Mapping Exposure-Induced Immune Effects:
Connecting the Exposome and the Immunome

NEWSLETTER
APRIL 2022

Welcome to the very first EXIMIOUS newsletter!

EXIMIOUS is an EU-funded project that aims to deliver a new way of assessing the human exposome, i.e., the exposures to environmental factors that one experiences throughout life, and shed light on its association to immune-mediated diseases. To achieve this aim, we are collecting clinical and socio-economic data as well as information on the exposome and the health status of the immune system (immunome) of participants from several cohorts, covering the entire lifespan, including prenatal life. In this newsletter you'll find an introduction to some of our cohorts, as well as the latest news from the project. Enjoy the read!

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The EXIMIOUS Project

**Mapping Exposure-Induced Immune Effects:
Connecting the Exposome and the Immunome**

EXIMIOUS in numbers

15
partners from
7 countries
collaborating

5
years of research and
innovation funded by
the EU

12
cohorts covering
the entire lifespan,
including prenatal life

1 of 9
projects within the
European Human
Exposome Network

News

Parrot nests (sources of antigenic exposure)

PARTNER IN THE SPOTLIGHT: VHIR

The Vall d'Hebrón Research Institute (VHIR), promotes and develops biomedical research, innovation and teaching.

TAKE-AWAYS FROM THE 2ND EXIMIOUS SYMPOSIUM

More than 70 participants joined the second EXIMIOUS Symposium. Did you miss it? Read about it here and watch the full recording.

PARTNER IN THE SPOTLIGHT: UCLOUVAIN

The Louvain Centre for Toxicology and Applied Pharmacology is a leading hub for research in the adverse effects of pollutants.

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ENVIRONAGE and LIFELINES
The effects of our environment on the health of children and the development of immune diseases

Age-related diseases, such as cardiovascular diseases, dementia and diabetes, have their origins early in life. Environmental factors including air pollution, can already affect the health of the baby from conception onwards. ENVIRONAGE (Environmental Influences on Early Ageing) is a birth cohort that to date includes more than 2200 mother-child pairs in Belgium. The cohort was first established in 2010 in cooperation with the hospital Oost-Limburg (Belgium), to investigate the influence of environmental exposures during pregnancy and early life on the health of children. Within the EXIMIOUS consortium, researchers from the University of Hasselt will collect and reuse data from this cohort from the prenatal period, at age 4-6 and at age 9-12, to investigate the effect of genes and environment on the health of children and gain more insight into the underlying mechanisms of diseases. This allows the researchers to look for predictive markers of ageing and health linked to environmental exposures.

For this cohort, pregnant women giving birth in the hospital Oost-Limburg are asked to participate in this study. The participating mothers first fill out a questionnaire, and after giving birth their placenta, urine and blood is collected. Finally, the child's blood pressure is measured at the hospital. About 4-6 years later, these children are invited at the university for a follow-up study, wherefrom 650 children have participated until now. At the age of 9-12 years old these children are invited once more for a second follow-up, of which to this date, almost 100 children have already participated.

Figure 2: A 10-year-old participant visiting for the second follow-up study within ENVIRONAGE.

During each of these follow-up visits the researchers try to gather more insight not only in terms of the health of these children, but also if they have been exposed to for example pollutants, medication or cigarettes' smoke. The University of Hasselt aims to assess about 200 more children within the next two years.

The health of these participants is assessed during these follow-up studies by performing multiple preclinical

Figure 1: UHasselt team involved in the scond follow-up.

Glossary

- **Black carbon:** Black carbon (BC) is the soot-like by-product of wildfires and fossil fuel consumption, able to be carried long distances via atmospheric transport (Elias, 2021).
- **Biobank:** A biobank is generally defined as a collection of human biological samples and associated information organized in a systematic way for research purposes (ScienceDirect, n.d.)
- **Immunomic:** All the genes and proteins that constitute the immune system are collectively known as the immunome; the immunome is a vastly complex and highly regulated structure that protects against infection and preserves health. (Biancotto & McCoy,2014)

measurements, including blood pressure measurements, cognitive tests, bone density measurements but also by taking a blood and a urine sample. Taking blood samples in children is challenging, but gives the researchers a very clear idea of the health of these children as well as where they are exposed to, is an ideal matrix to identify biomarkers and provides in depth information about molecular underlying mechanisms.

Researchers at the University of Hasselt recently developed a novel method to estimate a child's personal exposure to black carbon (an important compound of air pollution) using blood or urine. As EXIMIOUS aims to shed light on the association between these children's exposures and how the immune system works, the collection of blood and urine samples is essential. Lastly, extensive information about health, lifestyle and exposures is also collected by taking questionnaires from both child and mother each sampling time.

EXIMIOUS collects data within ENVIRONAGE but also uses data and biobanked samples that were collected during the last 12 years of this study to help find an answer to whther prenatal and postnatal environmental exposures relate to specific immunomic profiles early in life.

The University of Hasselt will also work on samples from adults and eldery within LIFELINES, a large biobank from the Netherlands. LIFELINES collects data and samples from 167.000 participants since 2006. Participants from three generations are followed for at least 30 years, to obtain insights into healthy ageing and the main factors relating to the onset and progression of diseases. EXIMIOUS will use LIFELINES samples (plasma, DNA and urine) together with data collected from these patients who have developed Rheumatoid Arthritis, Systemic Lupus Erythematosus and Type-I-diabetes. By measuring their exposures including black carbon exposure, EXIMIOUS aims to determine whether exposure to black carbon can predict the disease risk of these autoimmune diseases.

Understanding work exposures: where AI and epidemiological analyses meet

Method development in the Danish DOC*X and DOC*X-Generation register-based cohorts

Danish registers provide an exceptional opportunity within health research. They are based on the unique personal identification number assigned to each Dane or person residing in Denmark. This number makes it possible to merge data from different registers on an individual level, as was done in construction of the two Danish cohorts included in the EXIMIOUS project: DOC*X and DOC*X-Generation. The cohorts pose the possibility to investigate a large range of common and rare work exposures over a timespan of more than 35 years.

The main cohort is DOC*X, the Danish Occupational Cohort with eXposure data. The register includes data from a single survey in 1970 and register-based data continuously collected from 1976 onwards. The yearly registration of employment status of each person (industry and job codes) serves as point of departure. Furthermore, each person is linked to health and administrative data, e.g.,

any contacts had with hospitals, education, income, and family members. The cohort includes more than 6 million persons with a median occupational history of 15 years and between 2.0 to 2.9 million persons indicated as employed each year (Flachs et al, 2019). A range of different Job Exposure Matrices (JEMs) provide information on work exposures by link to the yearly job code assigned to each person. The matrices are constructed on job level, and each job is assigned a specific exposure value. Furthermore, four lifestyle JEMs have been developed. Based on four large population cohorts in Denmark, values of body mass index, smoking, alcohol consumption and fruit/vegetable intake can be assigned to each job code (Petersen et al, 2018).

The second cohort is the DOC*X-Generation cohort, which includes women from DOC*X who become mothers and their children. Data from this cohort analysed within

EXIMIOUS will cover approximately the same time period as included in the DOC*X cohort. We expect the cohort to include more than 1.2 million pregnancies divided between more than 600,000 women. The same type of health and administrative data collected for DOC*X will also be retrieved from the registers for the DOC*X-Generation cohort and combined with JEMs.

In the two cohorts, we have the opportunity to investigate several work factors in relation to: i) the development of autoimmune disease after years of exposure within the workers themselves; or ii) exposure to work factors during pregnancy and the children's risk of developing autoimmune diseases. Data will be analysed using machine learning and neural networks as well as epidemiological analyses.

Machine learning and neural networks

Modern artificial intelligence (AI) is evolving at a rapid pace, presenting researchers with new opportunities to handle large dataset, which traditionally have been hard to exploit. Within EXIMIOUS, experts in occupational health from the National Research Centre for the Working Environment (NFA) and Region Hovedstaden (RegionH), as well as AI developers from Biogenity and the Barham Institute (BI), collaborate closely to develop new approaches to analyse large datasets. While rigorous statistical models don't scale favourably to datasets like DOC*X, machine learning can deal with large and heterogenous data quite well. In addition, the strategy is centred on giving the models the tools to explain what information they have learned; this way, previous domain knowledge can be integrated with new insights from machine learning, in turn helping the execution of follow-up epidemiological analyses.

Epidemiological analyses

The results obtained by the machine learning and neural networks analyses, will inform hypotheses relating to the association between specific work exposures, either as a single or combined factor, and development of autoimmune disease. The hypotheses will be explored by NFA and RegionH using traditional epidemiological analyses. Furthermore, air pollution exposure modelled at the home address (by Aarhus University) will also be investigated, and we include external collaborators concerning JEMs (University of Utrecht). In the DOC*X cohort, cumulated exposure over time will be calculated for each work factor and investigated by regression analyses, alone and in combination, in relation to the risk of autoimmune disease later in life.
In the DOC*X-Generation cohort, exposure during pregnancy to selected work factors will be investigated by regression analyses, also as a single factor or in combination, and their children's risk of autoimmune disease during childhood.

EXIMIOUS represents a unique opportunity to bring data scientists, clinical experts, and institutions closer together, and allow us to better understand the interplay between established epidemiological methods and new technologies. This can open up exciting avenues for the future and generate new hypotheses to investigate for a better understanding, and ultimately prevention of, autoimmune diseases in society.

Glossary

- **Register-based cohort:** a collection (usually at national level) of information about individuals with a common trait.
- **Job Exposure Matrix (JEM):** A cross-tabulation between workplace hazards[/exposures] and occupational title (Choi, 2020). Each occupational title will receive a value of exposure. JEMs are commonly used to assign exposure level to a specific job group in occupational epidemiological studies, where no exposure data is accessible such as register-based studies.
- **Neural network:** A complex computational system made up of "artificial neurons", inspired by biology.
- **Epidemiology:** the field that studies the distribution of disease in human populations and factors determining that distribution. It concerns itself with groups of people rather than individual patients (Mullner RM, 2020).
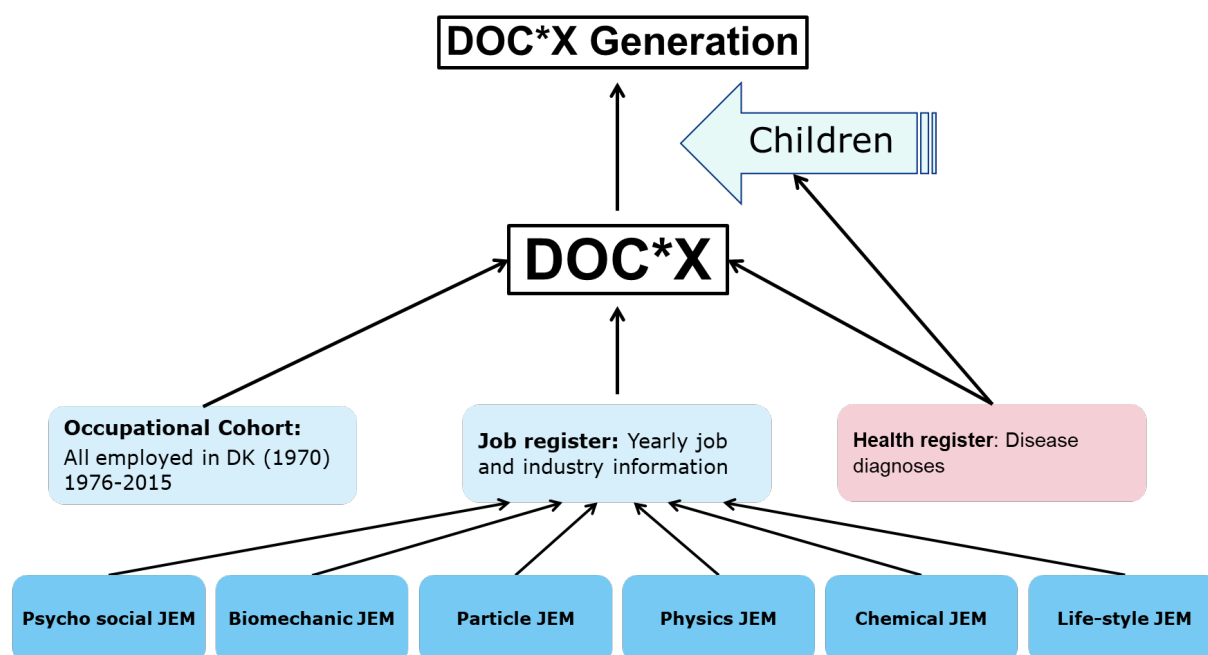
*Figure 1: Overview of the DOC*X and DOC*X Generation cohorts*

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Petersen SB, Flachs EM, Prescott EIB, Tjønneland A, Osler M, Andersen I, Juel K, Budtz-Jørgensen E, Kolstad HA, Schlünssen V, Bonde JP. Job-exposure matrices addressing lifestyle to be applied in register-based occupational health studies. Occupational & Environmental Medicine 2018;75:890-897.

The EXIMIOUS Symposium
## Launch of our own topical webinar series

As part of the EXIMIOUS project the symposium covers topics related to environmental and occupational exposures and measurements, exposure and immunity, and gene-immune-environment interactions.

Exposome-immunome interactions: A broad introduction | 15.06.2021
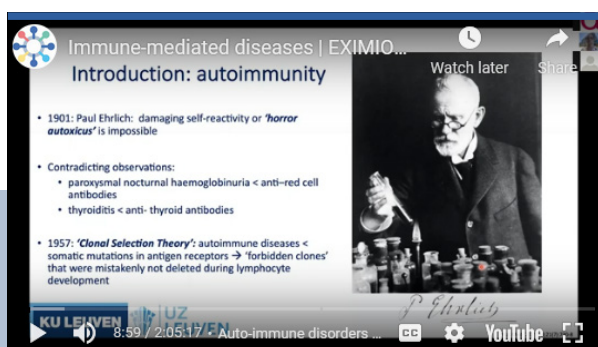
This first EXIMIOUS Symposium explores key aspects of the exposome-immunome interactions, providing a broad introduction to the topic and aiming to foster an interactive and constructive exchange. The invited guest speakers present their latest research, covering exposome-immunome interactions at different stages of life, starting from early life and moving on to environmental and occupational settings.

Immune-mediated diseases: an interplay between environment and genetics | 03.02.2022
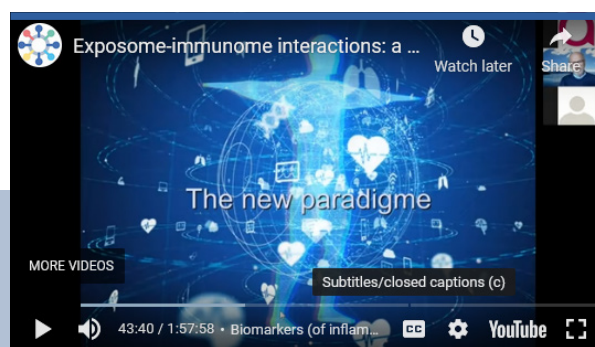
This second EXIMIOUS Symposium explores immune-mediated diseases and the interplay between environment and genetics. The invited guest speakers ease into the topic of immune-mediated diseases, providing an introduction to what these are, as well as presenting the latest research on how the working and living environments surrounding us play a role in the development of such diseases.

Upcoming Events and Symposia

- 23 May 2022
  EXIMIOUS Meeting | Barcelona, ES
- 24-25 May 2022
  European Human Exposome Network Scientific Meeting | Barcelona, ES
- June 2022, date to be defined
  3rd EXIMIOUS Symposium | online

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Scientific Publications
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The EXIMIOUS project—Mapping exposure-induced immune effects: connecting the exposome and the immunome.

Ronsmans, S., Sørig Hougaard, K., Nawrot, T. S., Plusquin, M., Huaux, F., Jesús Cruz, M., Moldovan, H., Verpaele, S., Jayapala, M., Tunney, M., Humblet-Baron, S., Dirven, H. Nygaard, U.C., Lindeman, B., Duale, N., Liston, A., Meulengracht Flachs, E., Kastaniegaard, K., Ketzel, M., Goetz, J., Vanoirbeek, J., Ghosh, M., Hoet, P. H. M, The EXIMIOUS Consortium. (2022) Environmental Epidemiology 6(1), e193. doi: 10.1097/EE9.0000000000000193

Exposure to silicates and systemic autoimmune-related outcomes in rodents: a systematic review.

Janssen, L.M.F., Ghosh, M., Lemaire, F. , Pollard, K.M., Hoet, P.H.M. (2022) Particle and Fibre Toxicology 19, 4. doi: 10.1186/s12989-021-00439-6

Human immune diversity: from evolution to modernity.

Liston, A., Humblet-Baron, S., Duffy, D., Goris, A. (2021) Human immune diversity: from evolution to modernity. Nature Immunology 22, 1479–1489. doi: 10.1038/s41590-021-01058-1

Associations between occupational and environmental exposures and organ involvement in sarcoidosis: a retrospective case-case analysis.

Ronsmans, S., De Ridder, J., Vandebroek, E., Keirsbilck, S., Nemery, B., Hoet, P.H.M., Vanderschueren, S., Wuyts, W.A., Yserbyt, J. (2021) Associations between occupational and environmental exposures and organ involvement in sarcoidosis: a retrospective case-case analysis. Respiratory research 22, 224. doi: 10.1186/s12931-021-01818-5

AutoSpill is a principled framework that simplifies the analysis of multichromatic flow cytometry data.

Roca, C.P., Burton, O.T., Gergelits, V., Prezzemolo, T., Whyte, C.E., Halpert, R., Kreft, L., Collier, J., Botzki, A., Spidlen, J., Humblet-Baron, S., Liston, A. (2021) AutoSpill is a principled framework that simplifies the analysis of multichromatic flow cytometry data. Nature Communications 12, 2890. doi: 10.1038/s41467-021-23126-8

A rapid test for the environmental detection of pigeon antigen.

Sánchez-Díez, S., Cruz, M-J., Álvarez-Simón, D., Montalvo, T., Muñoz, X., Hoet, P.M., Vanoirbeek, J.A., Gómez-Ollés, S. (2021) A rapid test for the environmental detection of pigeon antigen. Science of The Total Environment 778, 147789. doi:10.1016/j.scitotenv.2021.147789

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