more severe forms of the disease although we have confirmed the essential role of viral infections (particularly rhinoviruses). Moreover, we have identified in scholar asthmatics, the factors predicting their progression at 1 year of followup. The followup of prescholar asthmatic cohort (until adult age) is presently ongoing in order to identify the markers predicting the respiratory function evolution in adults. In paralle, a murine experimental approach has been initiated in oder to identify the specificities of the airway epithelial cell response during neonatal period and the consequences of atopy on this response. We have shown that neotal-derived epithelial immaturity is associated with altered expression of pathogen recognition receptors (PRR) and of signaling molecules associated with these receptors. These data allowed to imagine therapeutic approaches able to restore an efficient anti-viral response in airway epithelium and to prevent progression of chronic diseases.



Physiopathologic contribution of nAChR during COPD.

Although smoking is responsible for 80% of COPD, only 20-30% smokers develop this disease independently of their consumption suggesting the role genetic factors. Among human haplotypes including single nucleotide polymorphisms (SNP) associated with smoking and COPD, the variant present on CHRNA5/A3/B4 genes located on chromosome 15q24/25 are among the most frequent, particularly the α5SNP rs16969968 (α5 subunit of nAChR). The nAChR are pentameric receptors constituting ionic channels present on neurons and numerous lung cells and binding nicotine, a major effective molecule of cigarette smoke. In collaboration with the University of Reims and the Pasteur institute of Paris, we have initiated a program aiming to analyzed the role of this genetic polymorphisms in the development of COPD and during the exacerbation. We have preliminary data showing that a polymorphism of alpha5 subunit of nAChR induced important airway epithelium remodeling and lung inflammation that potentially mimick a COPD disease (Routhier et al, submitted). Moreover, exposure to an oxidative stress strongly amplify this process and promote alteration of lung function. Our present objective is now to demonstrate that α5SNP directly contribute to COPD pathology, sensitizing the lung to cigarette smoke, and altering lung defence mechanisms (project PINAChRAECOPD, IRESP).

The aim of this project is 1° to show that α5SNP is implicated in the development and the progression of COPD (by favoring bacteria-induced exacerbation) , 2) to characterize in COPD patients the phenotype and the endotype associated with this polymorphism and 3) to propose individual therapeutic tools targeting the signaling of nAChR including α5SNP. We have presently performed the first experiments with α5SNP mice.

In parallel, recent data obtained during the COVID19 pandemia showed a complex interaction between smoking and infection by SARS-CoV2, namely implicating nAChR.Based on these preliminary data, we have hypothesized that nAChR might participate in the control of the SARS-Cov2 infections and potentially, in virus-induced exacerbations of COPD. To show this, the project NirCOVID (ANR) aims to demonstrate the role of nAChR in the virus replication, the anti-viral and inflammatory responses against the SARS-CoV2. These data might lead to the identification of new therapeutic tools for viral infections.

Team : OpInfIELD
Philippe GOSSET

Les collaborations scientifiques « hors CIIL »

FHU

The university hospital federation (FHU) is dedicated to respond to major health problems in our region and at the same time, to promote the regional network of transdisciplinary research. This label FHU aims to sustain the common will and the ambition of hospital departments and research laboratories for medical research, formation and improvement of patient care with a quick benefit for them. In response to the last grant call, the CIIL has been involved in the project initiated by the Pr Claire Andrejak (CHU Amiens), called RESPIRE « Pathogènes, Environement et Hôte : an integrative approach in respiratory medicine ». This project perfectly fits with the objective of CIIL.

The objective of RESPIRE results from the major impact in term of frequency and severity for chronic respiratory inflammatory (bronchiolitis, COPD, asthma, cystic fibrosis) and infectious diseases. The consequences of these diseases are multiple including socio-economic and health costs as well as alteration of life quality. Compared with the national means, these diseases are implicated in a higher level of morbidiyty and mortality in children and adults of the Hauts de France. Recent studies showed that the emergence and the progression of these lung diseases is controlled by environmental factors (microbes, toxics and chemical compounds), the microbiota and host response. The COVID19 confirms this.

The major aims of RESPIRE are to improve respiratory health by integrative approach taking into account the host characteristics since childhood, environment, pathogens and their interactions in the lung. For this, the federation aspires to evaluate the impact of environment (particularly, air pollution, toxic agents and antimicrobial molecules) on inflammation, the microbiota and the host immune response in healthy subjects and patients with bronchial diseases (asthma, COPD, cystic fibrosis, bronchiolitis) and to define the molecular and functional characteristics of respiratory pathogens in the Hauts de France and Normandie. Our final goal is to identify and to evaluate new therapeutic drugs and to optimize the use of existing medicine drugs.

This FHU includes the four university hospital of Amiens, Caen, Lille and Rouen, with 6 universities (Picardie Jules Verne, Rouen, Caen, Lille, Artois and Technologic University of Compiegne) as well as the Pasteur institute of Lille with the CIIL. This consortium constitutes a unique opportunity to develop ambitious approaches dedicated to resolve clinic problems and at the same time by the valorisation of fundamental research. For this, our aim is to amplify or to create new collaborations between the different partners in order to address the major needs for personnalized medicine and of technologic evolutions.

Pr C. Andréjak will come to present the federation RESPIRE during the outdoor day of the CIIL the next 28th september. .

SF2I : A local structuring of the Infection-Inflammation axis

The federative research structure on Infection & Inflammation (SF2i) is one of the 11 structures supported by the University of Lille and is the continuation of the structure on Infectious, Inflammatory and Immune Diseases (SF3i, 2015-2019). The structure SF2i headed by B. Foligné and J-C. Sirard aims at promoting scientific collaborations between the research units CIIL-UMR9017-U1019 and INFINITE-U1286 that gather 300 people. The executive committee includes the research unit Directors and Deputy Directors as well as researchers, clinicians and engineers from the infectious axis (Magali Chabé, Guillaume Lefèvre, François Trottein), and inflammatory axis (Frédéric Gottrand, Bertrand Méresse, Nicolas Renault, Anne Tsicopoulos). Ms. Bernadette Leu provides with enthusiasm the general secretariat and the financial management of SF2i.

The objectives of SF2i are broken down into four strategic axes in the fields of infection and inflammation:

- Promote collaborations between CIIL and INFINITE
- Stimulate scientific discussion and dissemination of knowledge and know-how
- Promote international visibility and local attractiveness for young researchers and new teams
- Participate in academic education, learning resources and specific training.

The duties of SF2i include the organization of seminars and international symposia to provide up to date concept and knowledge in infection and inflammation, stimulate technological advances and build up innovative projects between the two units (calls for SF2i projects). In spring 2021, a first call for inter-units innovative project was launched; the INFINITE scientific committee performed the evaluation and selected two projects granted with 15 K€ each for 2 years. The grantees are: Laurye Van Maele / Julie Démaret-Guillaume Lefèvre, for an original project on vaccine strategy against S. pneunomiae; Laurence Coquerel / Anne Goffard - Jean Lesage, for a project to study the inactivation of viruses (Hepatitis E and SARS-CoV-2) by high pressure methods in a dairy matrix.

Finally, the discussions during the meetings of SF2i served as a leverage for the CPER RESISTOMICS which will be a structuring project with significant financial and human resources dedicated to infection and inflammation.

B. Foligné & J-C. Sirard

Eco-campus

The impact of research activities on the environment has become a priority for our institutions, particularly in the context of the UN's Sustainable Development Goals. The implementation of a «zero-carbon» and «sustainable development» policy within the units will be part of the evaluation criteria of the HCERES. In this context, the CIIL has recently formed a committee whose members are Cécile-Marie Aliouat, Alain Baulard, Mathieu Gissot and Frank Lafont. For a more global action, this group has joined the Eco-Campus initiative of the Pasteur Institute of Lille and participates in the meetings organized by the University contact points. Our committee has already led a phase of reflection on actions to be implemented with the other actors of the campus, such as the promotion of cycling use or the cleaning day of July 1st. Other projects are in preparation, so don't hesitate to join us to share your ideas on the ecological transition.

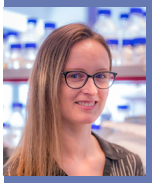
News from the scientific animation committee of the CIIL

Seminars in 2020-2021 : As you all know, most of our seminars were canceled because of health crisis. However, thanks to visioconference, we restarted our weekly meetings early March 2021. We chose to focus on student and post-doc research projects that have been performed within the CIIL. 14 of them have been so far presented. « Work in progress » meetings allowed interactive discussion, training and communication. Active participation has been recorded : an average of 48 connections per seminar were counted, highlighting our interest in the science conducted within the CIIL. The scientific animation team strongly hopes to welcome you again in the IBL auditorium for internal as well as external seminars starting from September 10th, 2021!

CIIL offsite meeting 2021 : **Save the date** ! After having postponed the date twice, the offsite day of the CIIL will be held on Tuesday, **September 28, 2021**. This event will take place at Lilliad on the campus of the University of Lille in Villeneuve d'Ascq. Such an event, intended to promote interactions between all CIIL members, will be an opportunity to discover the latest outstanding results from the CIIL teams, including those that have obtained intra-CIIL funding and those involved in the Covid Task Force. Surprises will also await the participants!

Director of publication:	Jean DUBUISSON
Editorial coordination:	Isabelle ASLANI
Design:	So phana UNG

En bref ...



Congratulations to Laurye Van Maele who has just been recruited as a CRCN at Inserm in the Bacteria, Antibiotics and Immunity team of Dr. Jean-Claude Sirard. Her project aims at developing a targeted immunotherapy to fight against antibiotic-resistant bacterial pneumonia.

The CIIL will soon welcome Alexandre Grassart, winner of the ATIP/AVENIR 2020 competition. His objective is to develop a new research team within the CIIL around a research project on the importance of the microbiota and mechanical forces during the passage of the intestinal epithelial barrier following a *Shigella* infection.

Fatima HAMMADI, currently manager at the CRIStAL laboratory, will join the Administrative team on October 1st.

Many thanks to our contributors :

- François TROTTEIN
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CIIL - CNRS UMR9017 - INSERM U1019
1, rue du Professeur Calmette - 59000 Lille
https://www.ciil.fr