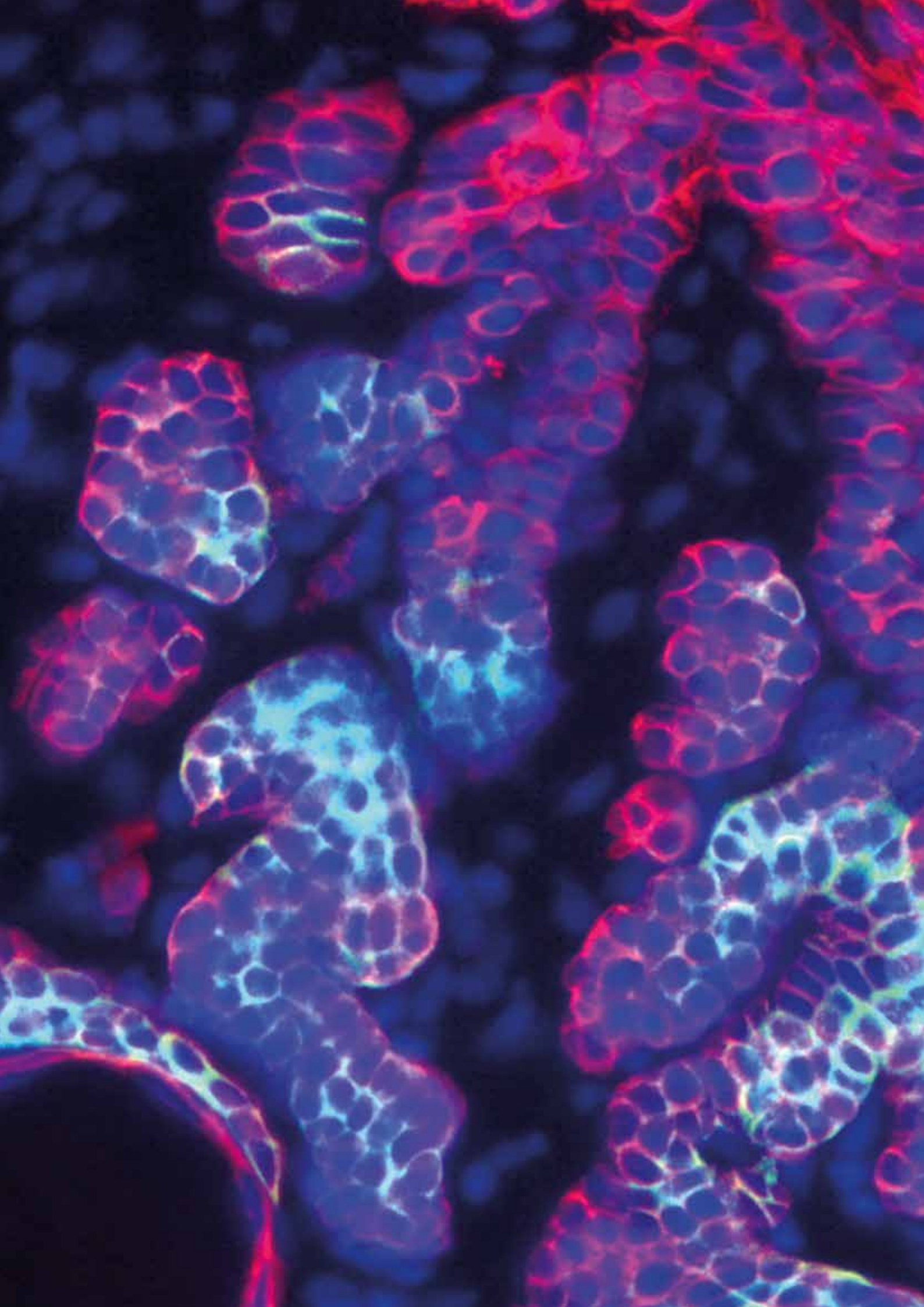
ANNUAL REPORT 2019

welbio

Walloon Excellence in Life sciences

CONTENTS



FOREWORD

WELBIO is an inter-university research institute financed by Wallonia.
Its mission is to support fundamental strategic research in the life sciences fields, with a view to enhancing discoveries towards industrial applications.

The first WELBIO projects were launched less than 10 years ago. This activity report is an opportunity to highlight our concrete results. Here are some key points:

BUSINESS CREATION

ChromaCure, the first Walloon company to spin off directly from a WELBIO project, after being launched in 2018 by Professor Blanpain, is continuing to develop molecules for treating advanced-stage cancers. In 2019, consideration began for various spin-off projects that would take over from various WELBIO projects. These spin-off projects will be continued in 2020.

HEALTH

The first patients were treated "thanks to WELBIO" in 2019. A Phase-1 clinical trial was initiated by AbbVie for a new immunotherapy treatment of advanced malignant tumours. This was based on the results of the WELBIO 2011–2015 project by Professors Coulie and Lucas. Furthermore, the first patients with a rare congenital disease (congenital neutropenia) have been treated based on the results of the WELBIO 2015–2019 project by Professor Van Schaftingen.

INDUSTRIAL INNOVATION

Patent applications are pending for 10 inventions in a variety of fields: cancer diagnosis and treatment, treatment of neurodevelopmental disorders, obesity, diabetes and rare diseases.

Various projects are being pursued in collaboration with Walloon, Belgian and international biotech firms (OncoDNA. MastherCell, NCardia, UCB, argenx and AbbVie), in order to utilise the results found by WELBIO researchers. This is done via projects that are supported by SPW Recherche, the BioWin Competitiveness cluster or through research and licensing agreements. WELBIO earns revenue from the intellectual property of its projects.

TALENT SOURCE FOR OUR COMPANIES

WELBIO researchers have been able to employ not only local staff, but also attract foreign scientists. Having trained in excellent labs, some of these scientists are continuing their careers in Walloon companies today. In this way, WELBIO contributes to providing a pool of talent for our companies.

SCIENTIFIC REPUTATION OF OUR UNIVERSITIES

After five calls for projects, 65 research projects, carried out by 47 principal investigators in 4 universities, were rigorously selected. The scientific excellence of the projects supported is demonstrated by 432 publications in peer-reviewed journals, including 161 articles published in the most prestigious journals. WELBIO financing also has a ripple effect. In 2019, two WELBIO researchers received a prestigious ERC Consolidator Grant from the European Research Council.

FRFS-WELBIO STRATEGIC FUNDAMENTAL RESEARCH PROJECTS

4 NEW PROJECTS SELECTED AFTER THE 5TH CALL FOR PROJECTS

After a period of uncertainty, early 2019 was a big relief for WELBIO and its researchers. Despite the decrees and results, WELBIO's financing remains chaotic. In March 2019, the Walloon government awarded €12 million in funding to cover the 2019–2021 period. This new funding has been added to the previously available reserves in the FRFS (Strategic Fundamental Research Fund). WALBIO was therefore able to launch its 5th call for projects, to select 14 new projects and to ensure renewals of the 14 projects that were launched in 2017. Since late 2015, WELBIO has maintained the same scale, annually devoting €7.5 million to 28 parallel projects.

The creation of the FRFS in 2012 aimed to ensure the sustainability of WELBIO. In practice, this aim has not yet been achieved. Without further financing by 2021, WELBIO will have exhausted its reserves and will no longer be capable of continuing its work. It is essential that the new government makes the necessary decisions for WELBIO to continue in 2020. A strategic fundamental research institute for life sciences meets the needs that were clearly formulated by various stakeholders in the last regional elections:

- The Union Wallonne des Entreprises noted that "companies that are members of competitiveness clusters do not require industrial or applied research projects alone. More upstream research is also important for developing their innovation pipeline" (Memorandum Heptathlon 2024);
- BioWin, the health cluster of Wallonia, explicitly recommended support for WELBIO, in order to strengthen fundamental upstream research for companies (Memorandum BioWin 2019);
- the Conseil des Recteurs has highlighted the importance of tools like WELBIO in attracting and retaining our best researchers for strategic interest (Memorandum 2019 from CReF).

The 2019–2021 projects were officially presented in the first "WELBIO researchers gathering" at the Théâtre de Namur in October 2020. This event, which was organised by the FNRS in collaboration with WELBIO ASBL, took place in the presence of Mr Willy Borsus, the Vice President and Minister of Economy, Foreign Trade, Land Use Planning and Agriculture. "Our goal with this programme is to effectively support fundamental research in a strategic field for our region."

The call for projects was managed by the FRS-FNRS. By the time the call was closed, 65 proposals that satisfied the eligibility criteria had been received from five universities. The assessment of the proposals was entrusted to an independent international Scientific Committee, which was chaired by Professor Heldin (Uppsala University). The final assessment and ranking of all the projects took place in June 2019, subsequent to an interview with ten Starting Grant candidates. Twenty-one files were deemed exceptional (A+). This highlights the generally excellent quality of the proposals. After being made aware of the results and consulting Professor Heldin, WELBIO's Board of Directors suggested to the Board of the FRFS to finance the six A+ Continuation Grant projects, five A+ Starting Grant projects and three A+ Advanced Grant projects with the highest rankings. Unfortunately, budgetary restrictions made it impossible to finance all of the projects that were deemed exceptional.

The 14 new projects are described below.

ADVANCED GRANTS

LUC BERTRAND
UCLouvain

CARdiovascular DIseases and o-GlcnAcylatioN: the case of cardiac hypertrophy.

cardiovascular diseases • biochemistry • cell signalling

Luc Bertrand is Senior Research Associate at the FNRS and professor at the Université catholique de Louvain. He works at the Pole of Cardiovascular Research within the Institute of Experimental and Clinical Research (IREC). His research focuses on post-translational modifications involved in the regulation of the metabolism and cardiac function, in relation to different cardiac diseases. He studies more specifically the role of the AMPK protein ("AMP-activated protein kinase").

This WELBIO project is based on his recent finding that the activation of AMPK blocks cardiac hypertrophy development by acting on a specific branch of glucose metabolism, the hexosamine biosynthesis pathway, known to regulate a post-translational modification of proteins, named O-GlcNAcylation. The tandem AMPK/ O-GlcNAcylation might represent a novel therapeutic avenue for cardiac hypertrophy treatment. This projects aims to validate this hypothesis. The molecular mechanisms linking AMPK, O-GlcNAcylation and cardiac hypertrophy will be investigated in detail, particularly by analysing the O-GlcNAcylated proteins. These proteins might be new targets for cardiac hypertrophy treatment.

SOPHIE LUCAS
UCLouvain

Targeting TGF-β1, β2 or β3 activation in auto-immunity and graft-versus-host disease.

auto-immune diseases • immunology • cytokines

Sophie Lucas is professor at the Université catholique de Louvain. Her work at the de Duve Institute focuses on the mechanisms whereby Regulatory T cells (Tregs) inhibit the immune system, preventing it from attacking healthy tissue. An insufficient activity of Tregs might lead to auto-immune diseases, as well as to the rejection of grafts or graft-versus-host diseases. Conversely, an excessive activity of Treg lymphocytes blocks anti-tumour immune responses and contributes to cancer progression. Sophie Lucas and her team have found that Treg lymphocytes produce active TGF-β1, a cytokine known for its immuno-suppressive properties. Among the 3 isoforms of TGF-β, TGF-β1 is the main form expressed by immune cells.

This WELBIO projects aims to develop antibodies able to activate TGF-β1 and to assess (in preclinical models) if these antibodies can treat auto-immune or graft-versus-host diseases. The cellular origin of TGF-β1 will be investigated in a model of Systemic Lupus Erythematosus, a chronic auto-immune disease which can affect multiple organs. Treg lymphocytes might express and activate TGF-β1 in other cells to block auto-immune reactions. A second part of the project will be dedicated to Systemic Scleroderma, an auto-immune disease characterised by a profound fibrosis which could be linked to an excessive activation of one of the TGF-β isoforms.

AGNÈS NOËL
LIÈGE université

Innovative roles of uPARAP in lymphatic vessel morphogenesis and functions.

cancer • lymphatic vessel morphogenesis • cell signalling

Agnès Noël is professor at the Université de Liège. Within the GIGA research centre, her work focuses mainly on tumour vascularisation, in particular on lymphatic vessel morphogenesis, the formation of new lymphatic vessels (lymphangiogenesis). Besides its role in homoeostasis and immunity, this complex biological process contributes to cancer progression and metastasis dissemination towards lymph nodes. Conversely, lymphatic vessel dysfunctions, tissue swelling and lymphoedema can arise from cancer treatment (irradiation or surgery). Agnes Noël and her team have found that the uPARAP protein, an endocytic receptor involved in collagen remodelling, is specifically involved in lymphangiogenesis.

This WELBIO project aims to understand precisely, at the molecular level, how the uPARAP receptor acts in lymphatic

morphogenesis, to investigate its role in different steps of the metastatic process and to identify its molecular partners. The potential of uPARAP (or its partners) as a therapeutic target will be assessed for cancer treatment, as well as for lymphoedema treatment.

STARTING GRANTS

DAVID ALSTEENS
UCLouvain

Deciphering the molecular mechanisms of reovirus and rotavirus entry at the nanoscale.

infections • biophysics • atomic force microscopy

David Alsteens is Research Associate at the FNRS and professor at the Université catholique de Louvain At the laboratory of Nanobiophysics of the Louvain Institute of Biomolecular Science and Technology, he investigates, at the molecular level, the forces at play in protein structures, in cellular adhesion and in the first steps of cellular signalling (ligand-receptor binding or the binding of the virus to the cell it is infecting).

This WELBIO project focuses on reovirus infection, a model of non-enveloped viruses. The mechanism whereby this type of virus penetrates the cellular membrane is not well understood. The role of external capsid proteins in the adhesion and infection of virus will be investigated using Atomic Force Microscopy (AFM). Strategies for interfering with these early interactions during infection will be developed.

GUIDO BOMMER
UCLouvain

Novel biochemical aspects of neurodegeneration in Parkinson's disease.

neurological diseases • biochemistry • metabolism

Guido Bommer is Research Associate at the FNRS and professor at the Université catholique de Louvain. With his research group at the de Duve Institute, he studies the role enzymes, the function of which is still unknown, might play in cancer metabolism. Unexpected results regularly lead Guido Bommer to look at other diseases.

This WELBIO project is focused on Parkinson's disease (PD), specifically on an enzyme that is potentially involved in both cancer and Parkinson's disease. The project aims to investigate how this enzyme protects cells from stress, and how metabolic damage might link metabolic activity with protein aggregation and sensitivity to oxidative stress observed in PD. This study may have a significant impact on our understanding of the pathogenesis of Parkinson's disease and might reveal new therapeutic targets.

AMANDINE EVERARD
UCLouvain

Identification of gut microbes and metabolites involved in the gut-to-brain axis controlling hedonic and reward system during food intake.

metabolic diseases • pharmacology • intestinal microbiota

Amandine Everard is Research Associate at the FNRS and professor at the Université catholique de Louvain. Her work at the Louvain Drug Research Institute focuses on the hypothesis that the bacteria of the intestinal microbiota are involved in the regulation of food intake. Her research on the link between intestinal microbiota, nutrition and the host in the context of obesity and metabolic diseases has led her to further investigate the intestine-to-brain axis.

During this project, Amandine Everard will aim to identify the bacteria that are specifically involved in the pleasure and reward systems. The control of food intake depends on a "dialogue" between bacteria and the host; the mechanisms of this dialogue will be investigated. The role and impact of specific metabolites will also be analysed.

ESTEBAN GURZOV

ULB UNIVERSITÉ LIBRE DE BRUXELLES

Early diagnosis: can protein tyrosine phosphatase activity predict obesity-induced hepatocellular carcinoma?

cancer • biological analysis • metabolism

Esteban Gurzov is Research Associate at the FNRS. At the Université libre de Bruxelles, he leads the " Signal Transduction and Metabolism " laboratory of the ULB Center for Diabetes Research. His laboratory aims to understand molecular basis of metabolic pathophysiology. He investigates more specifically the role of phosphatases in metabolic diseases and their complications, such as cancer.

This project is focused on obesity-induced hepatocellular carcinoma. Recent studies suggest that, under oxidative stress, protein tyrosine phosphatases play a key role in the transition from obesity to non-alcoholic steato-hepatitis and hepatocellular carcinoma. The expression and oxidation of protein tyrosine phosphatases will be characterised in human liver biopsies, based on which a risk profile will be defined for early diagnosis, stratification and personalised treatment of obesity-associated hepatocellular carcinoma.

RÉGIS HALLEZ

UNIVERSITÉ DE NAMUR

Molecular characterization of the cellular processes targeted by the second messenger (p)ppGpp in bacteria.

antibiotic resistance • bacteriology • molecular biology

Régis Hallez is Research Associate at the FNRS and professor at the Université de Namur. His work at the Namur Research Institute for Life Sciences focuses on the regulation of bacterial stress by the guanosine penta- or tetra-phosphate (p)ppGpp. This "alarmone", which is produced by virtually all bacteria in response to fluctuations in nutrient availability, profoundly reshapes the bacterial physiology.

This project aims to identify and characterise the cellular machineries targeted by the (p)ppGpp in bacteria. The (p)ppGpp targets involved in the survival of bacteria upon starvation or in reaction to antibiotics will be identified. This project will open avenues towards the development of new therapeutic approaches against multiple drug-resistant (MDR) bacteria.

CONTINUATION GRANTS

CÉDRIC BLANPAIN

ULB UNIVERSITÉ LIBRE DE BRUXELLES

Mechanisms controlling epithelial–mesenchymal transition related tumor heterogeneity.

cancer • stem cell biology • epithelial–mesenchymal transition

Cédric Blanpain is professor at the Université libre de Bruxelles. He heads the Stem Cells and Cancer Laboratory, which studies the role of stem cells in development, homeostasis and cancer. He studies the stem cells involved in development and tissue repair processes, and traces the "fate" of these cells, i.e. the process whereby they differentiate and form the tissues. He uses the same methods to uncover the cells that cause common human cancers and to understand the mechanisms behind tumour heterogeneity, metastasis and resistance to therapy.

This project focuses on epithelial–mesenchymal transition (EMT), a process whereby tissue cells lose their epithelial properties and acquire mesenchymal characteristics. The EMT is associated with tumour initiation, invasion, metastasis and resistance to therapy. During his previous WELBIO project, Cédric Blanpain and his colleagues notably demonstrated that the EMT is not a binary process, but occurs through distinct cellular states including hybrid epithelial and mesenchymal states. New models were designed and will enable, during the course of this new project, a more detailed study of EMT molecular mechanisms, metastatic progression and resistance to therapy, with a focus on a number of key molecular players. This project will uncover new therapeutic opportunities to treat cancer.

ALAIN CHARIOT

LIÈGE université

tRNA modifying enzymes and their targets in immunity and cancer.

cancer • protein reprogramming • cell signalling

Alain Chariot is Research Director at the FNRS and professor at the Université de Liège. Within the GIGA research centre, he investigates the role of genes that are not well characterised,

but which are associated with genetic disorders when they lose their function, in cancer models..

This project focuses on protein reprogramming (the modification of the translation "programme" of messenger RNA into proteins), which impacts immune responses and cancer. Modifications of transfer RNAs (tRNAs) play an essential role in this reprogramming. With his group, Alain Chariot showed the role of a tRNA modifying enzyme, the Elongator protein complex, in different cancer models. Currently, he studies the proteins whose translation depends on Elongator. This projects aims to understand their role in oncogenic pathways. Another part of the project focuses on the role of tRNA modifications in immune responses. He will further study the mechanisms by which Elongator impacts the differentiation of Tuft cells. These cells are involved in the immune response to parasites in the intestine.

JEAN-FRANÇOIS COLLET

UCLouvain

Exploring the cell envelope of Escherichia coli, a compartment that is an attractive target for innovative biotechnological and biopharmaceutical approaches.

antibiotic resistance • bacteriology • cell envelope

Jean-François Collet is professor at the Université catholique de Louvain. His work at the de Duve Institute aims to understand how bacterial cells defend themselves against external aggressions, in order to improve our ability to combat them. He studies, in particular, two types of stress: oxidative stress (e.g. by bleach) and envelope stress. His research is based primarily on Escherichia Coli, a Gram-negative bacteria. Gram-negative bacteria are characterised by a double membrane. The outer membrane is separated from the inner membrane by the periplasm, which contains a polymer named proteoglycan.

This project aims to understand how Gram-negative bacteria assemble their envelope, detect their envelope is damaged and respond to this stress. Jean-François Collet has already shown, in particular during his previous WELBIO projects, several mechanisms involved in these processes The expertise he developed, and the preliminary data and the molecular tools established, will now enable the resolution of two major mysteries: the physiological importance of the connection between the outer membrane and the peptidoglycan and the mechanism that allows lipoproteins to cross the outer membrane. This research will serve as a foundation for the identification of new antibiotics, as well as the engineering of optimised bacteria strains for protein and DNA production.

DECIO L. EIZIRIK

ULB UNIVERSITÉ LIBRE DE BRUXELLES

Beta cell splicing signature in diabetes.

diabetes • endocrinology • alternative splicing

Decio L. Eizirik is professor at the ULB Center for Diabetes Research, Université libre de Bruxelles. His research aims to understand the pathogenesis of type-1 diabetes (T1D), more specifically the role of diabetes genes, endoplasmic reticulum stress and alternative splicing in pancreatic β cell deficiencies.

His project is focused on alternative splicing, a process that affects more than 90% of human genes. This provides cells with an extraordinary capacity to modify their transcriptome and proteome in response to intra- and extra-cellular signals. By producing new proteins, the cells can generate new epitopes, which may contribute to triggering an immune response. During his previous WELBIO project, Decio L. Eizirik has shown that the pro-inflammatory cytokines interleukin beta and interferon gamma, which are released by immune cells in pancreatic islets at the advanced stages of insulitis, change the expression of alternative splicing-regulating proteins. Consequently, a large amount of splicing variants are produced in β cells. This leads to the generation of neo-antigens, which are recognised by cytotoxic T lymphocytes invading the islets of patients with type-1 diabetes, thus amplifying the autoimmune assault. This new project aims to characterise the alternative splicing regulatory networks and to identify the mRNA splice variants acting as neo-epitopes for T-cell activation. These variants will be validated as biomarkers for disease and as potential targets for new treatments based on splicing modulations.

BENOÎT VAN DEN EYNDE

UCLouvain

Identification and characterization of new cancer immunotherapy targets discovered by in vivo genomic pool screening.

cancer immunotherapy • tumour microenvironment

Benoît Van den Eynde is professor at the Université catholique de Louvain. His research at the de Duve Institute focuses on tumour immunology, in particular, on the mechanisms for the production of tumour antigens and on the mechanisms whereby tumours escape immune attacks

This WELBIO project focuses on the immunosuppressive mechanisms whereby the tumour microenvironment limits the efficacy of cancer immunotherapy. Benoît Van den Eynde and his team have designed a model (known as the TiRP model) of genetically engineered melanomas, which are particularly immunesuppressive. This model is used to screen for the genes responsible for this immunosuppression and, from there, investigating the immunosuppressive mechanisms. The first candidate genes were identified during Benoît Van den Eynde's previous WELBIO project. This new project will make it possible to characterise the mechanisms responsible for the immunomodifying effect of these genes, as well as to search for other candidates that could be used as a target for immunotherapy. During the previous project, an existing drug appeared to improve immunotherapy in different tumour models. Another part of this new project will be dedicated to the mechanism by which this drug acts. This project is expected to open new avenues for the development of anti-cancer medications.

MIIKKA VIKKULA

UCLouvain

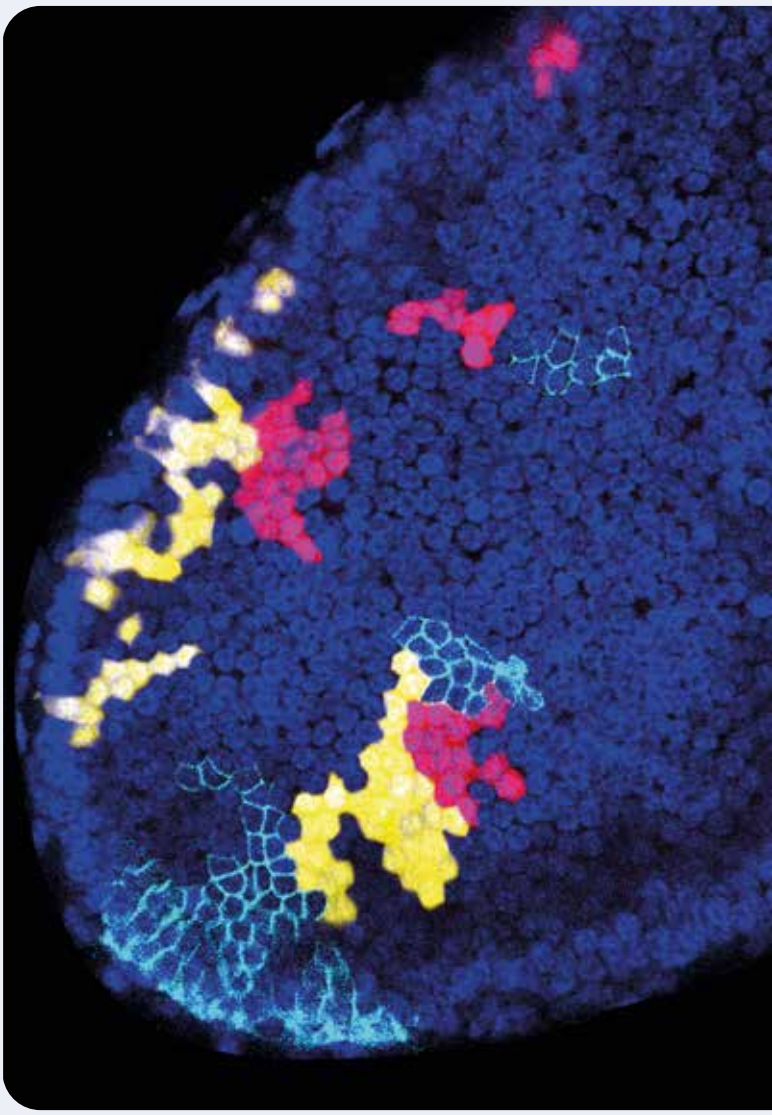
Towards novel treatments for primary lymphedema: from identification of genetic causes to in vivo modeling and preclinical trials.

lymphoedema • genetics • bioinformatics

Miikka Vikkula is professor at the Université catholique de Louvain. His research at the de Duve Institute aims to identify and characterise genetic variants that cause certain human diseases.

This projects draws on the results of Mikka Vikkula's previous WELBIO projects, focusing on anomalies of the vascular system, more specifically primary lymphoedema, a chronic, debilitating disease that results from the abnormal development and/or functioning of the lymphatic system. The lymph is not evacuated from the interstitial tissue and accumulates, most commonly in the lower limbs. This causes dilatation and fibrosis, and increases the risk of secondary infection. Lymphoedema affects more than one million people in Europe. There is currently no cure available.

This project aims to identify and characterise genetic causes of lymphoedema. It is not limited to monogenic causes, but also identifying digenic mutations that will be investigated by developing statistical, computational and machine-learning methods. The mechanisms whereby these mutations induce lymphoedema will be studied in murine models, which will also be used to develop pre-clinical models for testing treatment strategies.



14 PROJECTS RENEWED AFTER MID-WAY ASSESSMENT

FRFS-WELBIO research projects are intended to be four years long and divided into two periods of two years. The renewal of the research project is based on an evaluation of the intermediate scientific report by the Scientific Commission that assessed the initial application. In 2019, the 14 FRFS-WELBIO projects that started with the 2017 call for projects were renewed for their second two-year period.

ADVANCED GRANTS

JEAN-LUC BALLIGAND
UCLouvain

Cardiac Aquaporin-1: a new regulator of myocardial remodeling.

cardiovascular diseases • physiology • molecular transport

Jean-François Balligand is professor at the Université catholique de Louvain. His work at the Institute of Experimental and Clinical Research focuses on cardiac remodelling mechanisms, a collection of molecular and biological modifications of the cardiac muscle under stress (for example, a heart attack). This remodelling, which is characterised by cardiac hypertrophy, leads to heart failure. Jean-Luc Balligand and his team observed that cardiac cells express several water-channel isoforms on their plasma membrane – aquaporins – and discovered, unexpectedly, that mice deficient in Aquaporin-1 (Aqp-1) have a smaller heart and, when under cardiovascular stress, do not develop cardiac hypertrophy or fibrosis, phenomena that typically lead to heart failure.

The first two years of this WELBIO project shows that Aqp-1 not only allows for the transportation of water, but also hydrogen peroxide (H2O2), a molecule that is essential for mediating hypertrophic signals. A structural analysis of the Aqp-1 pore helped to identify the amino acids that are needed for the passage of H_2O_2 . These results have shown that Aquaporin-1 is, above all, a "peroxiporin", that is, a channel for H_2O_2 .

The next two years of this WELBIO project will allow for the study of cell signalling "downstream" of the Aqp-1/ H_2O_2 tandem in specific myocardial cells. The link between genotype and phenotype will be investigated for different polymorphisms of Aqp-1, in large cohorts of individuals that are at risk, or are not at risk, of heart diseases. Given the general expression of Aqp-1 and the pleiotropic role of the H_2O_2 signalling, this work may open up avenues for therapeutic applications in a large number of diseases, relating to the heart and otherwise.

STEFAN CONSTANTINESCU
UCLouvain

Targeting mechanisms of pathogenic mutant calreticulin signaling via thrombopoietin receptor and JAK2 in myeloproliferative neoplasms.

cancer • cell signalling • chaperoness

Stefan Constantinescu is professor at the Université catholique de Louvain. His work at the de Duve Institute is dedicated to myeloproliferative neoplasms (MPNs), a group of hematopoietic stem cell pathologies that lead to an excessive production of blood cells. Certain types of MPNs are caused by mutations in the calreticulin gene, a chaperone protein.

The first two years of this project made it possible to describe a novel oncogenic mechanism whereby the mutant calreticulin (mCALR) activates the thrombopoietin receptor (TpoR).

The mCALR-TpoR complex is abnormally brought to, and maintained on, the cell surface, where it continuously activates the JAK-STAT intra-cellular signalling path, which leads to the proliferation of blood stem cells. This discovery is the first example of a chaperone protein being transformed into an oncogene via a change in its specificity. This gives it a damaging chaperone activity. The next two years will make it possible to investigate the structural basis of the TpoR-mCALR interaction and attempt to inhibit this complex on the cell surface using small molecules and immunotherapy. They will also assess the effects of the secreted mCALR on patients, especially on blood stem cells.

PIERRE COULIE

UCLouvain

Cytolytic CD8 T lymphocytes in severe forms of human autoimmune diseases, towards diagnostic markers and new therapeutic avenues.

autoimmune diseases • immunology • T-cells

Pierre Coulie is professor at the Université catholique de Louvain. His work at the de Duve Institute focuses on tumour immunology. His expertise in CD8 cytolytic T-cells and the antigens they recognise is used here to study severe autoimmune diseases, the cause of which is as-yet unknown and for which there is not yet any satisfactory treatment.

This project aims to study the clonality, function and specificity of CD8 cytolytic T-cells in the diseased tissue of patients with severe forms of rheumatoid arthritis (RA) and lupus nephritis (LN). The hypothesis is that CD8 T-cells are not responsible for the onset of these two autoimmune diseases, but that their cytolytic activity plays a significant role in the chronic or severe breakdown of tissues. CD8 T-cells have been extracted from biopsies of diseased tissues. Their diversity, function and target antigen have been studied using a single cell approach. During the first two years of this project, methods were developed in order to maximise cell recovery and the detection of the genes expressed by a cell. The limited number of cells that could be isolated from biopsies posed a real challenge. CD8 T-cell clones were isolated in two cases of lupus nephritis. These were enriched in the kidney, by comparison to the blood, which suggests that they are specifically activated in the kidney. The next stage of the project aims to study the specificity of the receptors for these T-cells in more detail.

FRANÇOIS FUKS

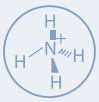
ULB UNIVERSITÉ LIBRE DE BRUXELLES

Unravelling the Role of RNA Epigenetics in Health and Disease.

cancer • RNA epigenetics • high-throughput sequencing

François Fuks is professor at the Université libre de Bruxelles and director of the ULB Cancer Research Centre. His work is dedicated to epigenetics and its role in cancer. Epigenetic alterations are changes in DNA and histones, which do not modify the DNA sequence itself. These epigenetic alterations play a key role in human diseases, such as cancer. DNA and histone modifications have long been considered to be the pillars of epigenetics. However, a brand-new field of research is emerging: RNA epigenetics.

This WELBIO project aims to understand the fundamental principles that underpin RNA epigenetics and its involvement in oncogenesis. The first two years of the project helped identify the target of one of these modifications, hydroxymethylation of RNA, in embryonic stem cells and breast cancer. The next stage of the project will make it possible to continue this work and understand the role of another RNA modification, the methylation of adenosine (m6a), in breast cancer and, more specifically, metastatic progression.



ANNA MARIA MARINI

ULB UNIVERSITÉ LIBRE DE BRUXELLES

Rh factors and the control of membrane permeability to ammonium.

cancer • cellular biology • molecular transport

Anna Maria Marini is a Senior Research Associate at the FNRS. Her work at the Institute for Biology and Molecular Medicine (Université libre de Bruxelles) is dedicated to the transport of ammonium ions ((NH_4^+) and the role this transport plays in various physiological and pathological contexts.

Ammonium ions are a major source of nitrogen for microorganisms and plants. In animals, it is primarily described as a pH regulator and toxic waste . In recent years, Anna Maria Marini and her team have been able to demonstrate that ammonium is much more than metabolic waste. It can promote cell

proliferation, in particular by stimulating the TOR signalling pathway, which is important for controlling growth and metabolism. The early years of the project made it possible to develop our understanding of the molecular mechanism that allows ammonium to cross biological membranes, thanks to transport proteins from the "Mep-Amt-Rh" family, to which the human Rh (Rhesus) factors belong. By deprotonating the ammonium ion during its translocation, these proteins acquire a specificity that allows them to differentiate between the ammonium ion and the potassium ion (with an identical charge and similar size). The next two years will make it possible to develop tools that can target the activity of Rh factors, in order to study the impact of their activation or inactivation.

PIERRE VAN DER BRUGGEN

UCLouvain

At the crossroads of cancer and autoimmunity: novel therapeutic targets on exhausted human T cells.

cancer • immunology • T-cells

Pierre van der Bruggen is professor at the Université catholique de Louvain. With his team at the de Duve Institute, he is attempting to understand why cytotoxic T-cells are not successful in killing tumour cells.

In chronic infections and cancer, T-cells are exposed to persistent antigens and inflammatory signals. This prolonged exposure is often associated with the deterioration of T-cell function, which in murine models is called "T-cell exhaustion". It is still not clear if this concept of T-cell exhaustion can be transposed to the biology of human tumours. This WELBIO project aims to research this issue. The functions and phenotypes of CD8 T-cells that infiltrate human ovarian carcinomas will be studied in-depth, particularly in terms of their expression of transcription factors. The role of specific transcription factors will then be studied, as well as the function of tumour T-cells. A murine model with human cancer will be used to monitor the behaviour of tumour T-cells on a functional and molecular level.

STARTING GRANTS

BENJAMIN BECK

ULB UNIVERSITÉ LIBRE DE BRUXELLES

Characterization of the Molecular Core of Esophageal Cancer.

cancer • transcriptomics • tumour heterogeneity

Benjamin Beck is a Research Associate at the FNRS and a member of the ULB Cancer Research Centre and the Institute for Interdisciplinary Research in Human and Molecular Biology (Université libre de Bruxelles). His laboratory studies oesophageal cancers.

It has been well established that tumours are heterogeneous. This heterogeneity partially reflects the different mutations that are found in tumour cells. Recent sequencing data has led to the identification of three different groups of spinocellular carcinoma-type (SCC) oesophageal cancers. It is important to determine whether these different mutations cause phenotypic differences and if there are targets that could be used to treat SCC, no matter its mutation. To this end, it is necessary to develop murine models that reproduce, as closely as possible, the heterogeneity of human SCC.

Using a multi-disciplinary approach in various murine SCC models, this project aims to identify the transcripts (the "transcriptional nucleus") needed for tumour growth and progression, as well as resistance to treatment. Benjamin Beck and his colleagues will study human cell lines of oesophageal SCC with mutations that correspond to the three identified sub-groups, in order to determine to what extent these transcriptomes are retained in human tumours. Finally, the functional aspect of this transcriptional nucleus will be studied using gene invalidation on murine and human cancer cells from various models. The results of these experiments will result in crucial data about the specificity of SCC subgroups and the therapeutic potential of the components of the transcriptional nucleus of these cancers.

PIERRE CLOSE

LIÈGE université

Translation reprogramming through wobble tRNA modification in cancer.

cancer • protein reprogramming • transfer RNA

Pierre Close is Research Associate at the FNRS and manages the Cancer Signalling Laboratory in the GIGA research centre (Université de Liège).

The regulation of mRNA translation has emerged as a central mechanism driving the adaptation of tumour cells during cancer progression and response to treatment. Cancer cells thus adapt to a hostile environment using a protein reprogramming mechanism (the modification of the mRNA translation "programme" into proteins).

This project is dedicated to the modification of transfer RNA (tRNA) on their "wobble" base (the 5' base of the anti-codon). The project is based on the hypothesis that this modification represents a new mechanism, which allows protein translation to be reprogrammed in cancers and supports the expression of specific proteomes that are required for the survival of cancer cells, the formation of metastases and resistance to treatment. During the first two years, Pierre Close and his team have discovered the central role of tRNA base modification in the resistance of melanoma to targeted therapies, through the establishment of specific oncogenic proteomes. It has been demonstrated that targeting this process is an important therapeutic option in patients with resistant melanoma. The next stage of the project will study codon-specific translation during cancer development and in the tumour micro-environment.

ABEL GARCIA-PINO

ULB UNIVERSITÉ LIBRE DE BRUXELLES

Cellular and molecular bases of the regulation of bacterial persistence by (p)ppGpp synthetases / hydrolase.

bacteriology • persistence • structural biology

Abel Garcia-Pino is professor at the Université libre de Bruxelles. He manages the Structural and Biophysical Biology lab and studies the molecular bases for the survival of bacteria.

Many of the difficulties associated with treating infectious diseases with antibiotics are not caused by an intrinsic genetic resistance, but rather the presence of quiescent cells called "persisters". Persistence is a physiological restart mechanism that allows certain cells in an isogenic bacterial population to resist a wide variety of stresses. The ppGpp (guanosine tetraphosphate) molecule is one primary regulator of the stringent response, as well as the effector that allows the shift towards persistence. Understanding the mechanisms that regulate ppGpp synthesis is still one of the most significant problems for modern microbiology. This project aims to understand the key stages in the molecular mechanisms behind ppGpp synthesis and hydrolysis in various species of bacteria, by studying the regulatory interactions between RelA and SpoT proteins, which control ppGpp levels during persistence. This work will make it possible to develop RelA/SpoT inhibitors that have the potential to inhibit persistence.

THOMAS MARICHAL

LIÈGE université

Epithelial cells as master regulators of mucosal homeostasis: unraveling the regulatory role of Rab guanine nucleotide exchange factor-1 (RABGEF1).

asthma • immunology • single cell sequencing

Thomas Marichal is Research Associate at the FNRS and manages the Immuno-physiology Laboratory in the GIGA research centre (Université de Liège).

Epithelial surfaces form a barrier between mammals and their environment and constitute the first line of defence against micro-organisms, foreign antigens and other environmental assailants. In the mucosa, homoeostasis relies on regulated interactions between the environment, epithelial cells (EC) and immune cells. Thomas Marichal's team aims to understand how epithelial cell (EC) dysfunction can contribute to inflammatory diseases, such as chronic intestinal inflammations or asthma. During the first two years of the WELBIO project, they have uncovered the crucial role of the RabGEF1 protein in maintaining intestinal homoeostasis in mice, by reducing the signalling dependent on MyD88 and p38, as well as producing chemokines via intestinal epithelial cells. The next stage of the project will focus on the pulmonary epithelium. They will study how pulmonary epithelial cells are involved in pulmonary homoeostasis and allergy-induced asthma. This will involve single-cell RNA sequencing techniques, as well as in vivo tools.

BENOÎT VANHOLLEBEKE

ULB UNIVERSITÉ LIBRE DE BRUXELLES

Deciphering the regulatory mechanisms of blood-brain barrier function.

neurological diseases • blood-brain barrier • neurovascular signalling

Benoît Vanhollebeke is professor at the Université libre de Bruxelles and manages the Neurovascular Signalling Laboratory at the Institute for Biology and Molecular Medicine.

Brain function depends on close communication between the nervous system and the vascular system. The endothelial cells that comprise the brain's blood vessels form a complex tube network that keeps neurons – which consume large amounts of energy – within a few micrometres of the nutritional elements and dissolved gases that are transported by the blood. The interface between the brain and the vascular system is very carefully regulated, in order to isolate synaptic communication from varying blood types. Thanks to its neuroprotective function, this blood-brain barrier (BBB) also acts as an obstacle to medications, which are unable to reach their target in the central nervous system. Conversely, BBB deficiencies contribute to neurological disorders, such as strokes or neurodegenerative diseases.

Benoît Vanhollebeke and his colleagues aim to gain a better understanding of neurovascular signalling, under normal and pathological conditions. They have recently characterised a specific receptor complex for endothelial brain cells. This complex is a major regulator of the neurovascular physiology of the brain. This project aims to study the signalling that relies on this receptor in the early stages of neurovascular development, as well as in the adult brain. A zebrafish model will be used to identify BBB regulators.

CONTINUATION GRANTS

FABRICE BUREAU

LIÈGE université

Lung regulatory macrophages: phenotype, function and therapeutic.

asthma • immunology • cell therapy

Fabrice Bureau is professor at the Université de Liège and manages the Cellular and Molecular Immunology Lab at the GIGA research centre.

Fabrice Bureau and his colleagues have recently demonstrated that interstitial macrophages (IM) play an important role in maintaining pulmonary immune homoeostasis. These cells impede the development of adaptive immune responses to inhaled allergens. During his previous WELBIO project, Fabrice Bureau demonstrated that IM play an important role in mediating the immunotherapeutic effects of CpG motifs in bacterial DNA. CpGs have the unique ability to induce a strong expansion of IM and to give them hyper-suppressive properties. The aim of this second project is to further develop the characterisation of IM in mice and humans. The first two years made it possible to create transgenic murine models, in order to formally demonstrate the regulatory role of IM and IL-10. Initial analyses of human samples have highlighted several macrophage populations, including potential human regulatory macrophages. The next stage of the project will aim to generate these regulatory macrophages ex vivo, with a view to using them to treat asthma in humans and other immune diseases.

PATRICE CANI

UCLouvain

Targeting NAPE-PLD, novel bioactive lipids and specific gut microbes to improve cardiometabolic disorders associated with obesity.

metabolic diseases • physiology • intestinal microbiota

Patrice Cani is Senior Research Associate at the FNRS and professor at the Université catholique de Louvain. He works at the Metabolism and Nutrition laboratory in the Louvain Drug Research Institute.

Obesity and being overweight are associated with various cardio-metabolic risks (steatosis, diabetes, inflammation). During his first WELBIO project, Patrice Cani and his colleagues demonstrated that intestinal microbiota contributes to the development of these disorders, in particular, by altering the production of bioactive lipids, including endocannabinoids (EC). The EC system plays a key role in regulating energy, carbohydrates and lipid metabolism, as well as inflammation and food intake (by acting on the gut-brain axis).

In parallel to the work of the EC system, new bacteria have been isolated during this WELBIO project. The next two years will allow for a study of the impact of these new bacteria on metabolic disorders associated with obesity, type-2 diabetes and disorders of the intestinal barrier.

MARC PARMENTIER

ULB UNIVERSITÉ LIBRE DE BRUXELLES

Chemerin and its receptors in tumoral angioge.

cancer • cell signaling • angiogenesis

Marc Parmentier is professor at the Université libre de Bruxelles and manages the Institute of Interdisciplinary Research (IRIBHM).

Marc Parmentier and his colleagues have demonstrated that chemerin, a multifunctional protein involved in recruiting leukocyte populations, has anti-tumour properties in various animal models. During his first WELBIO project, Marc Parmentier and his colleagues noted that chemerin inhibits the neoangiogenesis process. Since this is a key process in tumour progression, this inhibition subsequently impedes the effective vascularisation of tumours and their growth. This second project aims to more closely study how chemerin affects the angiogenesis process in physiological conditions and during tumour development, by using a collection of genetic models in mice and zebrafish. The next two years will allow for the development of small agonist ChemR23 molecules (the main functional receptor for chemerin) and to test the therapeutic potential of these agonists against cancer.

WELBIO RESEARCHERS

WELBIO researchers are FRS-FNRS fellows or nominated researchers in a university in the French Community of Belgium. In late 2019, 12 of the 28 WELBIO researchers were FRS-FNRS fellows (research associates, senior research associates or research directors); the others were directly funded by their university.

The excellent quality of the results obtained by WELBIO researchers is demonstrated by their publications and is highlighted, year after year, by the scientific awards and other prestigious funding received. In 2019,

David Alsteens (UCLouvain) received the Heinrich Emanuel Merck Award for Analytical Science.

Cédric Blanpain (ULB) received the biennial prize for biomedical research from the AstraZeneca Foundation, for his research on stem cells and tumour heterogeneity. He was also awarded the Collen-Francqui Chair 2018–2019 at the Faculty of Medicine and Pharmacology at the Vrije Universiteit Brussel (VUB).

Fabrice Bureau (ULiège) was named Vice-Rector for Research at the Université de Liège.

Stefan Constantinescu (UCLouvain) was elected as a full member of the Belgian Royal Academy of Medicine.

Pierre Coulie (UCLouvain) was elected President of the Belgian Royal Academy of Medicine for the year 2019.

Decio L. Eizirik (ULB) was given a prestigious Visiting Professor Chair at the Danish Diabetes Academy (DDA). Denmark is a country at the forefront of diabetes research and the Danish Diabetes Academy is an international benchmark in this field. Decio L. Eizirik was also appointed *senior research fellow* at the Lilly Diabetes Center of Excellence in the IBRI (Indiana Biosciences Research Institute) Diabetes Center.

Abel Garcia-Pino (ULB) was awarded a European Research Council(ERC) Consolidator Grant. His project concerns multi-resistant bacteria.

Sophie Lucas et son équipe de l'Institut de Duve (UCLouvain) received the prestigious GSK prize from the Academy of Medicine.

Benoit Vanhollebeke (ULB) was also awarded an ERC Consolidator Grant. His project concerns the blood-brain barrier.

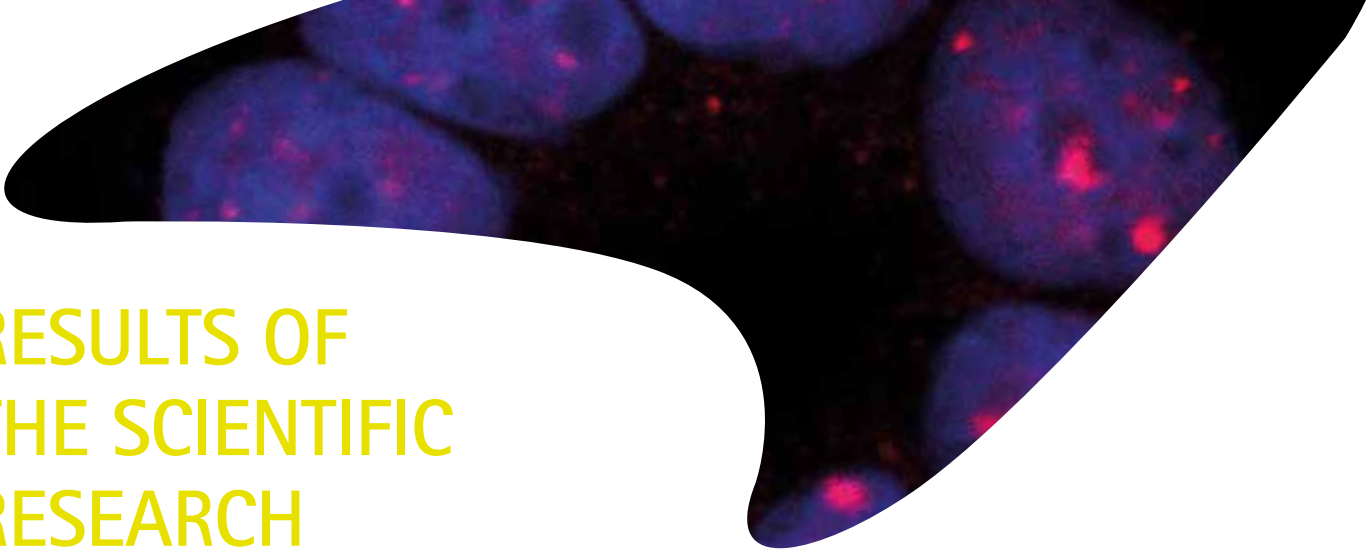
Kristel Van Steen (ULiège / WELBIO 2015-2019) is the coordinator of an ITN (Innovative Training Network) project that is financed (2019–2023) under the framework of the European Union's Marie Skłodowska-Curie actions (MSCA). This project (TranSYS) aims to train young researchers about the interdisciplinary tools needed to analyse Big Data, with a view to developing customised medicine.

RESEARCH TEAMS

Between 01 February 2011 and 31 December 2019, **599 people** have worked for WELBIO projects, alongside the principal investigators. The majority (3/4) were scientists, who were supported in their work by lab technicians.

Approximately **40% of the staff** is subsidised by WELBIO; the others are supported by the FNRS, the FRIA, Télévie, the European Research Council, the Anti-Cancer Foundation or universities.

In late 2019, **182 individuals** were working alongside WELBIO researchers with projects in progress. Thirty-eight scientists and nine lab technicians are beneficiaries of a contract directly linked to a WELBIO project, which represents a total of **45 FTE**.



RESULTS OF THE SCIENTIFIC RESEARCH

SCIENTIFIC PUBLICATIONS

Our researchers published 74 articles in 2019; 26 of these were in the most prestigious journals (those with an impact factor greater than 10), such as Cell Stem Cell, Nature Genetics, Nature Chemical Biology, Nature Immunology, Trends in Cell Biology, Cancer Cell, Neuron, Gut or Blood.

This is a selection of articles that illustrate the variety and innovative nature of the discoveries.

RARE DISEASES

Emile Van Schaftingen (a WELBIO researcher at UCLouvain) and his team are showing that two rare genetic diseases, in which neutrophils are too scarce, are caused by a defect in metabolic repair functions that cause a build-up of toxic products. This defect in the "cleaning" of sugar metabolism makes the patients more likely to suffer infection. This discovery makes it possible for the researchers to propose a treatment for people who are suffering from this congenital neutropenia.

Veiga-da-Cunha, M. et al. (2019). Failure to eliminate a phosphorylated glucose analog leads to neutropenia in patients with G6PT and G6PC3 deficiency. Proceedings of the National Academy of Sciences of the United States of America, 116(4), 1241–1250.
https://doi.org/10.1073/pnas.1816143116

OBESITY

Patrice Cani (a WELBIO researcher at UCLouvain) and his team, in collaboration with researchers from Canada, Italy, France and the Netherlands, successfully targeted the enzyme that malfunctions in overweight and obese individuals, which prevents the transmission of the message "I'm not hungry anymore" to the brain.

Everard, A. et al. (2019). Intestinal epithelial N-acylphosphatidylethanolamine phospholipase D links dietary fat to metabolic adaptations in obesity and steatosis. Nature Communications, 10(1), 457.
https://doi.org/10.1038/s41467-018-08051-7

BACTERIOLOGY

Abel Garcia-Pino (a WELBIO researcher at Université libre de Bruxelles) and his colleagues in the Cellular and Molecular Microbiology Department at the ULB have provided the first experimental proof of a long-standing hypothesis concerning small bacterial operons, which code for toxins and their corresponding anti-toxins. These are known as Toxin-Antitoxin (TA) modules. The anti-toxins act as protein chaperones, which are able to trap toxins that are produced by the ribosome. The anti-toxin binds and neutralises the toxin via its so-called "intrinsically disordered" C-terminal regions (IDR). This work casts a new light on the regulation of bacterial transcription.

Jurènas, D. et al. (2019). Mechanism of regulation and neutralization of the AtaR–AtaT toxin–antitoxin system. Nature Chemical Biology, 15(3), 285–294.
https://doi.org/10.1038/s41589-018-0216-z

EMBRYOLOGY

Isabelle Migeotte, a WELBIO researcher (2015–2019) at the ULB, and her team describe major differences between mesoderm cells, depending on whether they migrate in embryonic or extra-embryonic regions. These results establish a molecular framework that makes it possible to understand how cells adapt to their three-dimensional environment by differentiating and, probably, how they modify it.

Saykali, B. et al. (2019). Distinct mesoderm migration phenotypes in extra-embryonic and embryonic regions of the early mouse embryo. ELife, 8.
https://doi.org/10.7554/eLife.42434

BLOOD CANCER

Stefan Constantinescu, a WELBIO researcher at UCLouvain, and his team describe a new mechanism by which mutants of a chaperone protein, calreticulin, cause blood cancers known as myeloproliferative neoplasms. This is a prime example of oncogenic "rogue" chaperones.

> *Pecquet, C. et al. (2019). Calreticulin mutants as oncogenic rogue chaperones for TpoR and traffic-defective pathogenic TpoR mutants. Blood, 133(25), 2669–2681.*
> *https://doi.org/10.1182/blood-2018-09-874578*

NEUROBIOLOGY

A team of researchers led by Pierre Vanderhaeghen, a WELBIO researcher (2011–2019) at the ULB and VIB-KULeuven, and his colleague, Jérôme Bonnefont, are shedding light on a new molecular mechanism that encourages differentiation in neural stem cells during brain development. They are thus discovering a "molecular switch" to neural stem-cell differentiation: to be or not to be... a neuron.

> *Bonnefont, J. et al. (2019). Cortical Neurogenesis Requires Bcl6-Mediated Transcriptional Repression of Multiple Self-Renewal-Promoting Extrinsic Pathways. Neuron, 103(6), 1096-1108.e4.*
> *https://doi.org/10.1016/j.neuron.2019.06.027*

ASTHMA

Thomas Marichal (an FRS-FNRS research associate and WELBIO and ERC researcher) and Fabrice Bureau (a WELBIO researcher), along with their teams at the GIGA of ULiège, have discovered a completely unexpected player that represents a common denominator in different pro-allergic environments (such as pollution or excess hygiene): specific neutrophils are recruited in the lung and are responsible for allergic sensitisation and the development of asthma. This discovery makes it possible to envisage new treatment options for preventing and treating allergic asthma.

> *Radermecker, C. et al. (2019). Locally instructed CXCR4hi neutrophils trigger environment-driven allergic asthma through the release of neutrophil extracellular traps. Nature Immunology, 20(11), 1444–1455.*
> *https://doi.org/10.1038/s41590-019-0496-9*

CYSTIC FIBROSIS

Cystic fibrosis, the most common terminal genetic illness in our part of the world, is caused by mutations in the gene coding for the CFTR protein. This is normally responsible for the balance of fluids in vital organs, such as the lungs or the digestive system. Cédric Govaerts (a WELBIO 2013–2017 researcher) and his team have successfully isolated different nanobodies that are able to stabilise the defective CFTR protein. This breakthrough opens up a brand-new avenue for developing medication that combats cystic fibrosis. By studying the properties of these molecules in detail, in particular, the atomic structures of the CFTR-nanobody complexes, the team has not only been able to understand the stabilising mechanism on a molecular level, but has also been able to propose a strategy for designing therapeutic molecules in a rational manner.

> *Sigoillot, M. et al. (2019). Domain-interface dynamics of CFTR revealed by stabilizing nanobodies. Nature Communications, 10(1).*
> *https://doi.org/10.1038/s41467-019-10714-y*

DIABETES

Decio L. Eizirik, a WELBIO researcher at the diabetes centre at the Université Libre de Bruxelles, and his team are clarifying the role of pancreatic beta cells in type-1 diabetes. This work makes it possible to understand the genetic bases of type-1 diabetes by explaining why the immune system attacks the beta cells under specific conditions.

> *Ramos-Rodríguez et al. (2019). The impact of proinflammatory cytokines on the β-cell regulatory landscape provides insights into the genetics of type 1 diabetes. Nature Genetics, 51(11), 1588–1595.*
> *https://doi.org/10.1038/s41588-019-0524-6*

METASTASES

A team of researchers led by Cédric Blanpain, a WELBIO researcher and professor at the Université libre de Bruxelles, are revealing the importance of tumour plasticity in metastases formation. They are proving that tumour cells undergo an epithelial-to-mesenchymal transition during the beginning of the metastasis process, but also an inverse transition at the site of the metastasis.

> *Revenco, T. et al. (2019). Context Dependency of Epithelial-to-Mesenchymal Transition for Metastasis. Cell Reports, 29(6), 1458-1468.e3.*
> *https://doi.org/10.1016/j.celrep.2019.09.081*

BRAIN

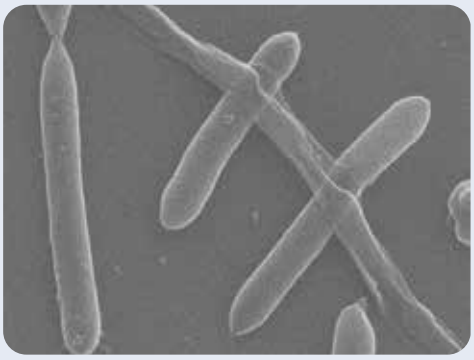
A team of researchers led by Pierre Vanderhaeghen and Vincent Bonin (VIB-KU Leuven, Université libre de Bruxelles and NERF) developed a novel strategy to transplant human neurons as individual cells into the mouse brain and to follow their development over time. They have successfully shown how human neurons can develop at their own pace, forming very accurate connections with the mouse neurons that surround them. This discovery sheds new light on the unique features of the human brain and opens up new avenues for treating lesions and studying brain diseases.

Linaro, D. et al. (2019). Xenotransplanted Human Cortical Neurons Reveal Species-Specific Development and Functional Integration into Mouse Visual Circuits. Neuron, 104(5), 972-986.e6.
https://doi.org/10.1016/J.NEURON.2019.10.002

Pierre Kroll, Le Soir - 22/11/2019

NEW TYPE OF BACTERIA NAMED AFTER LIFE SCIENCES RESEARCH INSTITUTE WELBIO

A newly discovered bacterium has been named after our research institute. The human gut microbe was discovered during a project led by Prof. Patrice Cani (WELBIO - FNRS - UCLouvain), who proposed the scientific name Dysosmobacter welbionis.



D. welbionis represents both a brand-new bacterial genus and species. The species name welbionis is derived from the WELBIO acronym (which stands for "Walloon Excellence in Life sciences and BIOtechnology"). The genus name Dysosmobacter means "bad-smelling rod", owing to the smelly nature of the rod-shaped microbe.

D. welbionis was isolated during a project aiming to investigate the link between gut microbes and metabolism. Like its sister species, D. welbionis produces butyrate, a type of short-chain fatty acid considered vital to maintaining a healthy gut. These types of butyrate-producing bacteria are increasingly being looked to for next-generation probiotics because of their anti-inflammatory properties.

Patrice Cani commented: "My post-doc Dr. Tiphaine Le Roy and I were very excited by the discovery of this novel human gut bacterium. We had the incredible chance, honor and privilege to propose a name for this new organism. WELBIO has been supporting my research for 7 years; this discovery was only made possible thanks to the institute's financial support. I immediately thought that this was a perfect time to honor WELBIO by naming the species welbionis. This means that, around the world, people are living with bacteria named D. welbionis; a nod to both Belgium and our Walloon region."

Le Roy, T. et al. (2019). Dysosmobacter welbionis gen. nov., sp. nov., isolated from human faeces and emended description of the genus Oscillibacter. International Journal of Systematic and Evolutionary Microbiology.
https://doi.org/10.1099/ijsem.0.003547

KEY FIGURES FOR 2019

66 M€
INVESTED IN RESEARCH SINCE 2011

5
CALLS FOR PROJECTS

65
RESEARCH PROJECTS

47
PRINCIPAL INVESTIGATORS

4
UNIVERSITIES

432
PUBLICATIONS INCLUDING

161
ARTICLES IN HIGH IMPACT FACTOR JOURNALS

PATENT APPLICATIONS FOR **10** INVENTIONS

8
ERC GRANTS

800 K€
REVENUE FROM INDUSTRIAL VALORISATION

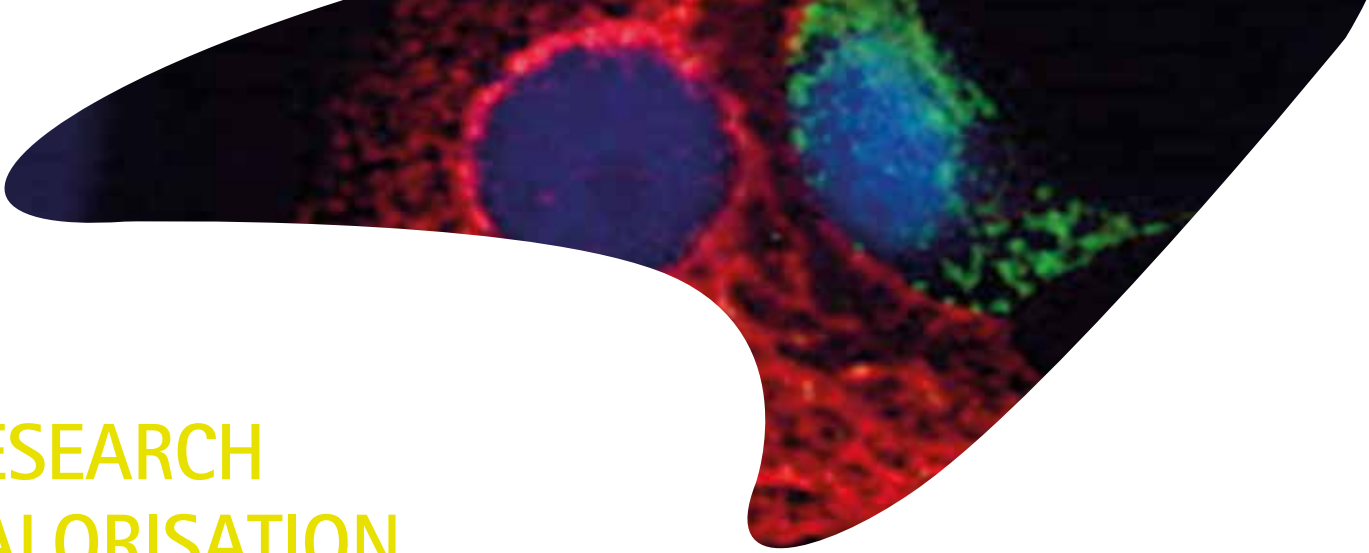
CANCER IMMUNOTHERAPY
1 LICENSE GRANTED &
1 INVESTIGATIONAL NEW DRUG

CANCER TREATMENT
1 SPIN-OFF

CELL THERAPY
1 BIOWIN APPLIED RESEARCH PROJECT

PERSONALIZED MEDICINE
1 ORIENTED RESEARCH PROJECT SPW RECHERCHE

RARE DISEASES
PATIENTS SUCCESSFULLY TREATED BY DRUG REPURPOSING



RESEARCH VALORISATION

The industrial valorisation of the research results constitutes the second essential element of WELBIO's mission. WELBIO projects are fundamental research projects.

These projects do not directly result in products or services that are sent to market. Our goal is that, thanks to WELBIO funding and individual support, WELBIO researchers will not only make significant scientific discoveries, but also develop new ideas, particularly in terms of treatment and diagnosis. These ideas must subsequently be explored further as part of translational, oriented or applied research projects. Partnerships must be established, or spin-offs created, to bring as many products or services as possible to market. Several projects have continued their journey in this way in 2019.

VALORISATION COMMITTEES

WELBIO's valorisation goal is implemented through individual support for researchers. A "valorisation committee" is formed for each project. This committee meets regularly to follow-up on any advances in the project, to reflect on any avenues for valorisation that emerge and to agree on a valorisation strategy for the results, particularly in terms of protecting intellectual property. The development and promotion of inventions are thus supported through close collaboration with members of the business-university interfaces in host universities.

INTELLECTUAL PROPERTY

Where possible, the intellectual property developed within WELBIO is protected by a patent application. Remember that the intellectual property of research results obtained through FRFS-WELBIO funding is the sole property of the university institutions.

As of 31 December 2019, patent applications were under way for ten inventions. In 2019, four patents reached the international phase (PCT) and three applications were published. A total of eight patent applications linked to WELBIO projects were published in late 2019:

WO/2014/037460: Immobilised Cyclindependent Kinase 4 Fusion proteins and uses thereof

WO/2015/015003: Anti-GARP protein and uses thereof

WO/2017/198685: Method for determining sensitivity to a CDK4/6 inhibitor

WO/2018/138358: PERK and IRE-1A inhibitors against neurodevelopmental disorders

WO/2018/167312: Detection, quantification and/or isolation of circulating tumor cells based on the expression of CD321 marker

WO/2019/175380: Antigenic peptides deriving from Secretogranin V and uses thereof for the diagnosis and treatment of type 1 diabetes

WO/2019/202149: sglt2 inhibitors for the treatment of neutropenia

WO/2019/207057: Combination of metformin and cyclophosphamide as an adjuvant in cancer immunotherapy

PROJECTS CONTINUING BEYOND WELBIO

A NEW IMMUNOTHERAPY FOR CANCER

One of the first projects financed by WELBIO (2011–2015) aimed to understand the mechanism used by regulatory T-cells (Treg) to prevent cytotoxic T-cells from killing tumour cells. This project made it possible to propose a new treatment strategy to block the Treg action and thus allow the immune system to eliminate tumour cells. This development continued within the framework of a research and licensing agreement with Argenx. The project has successfully passed through key pre-clinical stages and IND (Investigational New Drug) registration. The therapeutic antibody is now subject to an exclusive licence to the pharmaceutical giant AbbVie: ABBV-151 started clinical trials in early 2019 for patients with advanced solid tumours.

Furthermore, thanks to this successful industrial collaboration, WELBIO has received its first income from industrial development (€800,000 for this project).

NEW CANCER TREATMENT: AN INITIAL SPIN-OFF

The first WELBIO project (2011–2015) by Cédric Blanpain (ULB) aimed to study the role of tumour-based stem cells in the initiation, growth and recurrence of tumours after treatment. Results have shown the potential of a specific protein as a target for treating skin cancer. This work is the basis for the creation of the spin-off ChromeCure. In 2019, ChromaCure continued to develop molecules for treating advanced-stage cancers.

TOWARDS A CELLULAR THERAPY FOR THE CENTRAL NERVOUS SYSTEM: AN INITIAL BIOWIN PROJECT

Pierre Vanderhaeghen's (ULB) WELBIO projects (2011–2019) concerning the development of the central nervous system made it possible to develop a method for producing cortical neurons from induced pluripotent stem cells. In the long term, this technology makes it possible to envisage strategies for repairing brain lesions using cellular therapy. In the shorter term, human neurons that are produced in vitro may have applications, for example, to test new medications.

This technology has attracted the interest of industrial partners. A consortium has been established and obtained funding from the BioWin competitiveness hub for its iCone project. The iCone (iPSC-derived Cortical neurons) consortium comprises the companies MaSTherCell and Ncardia and the Pierre Vanderhaeghen (ULB) and Philippe Hubert (U Liège) labs. In 2019, this consortium reached a key stage and the project has now entered a larger-scale production phase using bioreactors.

BioWin, the Health Cluster of Wallonia (Belgium) is the regional reference player for all the stakeholders (companies, research centres and universities) involved in innovative R&D projects and/or skills development in the field of health biotechnology and medical technologies.

TOWARDS A DIAGNOSTIC COMPANION FOR A NEW CLASS OF TARGETED TREATMENT

Controlling the cell-division cycle in all cancers is primarily performed by cyclin-dependent kinase 4 (CDK4). Inhibiting this via targeted treatment specifically stops the proliferation of cells in which this enzyme is active. CDK4 inhibitors have been approved to treat advanced, hormone-dependent breast cancers. Given their efficacy as treatment and the multiple combinations that are currently envisaged with other treatments, CDK4 inhibitors will be expanded to other cancers. However, there is a lack of diagnostic tests to select which patients to treat.

Within the framework of one of the first WELBIO projects (2011–2015), Pierre Roger (ULB), Eric Raspé and their colleagues studied monitoring the cell cycle in cancer. They proposed a method that made it possible to identify patients that are likely to respond to treatment with a CDK4 inhibitor. This valorisation potential has been consolidated as part of a WELBIO Bridge Fund project. The development of this "companion diagnostic" is continuing in collaboration with OncoDNA, thanks to funding from the Walloon Region (the WALInnov programme from SPW Recherche). Moreover, a translational research project is being funded by the Fondation Contre le Cancer, in order to assess the phosphorylation of CDK4 in other types of cancer (including mesothelioma). The results obtained in 2019 make us hopeful for a favourable outcome to this project.

The goal of the Walloon Public Service is to implement the policy established by the Walloon government, within the scope and fields under its remit. The relevant research and technology services are integrated into SPW Économie Emploi Recherche.

A NEW METHOD FOR DETECTING CIRCULATING TUMOUR CELLS

Diagnosing cancer swiftly and easily is a major challenge. Cédric Blanpain (ULB) and his team identified a common marker for multiple cancers during their WELBIO 2015–2019 project. They developed a method for effectively detecting this marker and have validated its use for various kinds of cancers at various stages. The validation of this method continued as part of a WELBIO Bridge Fund, which came to an end in 2019. The industrial development of this invention will be continued in 2020.

The Bridge Fund allows WELBIO ASBL to independently formalise avenues for valorisation that arise during fundamental strategic research projects. This makes it possible to ensure continuity towards sources of funding for oriented/translational or industrial research. In this respect, it is a key tool for the WELBIO concept.

AN ANTI-DIABETIC DRUG THAT HAS BEEN REDIRECTED TO TREAT A RARE, HEREDITARY ILLNESS

Emile Van Schaftingen (UCLouvain) was supported by WELBIO between 2011 and 2019. His work focused on "metabolic repair", that is, mechanisms that allow cells to correct errors caused by enzymes with the wrong substrate.

In certain diseases, the number of neutrophils (white blood cells that kill bacteria) in the blood is reduced. These are known as "neutropenia". Patients suffering from these diseases are more susceptible to serious infections. This is what happens with a metabolic disease known as glycogen storage disease type 1B. The cause of neutropenia in this disease, as well as in a second, related rare disease, was discovered by the team led by Professors Maria Veiga-da-Cunha and Emile Van Schaftingen.

Researchers have shown that these patients' neutrophils are poisoned by a phosphorylated derivative of a glucose-like molecule (1-deoxyglucose). This is found in all of our blood. The genetic defect found in patients with this disease causes the phosphorylated derivative of 1-deoxyglucose to accumulate and significantly disturb the metabolism of the neutrophils. Based on this discovery, these researchers suggested treating this illness with an anti-diabetic drug. This makes it possible to reduce the concentration of glucose in the blood and eliminate greater quantities of it in urine. The 1-deoxyglucose is eliminated via the same mechanism. This reduces the build-up of its toxic derivative in the neutrophils. This work was published in PNAS in early 2019.

A clinical trial was approved and started in Belgium in collaboration with Dr Xavier Stephenne (UCLouvain – Saint-Luc). Other patients are treated this way, on the grounds of compassionate use, by doctors outside Belgium. The results are promising (publication is expected in 2020).

VISIBILITY

WELBIO IN THE MEDIA

Following their noteworthy publications, WELBIO researchers are regularly the subject of articles or reports in the media. These are some examples :

Decio L. Eizirik for his article in Nature Genetics in October 2019: "Auto-immune diseases: why diabetes instead of arthritis?", article published by Daily Science Brussels.

Thomas Marichal and **Fabrice Bureau** for their article in Nature Immunology in October 2019: "Asthma: a new discovery by ULiège researchers", report by RTC Télé Liège and "Asthma gradually reveals its secrets at ULiège", article published by Daily Science.

Pierre Vanderhaeghen for his article in Neuron in November 2019: "Human neuron grafts in a mouse brain integrate... by taking their time", report by JT RTBF; "Human neurons grafted into a mouse brain by Belgian researchers", article published by Le Soir; and "Human neurons successfully grafted in mice", article published by Daily Science.

Cédric Blanpain for his article in Cell Reports in November 2019: "Cancer: Belgian researchers discover how metastases migrate", article published by Le Soir; and "Tumour plasticity plays an important role in the formation of metastases", article published by Daily Science Brussels.

The **"Rentrée des chercheurs WELBIO"** organised on 21 October 2019 also inspired articles in L'Echo: "WELBIO: a useful observer of fundamental research in Wallonia", Daily Science: "After WELBIO, what about WELTECH and WELCHANGE? " and L'Avenir: "WELBIO finances 14 new projects"

PINT OF SCIENCE FESTIVAL 2019

The Pint of Science Festival invites scientists to bars to discuss their latest research and discoveries with the public, in an accessible, interesting and informal manner. As part of its mission to inform the public, WELBIO sponsored the 2nd Belgian edition of this festival, which saw contributions from Pierre Vanderhaeghen, Valérie Wittamer, Alban de Kerchove d'Exaerde, Patrice Cani and Abir Asmar (labs of Yves Dufrêne and Jean-François Collet).

PARTICIPATION IN THE STATE VISIT TO THE GRAND DUCHY OF LUXEMBOURG

At the request of Wallonia-Brussels International, Emile Van Schaftingen and Pierre Van Renterghem contributed to the academic seminar organised as part of the state visit to the Grand Duchy of Luxembourg. This seminar was organised to reflect on Belgian-Luxembourg collaborations regarding innovation in the health sector. Emile Van Schaftingen presented his collaborative research with Carole Linster, the director of the Enzymology and Metabolism group at the Luxembourg Centre for Systems Biomedecine. Pierre Van Renterghem presented the synergies between WELBIO and BioWin as an illustration of the innovation chain in life sciences in Wallonia.

Wallonie - Bruxelles International.be

Wallonia-Brussels International is the agency responsible for promoting Walloon and Belgian francophone talent abroad.

ADMINISTRATIVE AND FINANCIAL RESOURCES

MANAGEMENT OF WELBIO ASBL

BOARD OF DIRECTORS

The Board of Directors of WELBIO ASBL comprises representatives from academia, industry and the government. In accordance with Article 33 of WELBIO ASBL's regulations, directors do not receive any payment for their services, except reimbursement for all expenses incurred. The composition of the Board of Directors was amended in 2018. In late 2019, the Board was made up as follows:

Representatives of the Walloon government:

- **Cédric Volcke**, Research advisor, representing the Minister-President
- **Nathalie Leboeuf**, Advisor, representing the Minister for the Economye
- **Vincent Yzerbyt**, Professor, UCLouvain, representing the Minister responsible for research and new technologies

Representatives of the financial and industrial sector with an interest in life sciences:

- **Philippe Denoël**, Head of External R&D, GSK Vaccines
- **Frédéric de Sauvage**, Vice-President, Genentech
- **Jean Stéphenne**, director of several companies in the biotechnology sector, Chairman of the Board of WELBIO
- **Jean-Christophe Tellier**, CEO, UCB

Academic experts who are internationally recognised in the field of life sciences:

- **Louis Hue**, Professor, Université catholique de Louvain
- **Pierre Lekeux**, Professor, Université de Liège, Vice-President of the Board of WELBIO
- **Gilbert Vassart**, Professor, Université libre de Bruxelles

Representatives from the universities in the French Community:

- **Rudi Cloots**, Vice-Rector of Research, ULiège
- **Jean-Christophe Renauld**, Prorector of Research, UCLouvain
- **Oberdan Leo**, Vice-Rector of Research and Regional Development, ULB

Representatives of the Scientific Research Funds (FRS-FNRS):

- **Véronique Halloin**, General Secretary

Representing the Walloon Public Service – Operating Director for the Economy, Employment and Research (formerly DGO6):

- **Isabelle Quoilin**, Managing Director

The composition of the Board of Directors will be amended in 2020, following the government change. Professor Louis Hue has also decided to pass the torch. WELBIO thanks him kindly for his decisive role in the creation and operation of the Institute.

MANAGING DIRECTOR

Pierre Van Renterghem has been Managing Director of WELBIO since October 2015.

STRATEGIC FUNDAMENTAL RESEARCH FUNDS

In accordance with the decrees of 4 December 2012, which approved collaboration between the French Community and the Wallonia region in the funding of strategic fundamental research, WELBIO is currently integrated, as a delegate of Wallonia, into the FRFS (Strategic Fundamental Research Funds), as a strategic branch of Life Sciences. The FRFS is a fund associated with the FNRS. The Walloon government has made it responsible for overseeing the administrative and financial management of calls for projects for Wallonia's strategic research branch. WELBIO ASBL has been established as a valorisation platform for FRFS-WELBIO, for the strategic Life Sciences branch.

FINANCIAL RESOURCES

At the time of its creation on 12 December 2008 by the Walloon government, WELBIO was granted a starting budget of €15 million. In December 2012, the Walloon government and the French Community of Belgium decided to give WELBIO a minimum annual budget of €6 million. The WELBIO grant has been paid to FRFS since 2014. A sum that corresponds to 10% of this grant (reduced by 4% to cover the administrative operations of FRFS and the Scientific Commission) must subsequently be paid to WELBIO ASBL.

In practice, this grant is not paid systematically, or in its entirety, every year. The implementation of transversal management for the Strategic Fundamental Research Funds, which was decided by the Walloon government on 12 May 2016, made it possible to free up resources, in order to continue WELBIO's activities, in particular, launching the call for projects in 2017. In 2019, the Walloon government gave WELBIO multi-year funding for the first time. These new resources were added to the still-available reserves in FRFS and made it possible to launch a 5th call for projects. WELBIO's operations are thus guaranteed to continue until 30/09/2021.

Summary of WELBIO/FRFS WELBIO grants

"Re-WILL" project (Recherche d'Excellence – Walloon Institute for Life sciences Lead)	WELBIO asbl	€5 million	2009
	WELBIO asbl	€2.5 million	2009
	WELBIO asbl	€2.5 million	2012
	WELBIO asbl	€5 million	2013
2013 grant	WELBIO asbl	€1 million	2014
	WELBIO asbl	€2 million	2014
	WELBIO asbl	€3 million	2014
2014 grant	FRFS	€3.08 million	2014
	FRFS	€3 million	2016
2015 grant*	-	-	-
2016 grant*	-	-	-
2017 grant	FRFS	€1 million	2017
	FRFS	€5 million	2018
2018 grant	FRFS	€4.997 million	2019
2019 grant	FRFS	€4 million	Expected
Total WELBIO grants		€42,077 million	
Transversal management of the FRFS		€22.06 million	
WELBIO grand total		€64,137 million	

REVENUE FROM INTELLECTUAL PROPERTY

In accordance with the provisions of the framework agreement, WELBIO receives a portion of the revenue from intellectual property. This revenue is paid into the FRFS account. This revenue is assigned to the WELBIO strategic branch and is used, after a proposal to the Board of Directors of WELBIO ASBL, for investments concerning follow-up developments or calls for projects.

Revenue as of 31/12/2017	€351,562
2018 revenue	€110,075
2019 revenue	€338,645
Total	**€800,282**

WELBIO ASBL MANAGEMENT REPORT

This concerns the ninth fiscal year, which covers the period from 1 January 2019 to 31 December 2019.

Since 2015, funding for research programmes has been outsourced to FRS-FNRS, within the framework of the FRFS (Strategic Fundamental Research Funds). As a development platform, WELBIO ASBL receives an annual grant equal to 10% of the total funding for the WELBIO strategic branch in theory, after sums intended to finance FRS-FNRS have been subtracted. For the 2019 fiscal year, the ASBL received an annual grant of €384,000 (9.6% of €4,000,000) to cover operating costs; the balance was allocated to investments in follow-up developments (Bridge Fund).

Since the annual grant is now intended to cover the current activities of WELBIO ASBL, it was decided that, starting from 2017, the annual grant was considered as an operating grant. The ASBL has since shifted from a "small" ASBL to a "large" ASBL and the annual accounts have since been deposited in the National Bank, based on the standardised scheme.

ASSETS

Tangible fixed assets amount to €550.28 and concern IT equipment.

Commercial debts amount to €88.09 and concern credit notes from suppliers that are to be recovered.

Financial fixed assets amount to €3,450.00 and concern the guarantee on rented offices in Wavre.

Accounts receivable within one year amount to €384,000 and concern of the 2019 grant to be received.

Cash investments amount to €1,925,009.44 and take the form of two reserves, in order to distribute the remaining liquidity of WELBIO.

On 31 December 2019, the liquid cash sum available in WELBIO's different bank accounts amount to:

Green account	€972,645.31
Flexibonus	€798,686.93
Current account	€153,677.20
Total	**€1,925,009.44**

These liquid cash sums are allocated as follows:

These liquid cash sums are allocated as follows	€239,300.00
Bridge fund	€1,685,709.44
Total	**€1,925,009.44**

Adjustment accounts amount to €2,074.36 and concern charges that are to be carried forward.

Total assets amount to €2,315,172.16.

LIABILITIES

The balance as of 31/12/2018, under the heading of "other allocated funds", amounts to €2,209,923.16.

The result for the fiscal year is a profit of €76,700.30.

The balance as of 31/12/2019, for other allocated funds, amounts to €2,286,623.46.

Supplier debts amount to €71.41.

The estimated tax liability for 2019 amounts to €158.55.

Tax for 2018 amounts to €168.16.

The as-yet-undue withholding tax amounts to €3,777.86.

The as-yet-undue ONSS amounts to €3.262.35.

Salaries to be paid amount to €31.16.

Provisions for holiday payments amount to €21,079.21.

Total liabilities amount to €2,315,172.16

RESULT

The grant for 2019 operating costs amount to €384,000.00.

The statements of debt for the Bridge Fund have been paid up to a total of €85,077.49.

Miscellaneous services and assets amount to €53,816.05 and primarily concern operating costs, rent and fees.

Salaries and social contributions amount to €167,697.20.

Depreciations amount to €1,055.81.

The estimated tax liability amounts to €158.55.

Net bank interest, sans withholding tax, amounts to €950.08.

Financial charges amount to €444.63.

The result for the fiscal year is a profit of €76,700.30.

We suggest the following allocation:
Transfer to other allocated funds: €76,700.30

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CONTACT

ADDRESS
WELBIO a.s.b.l.
Avenue Pasteur, 6
1300 Wavre (Belgique)
Tél : +32 (0)10 68 63 55
Email: info@welbio.org

MANAGING DIRECTOR
Pierre Van Renterghem, Ph.D.
Tel : +32 (0)485 21 51 80

REGISTERED OFFICE
Avenue de l'Hôpital, 1
4000 Liège (Belgique)
RPM : Liège 0812.367.476

WEBSITE
http://welbio.org
@Welbio_asbl

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WELBIO a.s.b.l.
Avenue Pasteur, 6 • 1300 Wavre (Belgique)
+32 (0)10 68 63 55 • info@welbio.org
www.welbio.org

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