

As an interdisciplinary biomedical research centre at the University of Liège, the GIGA is structured around 4 key areas: research, technology platforms, training and the hosting of biotech companies. Its researchers develop advanced medical solutions based on cutting-edge university research, with the aim of improving research and having a real impact on health.

Located within the University Hospital on the Sart-Tilman campus, the GIGA has more than 600 scientists specialising in the development of healthcare solutions for the benefit of patients. GIGA scientists include molecular and cell biologists, physicians, pharmacists, veterinarians, psychologists, chemists, physicists, mathematicians and engineers.



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GIGA researchers are grouped into 5 domains: cancer, immunobiology, neuroscience, metabolism & cardiovascular biology and molecular and computational biology.

Academic excellence

GIGA members strive for academic excellence to foster groundbreaking medical innovations. The GIGA has the highest concentration of ERC (European Research Council) recipients in the Walloon Region. GIGA members publish a peer-reviewed article every day, including in the world's leading scientific journals. GIGA members have filed over 100 patent applications for medical solutions.

The GIGA comprises around fifty laboratories working in the 5 main areas.

Cancer

The cancer cluster comprises 12 laboratories (Metastasis Research Laboratory, Human Genetics Laboratory, Medical Chemistry Laboratory, Cancer Signaling Laboratory, Conjunctive Tissue Biology Laboratory, Experimental Pathology Laboratory, Gene Expression Molecular Analysis Laboratory, Tumour and Development Biology Laboratory, Tumour Cell Stem Cells Laboratory, Molecular Angiogenesis Laboratory, Zebrafish Development Laboratory, Cellular and Molecular Epigenetics Laboratory), 19 PIs, 3 clinicians, 18 seniors and postdocs, 84 PhD students and 18

technicians.

The cancer division's discoveries advance therapeutic prospects. Published on 20 August 2024 in the journal *Cell Reports Medicine* and entitled 'In vivo vulnerabilities to GPX4 and HDAC inhibitors in drug-persistent versus drug-resistant BRAFV600E lung adenocarcinoma', a 'multi-approach' study conducted by researchers from the Tumour and Developmental Biology Laboratory, in collaboration with their local and international partners, has highlighted new therapeutic vulnerabilities in BRAF mutated lung adenocarcinoma tolerant and resistant to targeted therapy. This discovery paves the way for better patient management and enables new treatment options for this highly aggressive cancer to be considered and tested.

In another study published in the journal *Nature Cell Biology* on 7 June 2024 under the title 'Valine aminoacyl-tRNA synthetase promotes therapy resistance in melanoma', an international research team led by GIGA scientists has discovered an interesting new therapeutic target for the treatment of melanoma resistant to targeted therapies. Inhibition of the VARS enzyme could prevent this therapeutic resistance by resensitising tumours resistant to these targeted therapies.



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Immunobiology

GIGA-Immunobiology brings together basic researchers and clinicians involved in fundamental, clinical and translational research in all areas of immunobiology (immunity, infectiology, inflammatory disorders). It comprises 9 laboratories (Cellular and Molecular Immunology Laboratory, Haematology Laboratory, Molecular Immunology and Signal Transduction Laboratory, Immunometabolism and Nutrition Laboratory, Translational Gastroenterology

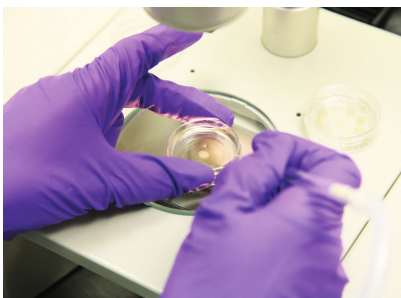
Laboratory, Pneumology Laboratory, Immunophysiology Laboratory, Rheumatology Laboratory, Inflammation and Rehabilitation Improvement Laboratory, Virology and Immunology Laboratory), 9 PIs, 9 clinicians, 19 Seniors & Postdocs, 34 PhD students and 17 technicians.

In a recent publication ('Recruited atypical Ly6G+ macrophages license alveolar regeneration after lung injury', *Science Immunology*, 2024), a team of researchers from the University of Liège identified a new population of macrophages, innate immune cells, which arrive in the lung following damage caused by respiratory viruses and play a crucial role in repairing the pulmonary alveoli. This discovery promises to revolutionise our understanding of the post-infectious immune response and paves the way for new regenerative therapies.

Another publication ("External validation of serum biomarkers predicting short-term and mid/long-term relapse in patients with Crohn's disease stopping infliximab", *Gut*, 2024 Aug 12) validated blood biomarkers predicting recurrence of Crohn's disease.

Metabolism and cardiovascular biology

This research cluster comprises 5 Laboratories (Translational Nephrology Research Laboratory, Cardiology Laboratory, Molecular Biomimetics Laboratory, Immunometabolism & Nutrition Laboratory, Surgical Research Centre - CREDEC), 2 PIs, 10 Clinicians, 4 Seniors & Postdocs, 7 PhD students and 7 Technicians. In 2019, the team led by Cécile Oury and Patrizio Lancellotti, directors of the Cardiology Laboratory, discovered that the drug used to prevent cardiovascular disease, ticagrelor, also had antibacterial properties against Gram-positive bacteria, including the most resistant. In a study published in the prestigious journal *JACC* ('Protective Effect of Ticagrelor Against Infective Endocarditis Induced by Virulent *Staphylococcus aureus* in Mice', Volume 8, Issue 11, November 2023, Pages 1439-1453), the same team described the drug's remarkable activity against infective endocarditis.



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Another study, published in 2023 ('Targeted deletion of vonHippel-Lindau in the proximal tubule conditions the kidney against early diabetic kidney disease', *Cell Death Dis.* 2023 Aug 26;14(8):562) targeted diabetes in relation to the kidneys. Diabetes attacks these organs by

creating a lack of oxygen. A new therapeutic strategy, based on the results of an international consortium co-directed by Prof François Jouret (Liège University Hospital), suggests acclimatising the kidneys to this lack of oxygen in order to prevent diabetic kidney disease.

Molecular and computational biology

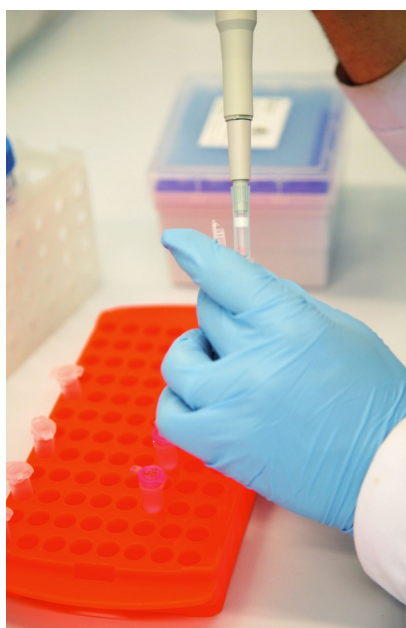
This research area brings together 13 laboratories (Human Genetics Laboratory, Gene Expression and Cancer Laboratory, Digital Therapies Laboratory, Radiochemistry Laboratory, Animal Genomics Unit, Biomechanics and Computational Tissue Engineering Laboratory, Molecular Pharmacology Laboratory, Molecular Biology and Functional Evolution of Sensory Systems Laboratory, Fundamental Research in Intensive Care Laboratory, Zebrafish Development Laboratory, Functional Genetics Laboratory, Viral Interactome Networks Laboratory, Systems and Modelling Laboratory - BIO3), 17 PIs, 2 Clinicians, 34 Seniors & Postdocs, 33 PhD students and 11 technicians.

Recent publications include 'GWAS reveals determinants of mobilization rate and dynamics of an active endogenous retrovirus of cattle', Nature Communications 2024 Mar 9;15(1):2154: Doctoral student Lijing Tang and colleagues from the Animal Genomics Unit have developed a molecular method for quantifying the transposition rate of DNA sequences in bovine semen. Using this method, they have also been able to pinpoint the cycle of endogenous retroviruses. This provides a better understanding of the birth, expansion and self-programmed death of endogenous retroviruses in cattle. Following this discovery, Lijing Tang initiated a collaboration with a Swiss group (Dr Etienne Bucher's team, Agroscope) to apply this method to transposable elements that are still active in certain wheat varieties.

In addition, ULiège and the CHU de Liège are jointly conducting the ENSEMBLE project, which has a threefold aim: to initiate the deployment of P3 (Preventive, Personalised, Precision) medicine in the Walloon Region, improve polygenic risk scores and adapt them to the specific profile of the diverse Walloon population. To this end, by mid-2025, 10,000 patients being monitored at Liège University Hospital will be included on a voluntary basis. By analysing and comparing the genes of individuals in a given population on a large scale, the aim is to assess, using a score, the risk of certain common and complex diseases (breast cancer, colon cancer, etc.) and, consequently, to step up screening and prevention of these diseases. This represents a new paradigm in prevention and medical monitoring over the next few years.

Another source of pride for the Molecular Biology and Computational domain, Grégory Fettweis was awarded a prize in April 2024 by the King Baudouin Foundation for his project entitled 'Targeting 3D chromatin architecture as a new therapeutic avenue in Ewing Sarcoma': as part of this project, he proposes to study the molecular mechanisms that establish genome architecture in Ewing sarcoma, a paediatric bone and soft tissue cancer caused by a chromosomal translocation leading to the fusion of 2 genes. In addition, he will characterise the impact of this

DNA reorganisation on the gene expression programme characteristic of Ewing’s sarcoma and on its development. It will also carry out screening to identify small molecules capable of inhibiting this restructuring of the genome. More broadly, this project aims to explore the role of the 3D structure of the genome in paediatric tumorigenic and metastatic processes with a view to establishing their therapeutic potential.



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Neuroscience

This research cluster comprises 14 laboratories (Neuroendocrinology Laboratory, Anaesthesia and Intensive Care Laboratory, Ageing and Memory Laboratory, Physiology of Cognition Laboratory, MOVERE Laboratory, Coma Science Group, Evolutionary Neuroethology Laboratory, Developmental Neurobiology Laboratory, Clinical Neuroscience Laboratory, Molecular Regulation of Neurogenesis Laboratory, Data Acquisition and Modelling Development Laboratory, Nervous System Diseases and Therapies Laboratory, Neurophysiology Laboratory, Sleep and Chronobiology Laboratory, Sensation and Perception Group), 20 PIs, 13 Clinicians, 39 Seniors & Postdocs, 82 PhD students and 16 Technicians.

In terms of publications, the study ‘Stress during pubertal development affects female sociosexual behavior in mice’ (Bentefour Y, Bakker J. Nature Communications 2024 Apr 30;15(1):3610) focused on puberty, a crucial phase in the development of female sexual behaviour (reproductive cycle and sexual performance). It is increasingly clear that exposure to major stresses during this period can lead to lasting sexual dysfunction. Hence the interest in studying the effects of chronic stress during the pubertal period on the neural circuitry regulating female sexual behaviour. The results of this study, conducted on female mouse

models, demonstrate the importance of nitric oxide-producing neurons, which are crucial in processing the olfactory signals required for the expression of female sexual behaviour.

Just as important, an international study launched in 2008 by Dr Nicholas Schiff (Weill Cornell Medicine), Steven Laureys (Université de Liège) and Adrian Owen (University of Cambridge, now at the University of Western Ontario) has recently shown that patients with severe brain damage can show clear signs of consciousness when examined by brain imaging and asked to perform a complex mental task, even if they are unable to move or speak. The study was published in the *New England Journal of Medicine* ('Cognitive Motor Dissociation in Disorders of Consciousness', *N Engl J Med.* 2024 Aug 15;391(7):598-608). This is the largest study ever carried out on the prevalence of this condition, known as cognitive motor dissociation. Of the 353 adults with consciousness disorders recruited for the study, 241 patients were unable to follow bedside commands (for example, 'open and close your hand' or 'imagine opening and closing your hand'). Yet 25% of these 241 patients were able to perform these cognitive tasks, as shown by patterns of brain activity measured by EEG and/or fMRI, comparable to those observed in control subjects. This suggests that many apparently unconscious patients may in fact be conscious and possess cognitive faculties. The results of the study should lead to new avenues of research, in particular the development of more accessible methods for detecting this dissociation, which, unlike task-based fMRI and EEG, could be used in a greater number of clinical centres. Ultimately, the absence of a response is not synonymous with unconsciousness and is much more frequent than the researchers in the study initially thought. It's easy to imagine the ethical implications of this type of discovery, with its expected repercussions on the treatment of patients suffering from disorders of consciousness.

Prestigious research projects

GIGA researchers are also involved in numerous European projects (ERC, Horizon 2020, Feder). For instance, Francesca Rapino has been awarded an ERC-Starting Grant for her 'tRNAtogo' project (2020-2024). The aim was to understand the silent conditions (tRNA) that induce a population of healthy cells to become tumorigenic. The use of cutting-edge technologies was used to profile, genetically screen and physiologically test the role of different tRNAs in the establishment of cancer stem cells (CSCs). In the near future, the researcher hopes to generate a new technology to improve the early diagnosis of highly incurable cancers such as lung and intestinal cancer.

Head of the biomechanical engineering laboratory, Liesbet Geris has been awarded an ERC Consolidator Grant for her 'INSTant CARMA' project (2022-2027). This grant will enable her to continue her research into the development of new cartilage regenerative medicine techniques to treat osteoarthritis. Similarly, an ERC Consolidator Grant has been awarded to Thomas Marichal,

Director of the Immunophysiology Laboratory and Welbio investigator, for his 'MoMacTrajectALI' project (2024-2029). This funding will enable him to continue studying the mechanisms of lung regeneration following respiratory infections such as Covid-19 or influenza, ultimately leading to the development of new therapeutic strategies to counter excessive damage and avoid severe forms of the disease.

The team led by Laurent Nguyen, Scientific Director of the GIGA, is taking part in the UNFOLD project (ERC-Synergy Grant 2024-2029), which is tackling the question of the mechanisms of folding of the cerebral cortex from all angles, with a particular interest in understanding its complexity with a view to gaining a better understanding of the development and formation of our brains.



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Finally, as part of the Horizon 2020 programme, Liesbet Geris is also involved in two projects: IN SILICO WORLD - Lowering barriers to ubiquitous adoption of In Silico Trials (2021-2024) and ONTOX - Ontology-driven and artificial intelligence-based repeated dose toxicity testing of chemicals for next generation risk assessment (2021-2026). These are all examples of research based on a commitment to scientific excellence, serving the patients of today and tomorrow.