PRESS RELEASE

For immediate release

Luxembourg, 4 December 2024

A new era of allergy treatment: scientists unveil the early molecular key to curing life-threatening allergies

Study uncovers the early immune responses that make insect venom immunotherapy the gold standard for curing severe allergies, offering hope for improving treatments worldwide

In a landmark clinical study just published in Nature Communications, researchers from the Luxembourg Institute of Health (LIH), the Luxembourg Centre for Systems Biomedicine (LCSB) of the University of Luxembourg, the Allergy Center Wiesbaden, Ulm University Hospital and Vrije Universiteit Brussels and UZ Brussel revealed the early immune mechanisms behind the exceptional success of insect venom immunotherapy. The study identified early molecular and cellular changes already at 8 hours immediately following the first immunotherapy administrations, changes that will pave the way for curative immune tolerance. Overall it provides novel insights that could revolutionise allergy treatment and improve outcomes for millions suffering from chronic immune disorders.

Allergic diseases are rapidly increasing globally, becoming the most common chronic immune-mediated conditions, largely driven by modern lifestyle factors and environmental influences. While allergen-specific immunotherapy (AIT) is the only available treatment that can potentially cure certain allergies, its effectiveness varies greatly among various forms of allergies. Insect venom allergies—such as those caused by bee or wasp stings—are the exception, with AIT offering clinical cure rates exceeding 90-95%.

A new study by the Luxembourg Institute of Health (LIH), in collaboration with the Centre Hospitalier de Luxembourg (CHL), the Allergy Center Wiesbaden, Ulm University Hospital and the Vrije Universiteit Brussels and UZ Brussel, shed light on the early immune mechanisms that underpin this remarkably successful therapy. By exploring how the immune system develops long-term tolerance to insect venom, the clinical research study identified key molecular and cellular switches that occur in the early stages of treatment, providing hope for improving AIT against other allergic diseases, where AIT is less successful, and contributing to the broader effort to combat the global allergy epidemic.

"*This work is a breakthrough for allergy science*," explained co-first author of the study Prof Sebastian Bode, jointly affiliated to the Luxembourg Institute of Health Department of Infection and Immunity (DII), the Ulm University Medical Center Department of Pediatrics and Adolescent Medicine, and the Department of General Pediatrics, Adolescent Medicine and Neonatology, Medical Centre–University of Freiburg, Germany. "*We've uncovered early immune responses, including the regulation of IL-6—a molecule usually linked to inflammation—that might play a completely unexpected crucial role in restoring immune tolerance. These findings could guide the development of more effective treatments for other allergies.*"

The study involved over 200 blood samples from patients recruited and treated at CHL by a team of allergy specialists, which then underwent detailed analysis at LIH's Department of Infection and Immunity (DII), the Integrated BioBank of Luxembourg (IBBL), and the Luxembourg Centre for

Systems Biomedicine (LCSB). This represents the deepest and most comprehensive data analysis ever performed in patients with insect sting allergy, which affects roughly 2.6%-4% of the population in Europe and worldwide—approximately 13-20 million people across the EU and UK—who are at risk of a fatal outcome from an insect sting if not treated by insect venom AIT. International collaborators from the VUB university hospital UZ Brussel in Brussels and Allergy Centre Wiesbaden in Germany provided additional expertise, ensuring a thorough and wide-reaching investigation.

"*The scope and precision of this study are unparalleled*," noted Professor Jorge Goncalves, a computational expert at the Luxembourg Centre for Systems Biomedicine, University of Luxembourg. "*We developed advanced algorithms to enable the analyses of the massive datasets of >200 millions of immune cells, which otherwise could not be handled at all by previously existing approaches.*"

"*We unbiasedly analysed each of the 25,000 genes in a pathogenic T-cell subset purified from ~ 200 blood samples*," added Assistant Professor Enrico Glaab, a big-data scientist, also from the Luxembourg Centre for Systems Biomedicine, "*Our novel tools have accelerated data processing, allowing us to uncover the hidden early molecular mechanisms driving immune tolerance.*"

"*One of the study's most revolutionary findings was the discovery of a controlled, low-level activation of the IL-6 pathway within a specific immune subset during allergen-specific immunotherapy (AIT) for insect venom allergies*," said Dr Feng Hefeng, one of the study's co-senior authors. "*While IL-6 is typically known for driving inflammation in chronic diseases, our research revealed its unexpected role in the immune system's transition to tolerance. We found that during AIT, IL-6 is temporally activated at much lower levels than in typical inflammatory responses, playing a crucial protective role. This subtle but crucial activation helps the body adapt to venom allergens, promoting long-term immune tolerance and preventing severe allergic reactions.*"

The research also highlighted the importance of B regulatory cells (Bregs) very early during AIT, which are vital by producing IL-10 for maintaining immune system balance in many diseases. Additionally, the study identified specific hybrid plastic immune cells that combine features of several well-known classical immune subsets. These hybrid cells play a key role in bridging the innate and adaptive immune responses, facilitating the immune system's transition to tolerance. The discovery of these flexible immune cells offers new insights into the "molecular magic" behind insect venom AIT.

"*Allergic diseases are the most common chronic immune-mediated conditions globally, affecting millions*," said Prof Ludger Klimek from the German Center for Rhinology and Allergology. "*By understanding why insect venom AIT is so effective, we hope to improve therapies for other allergens and ultimately combat the growing allergy epidemic.*"

In addition to its scientific contributions, the study has practical implications. It demonstrates the necessity of considering circadian rhythms when designing clinical studies, as immune responses fluctuate throughout the day. The findings have also inspired the creation of an interactive immune data platform that is directly linked to the publication and allows researchers worldwide to explore the study's results and use them as a foundation for further research.

"*This is translational research at its finest*," added Professor Jan Gutermuth, from the Department of Dermatology, UZ Brussel and Vrije Universiteit Brussel. "*Our work bridges clinical practice and cutting-edge science, using insect venom immunotherapy as a clinical model to unlock the secrets of immune tolerance. The potential to transform allergy treatments is immense.*"

"*The findings are expected to have far-reaching implications, not only for improving allergy treatments but also for understanding immune tolerance in other chronic conditions*," concluded Professor Markus Ollert, lead author of the work and Director of the LIH Department of Infection and Immunity. "*By unravelling the "molecular magic" of insect venom immunotherapy, researchers are one step closer to addressing the global allergy epidemic and advancing personalised medicine*."

The study was published in the renowned journal Nature Communications under the full title: *"*Multiomics approaches disclose very-early molecular and cellular switches during insect-venom allergen-specific immunotherapy: an observational study*."*

Funding and collaborations

This study, registered in ClinicalTrials.gov, was conducted in collaboration with the Centre Hospitalier de Luxembourg (CHL), where patients were recruited and treated by allergy specialists following standard clinical protocols. Immune profiling and sample analysis were performed by LIH's Department of Infection and Immunity (DII) and the Integrated Biobank of Luxembourg (IBBL), with data analysis supported by international partners including EMBL Heidelberg and the Luxembourg Centre for Systems Biomedicine (LCSB). Contributions from clinical laboratories in Belgium and Germany enabled the processing of thousands of allergen-specific antibody tests, demonstrating a multidisciplinary approach.

Funding and collaboration support were provided by the Luxembourg Personalized Medicine Consortium (PMC), Luxembourg National Research Fund (FNR) programs (PRIDE, AFR, CORE), European Academy of Allergy and Clinical Immunology (EAACI) long-term fellowship, Horizon Europe project COMMUTE, the European Research Council (ERC) under Horizon 2020, the HPC Bridges programme, the Luxembourg Government's CoVaLux programme, and Action Lions Vaincre le Cancer.

About the Luxembourg Institute of Health (LIH)

The Luxembourg Institute of Health (LIH) is a public biomedical research organisation focused on precision health and invested in becoming a leading reference in Europe for the translation of scientific excellence into meaningful benefits for patients.

The LIH places the patient at the heart of all its activities, driven by a collective obligation towards society to use knowledge and technology arising from research on patient derived data to have a direct impact on people's health. Its dedicated teams of multidisciplinary researchers strive for excellence, generating relevant knowledge linked to immune related diseases and cancer.

The institute embraces collaborations, disruptive technology and process innovation as unique opportunities to improve the application of diagnostics and therapeutics with the long-term goal of preventing disease.

About the LCSB

The Luxembourg Centre for Systems Biomedicine (LCSB) is an interdisciplinary research centre at the University of Luxembourg. Its 250 staff members combine their expertise in a broad spectrum of disciplines - from computational biology to clinical and experimental neuroscience – to study the brain and its diseases. Research at the LCSB focuses on neurodegenerative disorders such as Alzheimer's or Parkinson's. Collaboration between biologists, medical and computer scientists, physicists, engineers

as well as mathematicians offers new insights into complex biological mechanisms and disease processes, with the aim of developing new tools for diagnostics, prevention, and therapy.

The LCSB has established strategic partnerships with scientific partners worldwide and with all major biomedical research units in Luxembourg. The centre also carries out collaborative projects with hospitals and research-oriented companies, accelerating the translation of fundamental research results into clinical applications, for the benefit of patients.

About the Centre Hospitalier de Luxembourg

A state-of-the-art hospital with 581 beds and a national reference centre for many disciplines, the Centre Hospitalier de Luxembourg (CHL) provides innovative diagnostic and treatment services that meet internationally recognised quality standards accredited by the Joint Commission International (JCI), as well as a teaching and research mission as a public institution. www.chl.lu

About the Vrije Universiteit Brussel

Vrije Universiteit Brussel (VUB), a dynamic, modern, public university with four campuses in the Brussels-Capital Region. Ranked as one of the world's top comprehensive universities with a history spanning 180 years, the VUB combines award-winning research and accredited English and Dutch-taught study programmes (Bachelors, Masters and PhDs) with high impact on social, economic and cultural innovation.With more than 150 internationally recognised research teams, VUB prepares students in many disciplines of fundamental and applied research. VUB counts over 17,000 students, 23% of which are international, representing about 140 different nationalities.

At the VUB, students and professors work closely together. We coach our students to become open-minded world citizens, with a strong commitment towards sustainable humanistic societal values. Our graduates are well prepared for professional careers in an increasingly multilingual and international environment. An independent research attitude, as well as a multidisciplinary, international and intercultural environment are key features in the VUB's ambition to be an open, international university platform. Our expertise and strategic position at the heart of Europe makes us an ideal partner for excellent research and education with a wide outlook on Europe and the world.

About UZ Brussel

UZ Brussel (University Hospital Brussels) has a staff of almost 5,000 employees. It is attached to the Faculty of Medicine and Pharmacy of the Vrije Universiteit Brussel (Free University of Brussels) on the Brussels Health Campus in Jette. With 721 hospital beds, it accounts for more than 30,000 admissions of patients each year from Belgium and abroad, 445,000 consultations (emergencies not included) and 75,000 patients at the emergency care. Its philosophy is founded on three principles: Dutch-speaking, pluralist and social. As a university hospital, it also has a teaching mission and conducts scientific research.

About Ulm University Hospital (UKU)

Ulm University Hospital provides highly specialised healthcare, pioneering research and excellent teaching in southern Germany. With over 1,200 beds, around 50,000 inpatients treated annually and almost 300,000 outpatient quarterly cases, the UKU offers university healthcare at a high level.

Scientific contact:

Prof. Dr. med. Markus Ollert

Director, Department of Infection and Immunity

Luxembourg Institute of Health

Email: markus.ollert@lih.lu

Press contact:

Arnaud D'Agostini

Head of Marketing and Communication

Luxembourg Institute of Health

Tel: +352 26970-524

Email: communication@lih.lu