AAPG ANR 2018

Mise en évidence des particularités environnementales dans des zones épidémiques de Maladie de Crohn
"Highlighting EnviROnmental features in epidemic areas of Crohn's disease" (HEROIC)

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B11 : Les recherches à mener en appui de grands enjeux transverses
Axe n°6: Contaminants, écosystèmes, et santé **Requested Grant: 620 880€**

1. Contexte, positionnement et objectif(s) de la proposition

Crohn's Disease (CD) is a chronic disease with unknown cause, evolving in a relapsing-remitting pattern, characterized by an uncontrolled over-activation of the intestinal immune system. It is a **multifactorial disease** implicating genetic and predominately environmental risk factors. Urbanization of societies, diet change, hygiene status, change in farming practice, pollution and microbial exposures have been implicated as potential environmental risk factors for CD. **Different changes in environmental factors might occur in various geographical areas** and populations; consequently, it is important to consider both the heterogeneity and the common history of risk factors in "epidemic CD areas". Using the **world's largest population-based study on CD incidence** (EPIMAD Registry), we identified in Northern France 5 clusters of very high incidence of CD, considered as "epidemic areas of CD", including a total of 2824 CD patients. Epimad Registry **only reports data at the time of CD diagnosis** and currently includes near of 15000 CD incident cases since 1988. The excess risk presents in these areas could be due to some variations in life style, economic, social and cultural context, as linked to exposure of pollutants. Therefore, **the analysis of these clusters represents a great opportunity to identify new environmental etiological factors of CD.**

Relevance in regards to ANR requests.

Our project meets all the needs of the **challenge "life, health and well-being**": this challenge is interested in **changes in lifestyle and social behavior that may favor the development of diseases, requiring measures to take into account at the national level.** Our purpose is to evaluate the link between these changes and the development of CD. Our proposal is based on a **transversal multidisciplinary approach** involving clinicians, epidemiologists, environmentalists, historians, geography and toxicologist. The final objective of our proposal is **to optimize health policy**. Our project fits the **axis 10**, because it is a **translational project** exploring the **pathophysiology** of CD and looking for various **extrinsic factors** such as **contaminants** but also **social and behavioral factors**. As recommended, our proposal **addresses all biological and social determinants** by its exploration of incidence levels of CD, clinical phenotype of patients and by the global territorial and ecological diagnosis of the clusters.

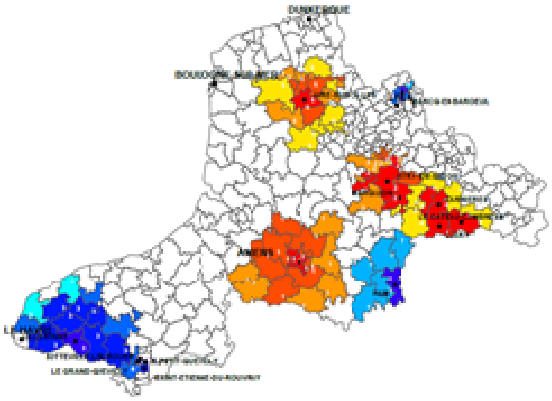

Figure: Space clusters including all incident CD cases from 1990 to 2014 (n=10420). Epidemic areas (epicenter in red) are represented in warm colors and low CD incidence clusters in blue. The white part corresponds to "the mean CD incidence."

In these epidemic areas of CD, our objectives and methodologies are divided into 3 parts:

Part 1) To identify **particular phenotypic features of CD outcome** among all the patients living in these clusters (n=2824) in terms of disabling, associated co morbidities as cancer, particular phenotype association or particular clinical outcome.

Part 2) To perform a deepened descriptive and exhaustive study of these CD epidemic areas. All existing data on soil, water and atmospheric pollution in the study area will be included in a unique database allowing the **production of geospatial studies and ecological correlations**. **To characterize atmospheric pollution** in epidemic and non-epidemic CD areas, we will collect data from automatic network of atmospheric pollution survey and emissions data (ATMO) from our own environmental biomonitoring data, notably epiphytics lichens.

2-a) Using sociological (including affluence) and historical investigations, relating to lifestyle and relationships in the microenvironment of CD patients.

2-b) Using mapping and identification of the atmospheric pollutants;

2-c) Based on all the data collected in the parts 1 and 2-a and 2-b, **ecologic correlation studies** will be performed in order to highlight potential relationships between environmental features of the epidemic areas and either the incidence levels, or the phenotypic features of CD.

Part 3 3-a) To perform an epidemiological case-control study on diet, atmospheric, pollutants and water environmental risk factors (questionnaires and biological samples) between CD patients living in the epicenter of clusters with high incidence (n=300) and 2 controls by case issued from epidemic and normal CD incidence area (n=2*300).

3-b) To implement a biobanking of 300 patients and 600 controls including sera, DNA, stools, saliva, urine and hair.

3-c) To implement a biobanking of lichens and tap water in the CD epidemic areas. As many pollutants are not monitored by associations monitoring air quality, we will complete the database by **measuring bioaccumulation of metals and organic compounds in epiphytic lichens** in the most polluted cluster.

2. Organization of the project and justification of the requesting grant

Consortium organization and description

Partner 1: The project will be coordinated by **Corinne Gower-Rousseau**. She is gastroenterologist and epidemiologist in Lille University Hospital and the **Scientific Head of Epimad Registry.** She is **member of the Inserm LIRIC Centre** (Lille University) and **research head of the Lille University Hospital Federation on inflammatory disorders (IMMINENT).** She is an **international leader** in the field of epidemiology in IBD and was one of the responsible of the research subgroup for epidemiology at the **European level** (Epicom/ECCO). She is the scientific head of Epimad Registry.

1) Ghione S, Sarter H, Fumery M, Armengol-Debeir L, Savoye G, Ley D, Spyckerelle C, Pariente B, Peyrin-Biroulet L, Turck D, **Gower-Rousseau C**; Epimad Group. Dramatic Increase in Incidence of Ulcerative Colitis and Crohn's Disease (1988-2011): A Population-Based Study of French Adolescents. Am J Gastroenterol. 2017 Aug 15. doi: 10.1038/ajg.2017.2282).

2) Declercq C, **Gower-Rousseau C**, Vernier-Massouille G et al. Mapping of inflammatory bowel disease in northern France: spatial variations and relation to affluence. Inflamm Bowel Dis. 2010 May;16:807-12.

WP1: Study of particular phenotypic features of CD and environmental risk factors in patients living in epidemic areas of CD: case-control study. Partners 1 & 2

Partner 2: EA 4483 "Impacts de l'environnement chimique sur la santé humaine, Faculté de Médecine, Lille, Occupational and Environmental Health Department (Drs C Nisse & A Leroyer)

The Catherine Nisse team is part of EA4483 **specialized in the environmental and occupational exposure assessment**, particularly in human biomonitoring. Indeed, this team performed a regional study about environmental levels of metals metalloids and platinoids, polycyclic aromatic hydrocarbons and glycolethers (IMePoGe study).

Aims: Epidemiological studies and building a **biobanking** including blood, saliva, urinary, stools and hair samples and atmospheric and top water in the house of patients and controls. The different tubes and the

type of conservation will be the expertise of partner 2. The biobank will rely on existing **pan-European Biobank and Biomolecular Resources Research Infrastructure** (BBMRI) facilities.

1) **Nisse C**, et al. Blood and urinary levels of metals and metalloids in the general adult population of Northern France: the IMEPOGE study, 2008-2010, Int J Hyg Environ Health, 2017 Apr;220 (2 Pt B):341-363.
2) Tagne-Fotso R, **Leroyer A**, Howsam M, et al. Current sources of lead exposure and their relative contributions to the blood lead levels in the general adult population of Northern France: The IMEPOGE Study, 2008-2010. J Toxicol Environ Health. 2016;79:245-65.

WP2: Sociological and historical investigations in CD epidemic areas. (Partners 3 & 4)

Partner 3: UMR-CNRS 8529 IRHiS Lille University (Pr B Touchelay)

Partner 4: UMR-CNRS 8911 CLERSé Lille University (Pr I Sainsaulieu)

Aims: To perform an **industrialization historical survey, a territorial diagnosis and a sociological survey** among patients in the epidemic areas of CD. Pr Touchelay's team is specialized in **contemporary economic and social history and Ivan Sainsaulieu is specialized in socio-anthropology and in community and healthcare professional studies. The key objectives are to outline the main characteristics of the clusters' local people, the transformation of their living and working conditions and to measure and track their environment quality since the XXth century.**

1. 38th Congress of the Social Science History Association (SSHA), Chicago (USA), November 2017 Participation in the workshop: " Crises of confidence: State, statistics and the production of economic and social knowledge,"
2. Book : With Isabelle Bruno and Florence Jany-Catrice (ed.), The Social Sciences of Quantification. From Politics of Large Numbers to Target-Driven Policies, Springer, 2016. http://link.springer.com/book/10.1007/978-3-319-44000-2
3. 2017 / Paris, « La réalité virtuelle en santé mentale : un jeu de miroir dans une expérimentation scientifique interdisciplinaire", avec Manuel Boutet, Daniel Mestre et Anne Vega, in Sainsaulieu et Saint-Martin dir., L'innovation en eaux troubles. Sciences, techniques, idéologies, Vulaines-sur-Seine, Editions du Croquant, p. 189-209.
4. Septembre 2012 / Paris, « Collective Mobilization in Hospitals : Confrontational or Consensual ? », Revue française de sociologie (English), 53-3, p. 316-346.
5. Décembre 2009 / Londres (GB), « New Public Management and New Professionalism across Nations and Contexts », with Kevin T. Leicht, Tony Walter, Scott Davies, in New Governance and New Professionalism, n° spécial, Current Sociology, Sage, 57-4, p. 581-605.

WP3: Mapping and identification of the various pollutants in CD epidemic areas and ecologic correlation studies. (Partners 5 & 6).

Partner 5: ***EA 2694 "Public Health and quality of care" Lille University (Pr A Duhamel & Dr M Génin).***

Aims: To perform biostatistics ecologic correlation. Dr Génin is now a well-recognized French specialist of geospatial biostatistics and is able to highlight space clusters of different diseases (particularly in IBD) using isotonic spatial scan statistics models.

1. Occelli F., Deram A., **Génin M**., et al. Mapping end-stage renal disease: spatial variations on small area level in Northern France, and association with deprivation, earlier renal replacement care and related diseases, PLOS One 2014; 9 (11):e110132. doi: 10.1371/journal.pone.0110132. eCollection 2014.
2. **Génin M**, **Duhamel A**, Preda C, et al. Space-time clusters of Crohn's disease in Northern France. J Public Health 2013; 21:497-504

Partner 6: EA 4483 "Impacts de l'environnement chimique sur la santé humaine, Faculté de Pharmacie, Lille (Pr D Cuny, Pr A Deram, Dr C Lanier et Dr F Occelli)

Aim: To identify and to map pollution. Pr D Cuny is specialist of ecotoxicology and on air biomonitoring. He's involved in the Regional Program for Environmental Health. He's involved in a large study associating **air pollution biomonitoring** with lichens and epidemiological population survey. His team, specialist of toxicology, disposes of existing data on contaminants of soils, water and atmospheric pollution of CD epidemic areas.

1. **Occelli F**., Deram A., Génin M., et al. Mapping end-stage renal disease: spatial variations on small area level in Northern France, and association with deprivation, earlier renal replacement care and related diseases, PLOS One 2014; 9 (11): e110132. doi: 10.1371/journal.pone.0110132. eCollection 2014.
2. **Occelli F**., Bavdek R., Deram A., et al. Using lichen biomonitoring to assess environmental justice at a neighbourhood level in an industrial area of Northern France, Ecological Indicator, 2016;60:781–788.

WP4: Toxicologic expertise of the WP2 and WP3 results and identification of relevant biomarkers to be analyzed on biological materials previously collected (Partners 2 & 7)

Partner 7: LIRIC – UMR 995 – Pr Benoit Foligné "Inflammatory Digestive Diseases: Pathophysiology and new therapeutic targets development"

Aim: to synthetize and elaborate an **environmental hypothesis** about the origin of CD in ways 1) to **determine and prioritize** chemicals to be analyzed through the samples obtained from the case-control study and stored in the biobanking; 2) **to select suitable laboratories** to perform the analysis of the retained environmental pollutants; as far as the **environmental exposome** may specifically impact on the structure of the **gut microbiota**, the rationale to manage/achieve further metagenomic studies could also be considered at this stage in order to identify environmental-based microbial marker(s).

Justification of the requesting grant

Partner	Personnel	Subcontracting	Travels	Other costs	Costs structure (4%)	Total
Partner1	223 300 €		11 500€	121 200 €	14 240 €	370 240 €
Partner2	14 000€		10 000€	7 000 €	1 240 €	32 240€
Partner3	30 000€	2 500€	2 500€		1 400 €	36 400€
Partner 4	30 000€		10 000€		1 600€	41 600€
Partner5	55 000€				2 200 €	57 200€
Partner 6	3 500 €	40 000 €	1 500 €		1 800 €	48 800€
Partner 7	30 000€	2 500 €	2 500 €		1 400 €	36 400 €
Total	**385 800€**	**45 000€**	**38 000€**	**128 200 €**	**23 880 €**	**620 880 €**

3. Impact et retombées du projet

Crohn's disease is a major public health concern in France. Its frequency is increasing all over the world and the lifetime risk of developing IBD has been calculated to be around 0.7%. It has been estimated that around 1.5 million persons are affected in Europe, including at least 150 000 in France. The impact of the HEROIC project for CD patients will come from:

1) The **identification of new potential environmental factors** for CD

2) The **identification and development of innovative pathways and strategies in practical approaches** to CD prevention, limiting exposition to identified factors, especially in high-risk areas, to prevent of incident CD cases but also to influence positively the disease course in prevalent CD patients.

3) **Development of devices to allow earlier diagnosis,** before irreversible destructive damage, in these high risk areas and development of prevention measures to decrease illness incidence, and consequently perform health economy.

Public health: The environmental factors identified as potentially involved in Crohn's disease could also be associated with other immune-mediated inflammatory diseases such as multiple sclerosis, rheumatoid arthritis, ankylosing spondylitis, psoriasis, type 1 diabetes, …, which all have a strong environmental etiology. Furthermore, the environmental data collected and the inventories performed will bring a better understanding of global environment context in the studied areas, which can participate in improving public health management.

Dissemination: Results will be published in scientific literature and through presentations during national and international congresses. Communication to the patients and health providers will be ensured all along the project. This commitment is required to detect patients' needs but also to help the recruitment of the patients in the studies. Results will be also published towards national and regional press through general communication of Lille University hospital. Moreover, the clinical and biological database described in the HEROIC project will also be re-used for other international collaborations, for instance for microbiota analyses. Results will also enable the formulation of new hypotheses that could be tested in clinical studies as the early detection of CD in risk areas, and cost effectiveness studies of prevention campaign to clusters' citizens.