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GRAND CHALLENGES PROGRAM

ENHANCING THE SOCIETAL IMPACT OF RESEARCH

Sofie Bekaert

In the first two decades of its existence, VIB has achieved remarkable productivity in both knowledge creation and translating this knowledge into societal and economic benefits through a professional process of proactive technology transfer.

Thanks to its current maturity, VIB can pursue new strategies to achieve the next level of value creation: an extra layer of translational approaches to increase the societal impact of VIB research, building further upon its formula of success: bottom-up research.

To this end, VIB developed two translational initiatives. VIB Discovery Sciences, the focus of the previous edition of VIB News, which aims at 'forward translational research', translating VIB knowledge into applications by further de-risking the research assets beyond the 'academic' proof of concept, generated in the VIB research groups.

The VIB Grand Challenges Program (GCP) finds itself on the other end of the translational process. It is a program of reverse translational research and starts from the societal challenges to create new knowledge and opportunities, which will depend on multidisciplinary collaborations with skilled teams outside VIB (such as hospitals) to realize preset goals in delivering high impact solutions.

The projects are induced by 'reverse' translational questions and issues which are triggered in daily practice. They are developed 'backwards', starting from the patient or crop and leading to new insights and applications. The projects involve an iterative process in which new observations are translated into testable hypotheses and validated solutions. Throughout the process, VIB expertise and enabling technologies are used with the aim to impact pertinent challenges in healthcare and agriculture, framed within the United Nations Sustainable Development Goals.

So far, there have been two institute-wide calls for projects. A third call has just been launched and this round of selected projects will be announced in June 2020. The project applications are evaluated in a 2-step-procedure with involvement of both external scientific experts in the respective thematic domains and experts assessing societal impact potential, and a panel review.

The final purpose of the program is to contribute to a better future for the world and to leave a positive mark on society, help stakeholders to be, think, live better with VIB innovations, by thinking about practical applications based on VIB's research and excellence areas.

The goal is not just funding (societal and economical) value creation, but supporting innovative new approaches, addressing societal need gaps, and bringing the right solutions to the places where they are most needed in a dialogue with all stakeholders.

Sofie Bekaert
Manager Translational Program & coordinator of the Grand Challenges Program

Picture on front cover: On March 17, 2019 researchers and clinicians involved in the PID Grand Challenge Project welcomed 115 patients and their family at the VIB-UGent Research Building for an interactive morning program. The event was co-organized with Bubble ID, a PID fund from UZ Gent that wants to pierce the bubble of isolation that surrounds both the condition and the patients.

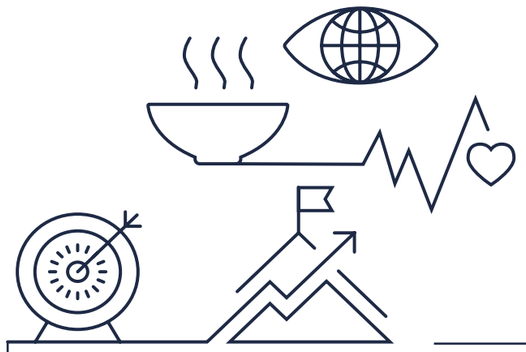
INTRODUCING THE GRAND CHALLENGES PROJECTS

VIB's Grand Challenges Program has been set up, supported by a crucial investment from the Flemish Government, to increase the societal impact of VIB by addressing scientific challenges with a substantial significance. Through the Program's funding, the selected projects will be able to initiate collaborative efforts with transdisciplinary external experts.

Together, the project teams will build the foundations that will enable them to quickly implement their discoveries for the benefit of patients, customers, and society at large. In the initial phase the researchers will also develop plans to ensure that the projects will translate into long-term implementation strategies with continued involvement of various stakeholders from the start.

Professor Peter Piot (Director of the London School of Hygiene & Tropical Medicine and Professor of Global Health), one of the most recent members of VIB's Institutional Board lauds the program: "The Grand Challenges Program is an excellent initiative to increase the direct social impact of world-class science, inspired by the UN's Sustainable Development goals."

So far, there have been two calls for project applications. In each of these calls, three projects have been selected. The applications were evaluated in a 2-step-procedure with involvement of both external scientific experts in the respective thematic domains and experts assessing societal impact potential, and a panel review. Here, we introduce these projects, their goals, and the partners that work together to achieve their objectives, as well as a brief description of how the reach of the research extends beyond the laboratory and into broader society.

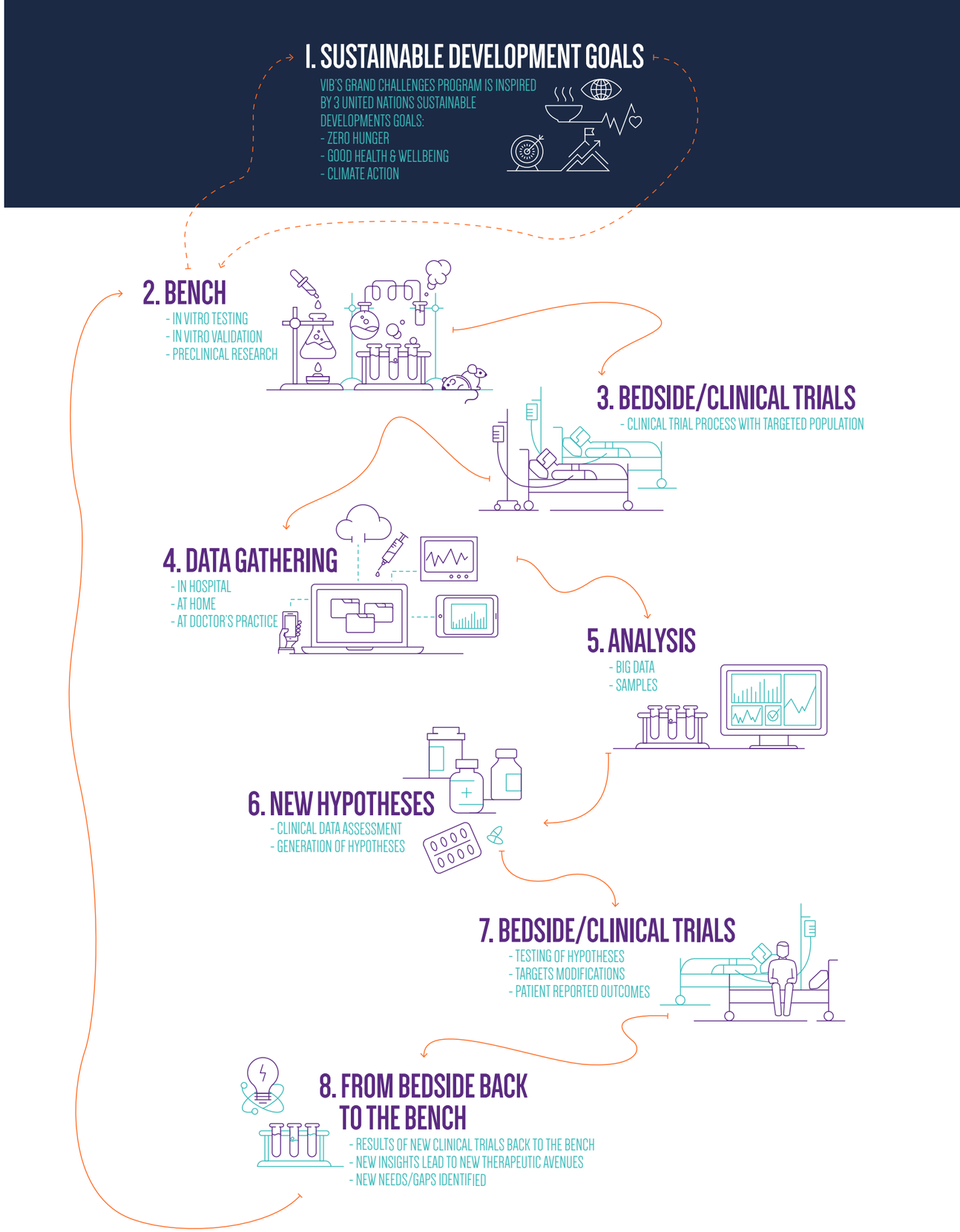


"VIB wants to further elaborate on the essence of a strategic research institute: 'enhancing impact on society'. Supported by a crucial investment from the Flemish Government, our Grand Challenges Program aims to find solutions for the huge challenges society faces. We do so by teaming up with relevant partners, thus combining complementary expertise within a very focused strategy. This will enable all stakeholders to increase their beneficial impact on society."

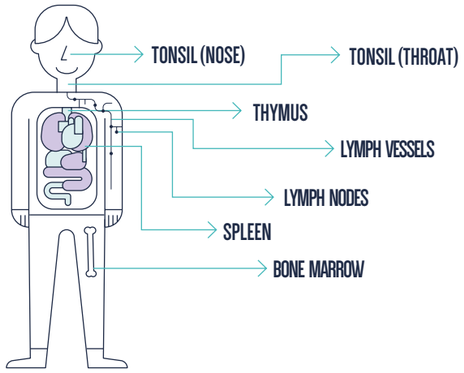
Jo Bury and Johan Cardoen, managing directors of VIB

Based on three of the UN's Global Sustainable Development Goals (Health & wellbeing, Zero hunger, and Climate action), the Grand Challenges Program seeks projects that align with the following five thematic domains:

- Innovative diagnostics
- Innovative treatment
- Personalized treatment strategies
- Epidemic control
- Sustainable agriculture



PRIMARY IMMUNE DEFICIENCIES



BACKGROUND
Primary immune deficiency diseases (PIDs) are a heterogeneous group of life-threatening genetic disorders of the innate and adaptive immune system. To date, there is still a lot of under-diagnosis as PIDs are very complex and can present clinically in many forms. A large number of PID patients remain undiagnosed or get a label of undefined PID, preventing the design of a rational therapeutic approach.

PID can lead to increased susceptibility to severe and/or recurrent infections and malignancy, which can easily be diagnosed by specialized centers. The condition, however, can also lead to immune dysregulation resulting in auto-inflammatory diseases related to excessive innate immune activation and auto-immunity. Such immune dysregulations are much harder to diagnose and manage.

Therapeutic options are currently limited due to a lack of molecular insight into PID's mechanisms and progression. This places a heavy burden not only on patients and families, but also on health care systems.

Jan Phillipé (UZ Gent) highlights another aspect of the social impact plans that are part of this project: "With government support, we will also endeavor to set up a PID screening program for newborns in Belgium."

GOALS
The VIB-GCP PID consortium will address the urgent need for molecular diagnostic tools to better identify and classify PID patients and guide therapeutic decisions in the clinic. Additionally, research into novel targeted therapeutic concepts based on deep insight in the core immunological and molecular mechanisms driving PID will be performed.

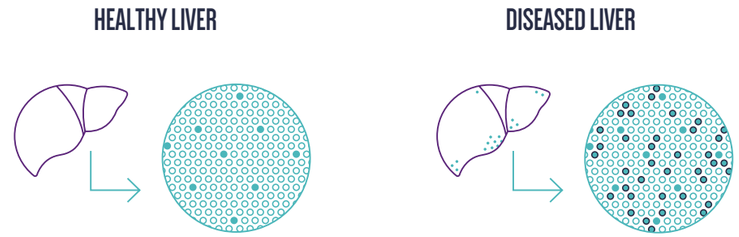
The development and practical implementation of this new knowledge will expand therapeutic options available to physicians and their patients. Not only will this have important and immediate impact on the life of affected patients, it will also have a tremendous scientific impact on reverse translational research.

The project consortium concentrates on two main goals:
- innovative biomarkers: standardized high-throughput screening of potential PID patients combined with immunophenotyping and whole genome genetic analyses to detect rare or novel PID disorders
- innovative treatments: establishment of reliable and powerful methods to generate patient-specific laboratory model systems to test innovative patient-specific treatments (e.g. drug re-purposing).

PARTNERS
The PID project assembles the combined expertise of the VIB-UGent Center for Inflammation Research, with participation of Bart Lambrecht, Rudi Beyaert, Yvan Saeys, Martin Guilliams, and of the Adrian Liston lab (VIB-KU Leuven Center for Brain & Disease Research). Added to their expert knowledge in cellular and molecular immunology comes the clinical acumen of pediatric and adult internal medicine specialists with proven track records in PID at UZ Leuven, UZ Gent, and UZA (Isabelle Meyts, Filomeen Haerynck, Bart Lambrecht, and Rik Schrijvers). Proper laboratory diagnostics (TREC screening, immunophenotyping, functional immune assays) will be performed in university hospital clinical biology and hematology labs at KU Leuven/UZ Leuven (Xavier Bossuyt, Isabelle Meyts, Rik Schrijvers) and UGent/UZGent (Jan Philippé, Filomeen Haerinck, Elfride de Baere).

SOCIETAL IMPACT
Beyond the scientific insight this project will lead to, the project members will contribute to increasing awareness about PID within the broader public. They will shed a light on this rare disorder with substantial impact. An example is the successful PID event held earlier this year, where the project leader Rudi Beyaert joined other project scientists during a day of interaction with PID patients, family and friends. The event was co-organized by Bubble ID, an initiative of the CPIG, the Center for Primary Immune deficiencies Gent, that seeks to remedy both the lack of knowledge concerning PID and the isolation of PID patients.
A similar event will be organized in spring 2020 in Leuven.

IMPROVED DIAGNOSIS OF LIVER DISEASE



BACKGROUND
Chronic liver disease is a major cause of morbidity and mortality worldwide, with increasing prevalence. In terms of total years of life lost, it is now the thirteenth most burdensome disease overall and the fifth leading cause of death in the young adult age group of 25 – 50 years. In Europe, liver disease causes 2% of all deaths. The main culprits are alcohol abuse, and, rapidly increasing, nonalcoholic fatty liver disease (NAFLD) that is associated with diabetes and obesity. All of these lead to hepatocyte cell death and chronic liver inflammation, often triggering liver fibrosis and progressive loss of functional liver architecture. In the cirrhosis stage of the disease, the risk of liver cancer increases up to 40-fold. Furthermore, progressive cirrhosis leads to complications that eventually require liver transplantation.

Preventive approaches to date are difficult to comply with. Without improved diagnostics, the cost-effectiveness of interventions using existing and emerging pharmacological and surgical treatments will remain suboptimal.

GOALS
The main diagnostic challenges that drive the hepatology biomarker project, are:
- biomarker-based detection of nonalcoholic steatohepatitis (NASH) and the activity of the pathogenic processes in NASH in patients with steatosis, to guide treatment decisions and monitor the outcome of treatment.
- increase the proportion of hepatocellular carcinomas that are detected at an early stage, to enable curative treatment in a higher proportion of patients.
- avoiding transplantation of livers that will lead to catastrophic Primary Non-Function (failure of the donor liver to function after transplantation).

This VIB-GCP collaboration guarantees the further translation of established glycomics-based candidate biomarkers for the three diagnostic challenges listed above. These can go straight into validation studies and alpha site usage along current clinical practice to start yielding benefit for the patients in our university hospitals. On top of that, the core analytical technologies proposed are all ready to go to clinical validation or exploration after these years of prior technology development.

The team will also develop new biomarkers with clinical proof of concept. These biomarkers will be clinically validated and provide a solid foundation for rapid further development and implementation in clinical practice.

PARTNERS
The VIB Center for Medical Biotechnology, directed by Nico Callewaert, coordinates the project and serves as the home base for the team that develops and performs the wet lab analytics as well as the data warehousing and data analysis.
This VIB center has joined forces with expert hepatologists from the three leading university hospital hepatology and transplantation centers in Flanders: UZ Gent (Hans Van Vlierberghe, Xavier Verhelst), UZA (Sven Francque), UZ Leuven (David Cassiman).
Finally, three VIB core facilities are involved: the Proteomics Core, the Metabolomics Core and the Nucleomics Core partners.

"As involved researcher, this project allows me to close the gap between research and healthcare, something I consider to be very important in pursuing research beneficial to patients," says Leander Meuris, (VIB-UGent Center for Medical Biotechnology).

SOCIETAL IMPACT
This project will draw attention to chronic liver diseases as a prevalent and 'invisible' scourge of 21st century healthcare with a huge impact on patient lives, healthcare systems, and clinical developments. As part of this project, multiple stakeholders will be involved in empowering patients to make the case for prioritization of research into chronic liver failure and potential new diagnostics and treatment options.

POINTILLISM

BACKGROUND

Today, the spiraling prices of immuno-oncology agents threaten the financial sustainability of cancer treatment. This situation has only worsened since it became clear that these drugs need to be combined for optimal clinical results. With a lifetime risk of developing cancer of close to 40%, the disastrous financial impact on society is clear. To add insult to injury, the efficacy of immune therapies against various types of cancer is highly variable.In this Grand Challenge project, the aim is to discover why immunotherapy is effective in some patients or in specific cancer types, but not in others. Building on this knowledge, biomarkers will be identified that predict response to Immune Checkpoint Blockade (ICBs). These biomarkers can then be used to tailor treatments to specific patients and cancer types. Furthermore, the cellular and molecular mechanisms by which immune and cancer cells interact will be further unraveled to ultimately guide the clinical implementation of more effective and truly transformative cancer immune-oncology treatment combinations.

GOALS

Four immunotherapy trials were initiated which involve anti-PD1/PDL1 compounds in indications of unmet clinical need. A comprehensive and unique collection of pre- and on-treatment biopsies from all patients will be assembled. These samples will be used to establish dynamic maps of the entire tumor ecosystem before and during ICB using innovative and integrative single-cell profiling methods. On the short term, this will allow:

- monitoring of therapeutic response at unprecedented resolution
- acquisition of information on resistance (patient- or treatment level) to ICB
- distilling novel biomarkers predictive of response to ICB

In the long run, these insights are expected to enable the design of novel treatment combinations that provide long-term therapeutic responses in refractory patients.

Marlies Vanden Bempt (VIB-KU Leuven Center for Cancer Biology): "As early career researcher, the Grand Challenges projects present a unique opportunity to have a direct impact on society and healthcare."

With this project, the understanding of the molecular and cellular mechanisms underlying resistance to ICB will be unraveled by establishing dynamic (spatial) maps of the tumor ecosystem exposed to ICB at single cell level. From these studies novel predictive biomarkers will be distilled, and ultimately novel effective combination regimens will be proposed.

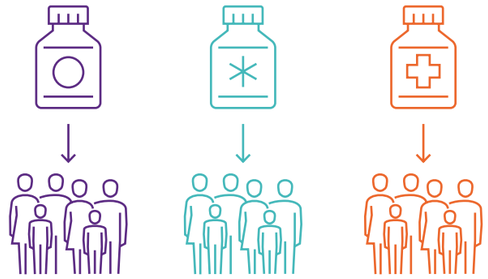
PARTNERS

The POINTILLISM project involves a multidisciplinary collaboration of the VIB-KU Leuven Center for Cancer Biology (supervised by Diether Lambrechts and Jean-Christophe Marine) with skilled teams from the KU Leuven as well as multiple oncologists working under the umbrella of the Leuven Cancer Institute (LKI). The VIB-KU Leuven Center for Cancer Biology has a unique expertise in studying the tumor microenvironment (TME) and a strong expertise in single-cell profiling techniques and bioinformatics analyses of single-cell data. The Lab of Thierry Voet (KU Leuven) has world-wide recognized expertise in single-cell omics. The Leuven Single-Cell Center (VIB, KU Leuven) spearheaded the initiation of the Single-Cell Analysis Core within the Genomics Core Leuven. The Leuven Cancer Institute aims to unite all activities related to cancer care and research within UZ Leuven and KU Leuven. Within Belgium it represents the largest referral center for cancer patients (34,000 cancer patients in 2017). LKI physicians initiate on average 200 clinical trials per year.

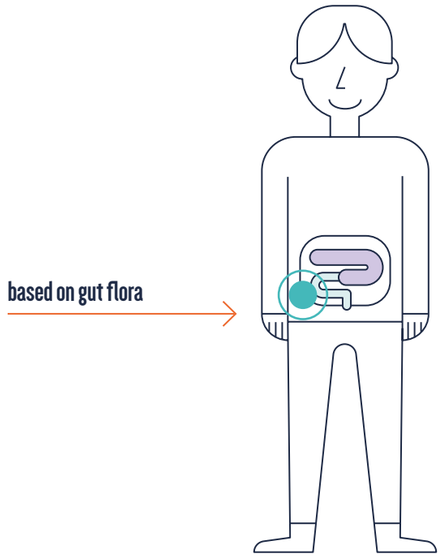
SOCIETAL IMPACT

The societal aspect of the project is an extra motivation for the researchers. Some of the most innovative technologies, more specifically multi-omics single-cell profiling, will be used for the first time in the context of clinical trials (as opposed to the 'classical' approach to apply omics analysis on tumor bulk). Specifically, tumor biopsies will be collected in patients receiving ICB before and during treatment, as well as during disease progression.

As such, the single-cell approach is unique, and it is expected to yield extremely rich and fine-grained data at the highest resolution possible. These data, including biomaterials collected during the project, will be collated into an extensive databank to facilitate future research.



MIMOSA: MICROBIOTA AGAINST INFLAMMATORY BOWEL DISEASE



BACKGROUND

Inflammatory bowel disease (IBD) is a term to describe conditions that are characterized by chronic inflammation of the bowels, such as Crohn's disease and ulcerative colitis. IBD occurs in about 8 out of each 1000 people and tends to start between 15 – 25 years of age. These conditions cannot yet be cured, and their treatment options and indirect costs are a substantial drain on the healthcare system.

Current treatments include medication, lifestyle changes, and – if no other solution provides relief – surgery. Roughly 10% of Belgium's healthcare budget goes to IBD treatments. But only 30% of these treatment options proves efficient and many patients relapse. Recent research, however, has shown us a glimpse of the microbiome's potential in remedying various gut-related conditions. Therefore, MIMOSA will explore microbiome-based strategies (fecal transplants, development of new probiotics and refinement of existing ones, and the repurposing of existing medication) for IBD treatment and relief.

GOALS

The project aims to formulate microbiota modulating strategies in inflammatory bowel disease and includes the set-up of a validation pipeline that starts in the lab and ends in the clinic. This pipeline streamlines the translational trajectory of the four strategies pursued in parallel:

- fecal transplants
- developing new probiotics
- refining existing probiotics
- repurposing existing medication that may affect microbiome composition

Combining these different strategies increases the potential to achieve fast measurable results with a maximal impact on an important societal health issue.

PARTNERS

The project combines the expertise of Jeroen Raes and Johan Thevelein (VIB-KU Leuven Center for Microbiology), Séverine Vermeire (UZ Leuven), and Peter Bossuyt (Imelda General Hospital Bonheiden).

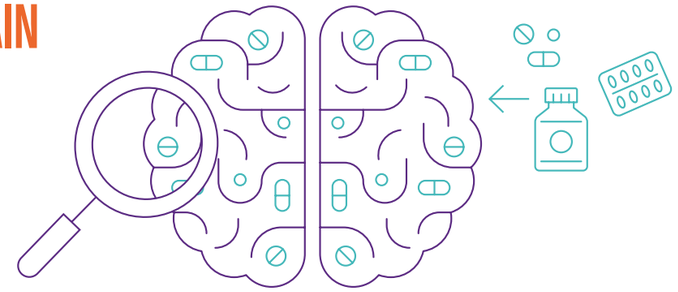
SOCIETAL IMPACT

Through this project, the researchers will spread awareness about the potential of microbiota-mediated treatment options in treating IBD. The development of alternative treatment strategies for IBD will also decrease the healthcare burden of this group of conditions and the impact on patients' personal lives.

Séverine Vermeire (UZ Leuven) explains the impact of IBD on patients' lives: "These conditions have a major impact on the quality of life of the patients. Up to a quarter of people suffering from ulcerative colitis and over half of Crohn's disease patients will have to undergo surgical removal of significant parts of their bowels."

More info on the gut enterotype research on page 24

TARGETING DRUGS TO THE BRAIN



BACKGROUND
According to the World Health Organization (WHO), neurological disorders, ranging from epilepsy to Alzheimer's disease, affect up to one billion people worldwide. These neurological disorders affect people in all countries, irrespective of age, sex, education, or income. The impact of these conditions on healthcare systems across the globe is enormous, and with an aging population in many countries this burden is likely to increase. Patients do not only experience difficulties in the practicalities of life, but also in their emotional and psychological experiences.

It is clear that the quest for new and improved medication should proceed unabated. There is, however, a major challenge affecting potential treatment for all brain disorders: the blood-brain-barrier (BBB). This barrier protects the brain from external threats while allowing nutrients to pass through. Unfortunately, very few drugs can easily cross the BBB, which renders many potentially promising treatment options practically useless.
This Grand Challenges project will explore an advanced approach to ferry drugs across the BBB and transport them to the sites where they are needed to have maximum impact.

GOALS
The project aims to identify Nanobodies® that can cross the BBB or the blood-cerebrospinal-fluid barrier by receptor-mediated transport (RMT) in a smart *in vivo* screen that bypasses the current limitations of lab models.

Main milestones in the project will be:
- the development of a Nanobody®-based strategy that enables drugs to cross the BBB
- testing this strategy in late-stage preclinical models representing breast cancer patients with metastases in the brain that are unamenable to surgery or other forms of treatment

If the approach is successful, the strategy will be further developed to enable its use for a multitude of drugs tackling various brain conditions.

PARTNERS
The multidisciplinary consortium includes Bart De Strooper (VIB-KU Leuven Center for Brain & Disease Research), Maarten Dewilde (VIB Discovery Sciences), Roosmarijn Vandenbroucke (VIB-UGent Inflammation Research Center).

Also involved are Peter Janssen (KU Leuven), Frederik De Smet (KU Leuven), Paul Declerck & Nick Geukens (PharmAbs, KU Leuven), Sebastian Haesler (Neuro-Electronics Research Flanders, VIB- KU Leuven-Imec) and Benedikt Kessler (University of Oxford, UK).
The project in addition is supported by Johannes Van Loon & Tom Theys (University Hospitals Leuven-KU Leuven) and Thomas Birngruber (Joanneum Research, Austria).

Frederik De Smet (KU Leuven) emphasizes the translational aspect of the project: "Once we get the transport mechanism working, we want to bring this to clinical practice quickly and develop it into applications that benefit patients, for example people suffering from metastasized tumors in the brain."

SOCIETAL IMPACT
This project will greatly increase our current understanding of the challenges in drug delivery to the brain and their impact on the treatment of neurological disorders. If successful, this opens a completely new field of options to treat neurological and neurodegenerative disorders. Such a high-risk but high-gain milestone technology platform can enable large-scale societal alleviation of brain disease burden on both the individual patient level and healthcare systems.

SPARTACUS: BETTER TREATMENT OPTIONS FOR SPONDYLOARTHRITIS

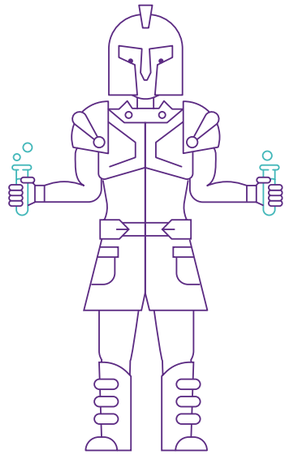
BACKGROUND
About a fifth of Europeans suffers from musculoskeletal disorders. A substantial subgroup are the rheumatic conditions. Within the rheumatic disorders, spondyloarthritis (SpA) is a group of inflammatory diseases that cause joint inflammation, or arthritis. It occurs in about 0.1 – 1% of the population, markedly more in men.

Traditional management of SpA is a step-up strategy where anti-inflammatory drugs and conventional synthetic disease-modifying anti-rheumatic drugs are administered to fight SpA symptoms. Biologics are used in second-line refractory patients.

SPARTACUS will address the hypothesis, based on a recent pilot project, that first-line use of biologics in early peripheral SpA would lead to a better response that could permit temporary use of medicine and even drug-free remission in over half of the patients quickly after diagnosis. In other words, there could be a 'window of opportunity' for a more effective SpA treatment with long-lasting effects.

Annelies Boonen (Maastricht UMC, NL): "Even during the project's early phases, we will be analyzing the potential benefits for the healthcare budget."

GOALS
The project aims to compare effectiveness of inducing clinical remission in early forms of spondyloarthritis with biologic treatment as compared to standard of care. Furthermore, the project team intents to establish new prognostic biomarkers using cutting edge single-cell technology. Concrete aims are:
- to show the superiority of treatment with biologics compared with a standard step-up approach in patients with early SpA.
- to delineate the window of opportunity for SpA treatment: <6 months vs. between 6 and 12 months of symptom duration.
- to explore the rates of drug-free remission by contemporary use of therapy in early SpA.
- to unravel new biomarkers indicating therapy response.



SPARTACUS will also explore the societal and economic impact of this new, temporally restricted biologics treatment and improved diagnosis.

PARTNERS
Dirk Elewaut and Martin Guilliams (VIB-UGent Center for Inflammation Research) deliver their expert knowledge on molecular immunology and inflammation, as well as access to the Single Cell Platform.

Rik Lories and Frederik De Smet (KU Leuven Lab of Tissue Homeostasis and Disease) bring their expertise on epigenetics and CyTOF, while Annelies Boonen (Maastricht UMC, NL) will perform the health economic evaluation and budget impact analysis.

Finally, the Department of Rheumatology at UZGent will be involved, as will the Be-GIANT Consortium (Gent university hospital, Maria Middelares-Gent, ASZ Aalst, AZ Sint-Jan Brugge, AZ Sint-Lucas Brugge, ZNA-Antwerpen, Sint-Augustinus Antwerpen, Leuven university hospital, Reuma Instituut Hasselt), which was set up to create a unique cohort of newly diagnosed SpA patients (currently 400 patients and counting).

SOCIETAL IMPACT
SPARTACUS will determine the health-economic and societal impact of earlier and more biologic intensive treatment through the use of 2 years' worth of actual patient data and a model-based lifelong incremental cost-utility analysis from a healthcare and a societal perspective.
The researchers will also work to increase awareness about the value of early recognition and treatment in rheumatology among referring physicians and patient-advocacy groups.
These results will be used in direct negotiations with health authorities in Belgium to change current reimbursement criteria for SpA therapy.

STAKEHOLDER VIEWS

"With the Grand Challenges Program, we can face challenges that we couldn't otherwise. The focus of VIB's strategy for the future is translational. It's about translating knowledge into value for society; and as such, making sure that innovation leads to growth and more jobs. I fully support this inspirational strategy and I'm convinced that this will take the very dynamic Flemish biotech industry to another level."

Ajit Shetty, Chairman of VIB's Board of Directors

"I think it's very relevant that scientists, physicians, and patients can share their experiences because each of those groups has its own perspective on the issues. You notice that certain aspects are very important for patients, but that these same aspects often fly below the radar of the scientists and physicians. Vice versa, when patients come into contact with the research world, they understand that not everything can be solved in the blink of an eye."

Krista Bracke, PID patient & honorary doctor Ghent University"

"The Grand Challenges Program allows us to initiate projects that are larger than usual in the academic world. The extensive international collaboration allows us to work on projects of an almost industrial approach and scale – even though industry has significantly more means. I expect that the Grand Challenges projects will lead to substantial leaps forward."

Bart De Strooper, VIB-KU Leuven Center for Brain & Disease Research

"These are very thorough projects, with clear endpoints aimed at improving the therapy options for patients, which is a unique opportunity for clinicians who all aim to help us much people as possible."

Sabine Tepjar, UZ Leuven

"This kind of projects is essential to unite several research centers in the fight against important and/or rare conditions. Gathering forces and expertise in such a manner creates a lot of value for Flemish research and – by extension – for the patients suffering from these conditions."

Isabelle Meyts, UZ Leuven

"The microbiome treatment had a phenomenal effect on my inflammation. Unfortunately, it was relatively short-lived, but this shows – again – how important it is to do more research on these types of treatment approaches. That's why I applaud every inititative that seeks to improve the treatment of IBD."

Maarten Sintnicolaas, IBD patient

"As researchers, we spend our time 'discovering' and publishing our results. But often it takes several years to bring our findings to the patients, with a lot of financial investment, upscaling and large-scale clinical trials. As researchers, we can't do that because we lack the financial strength to do so. This project helps us bridge that gap."

Nico Callewaert, VIB-UGent Center for Medical Biotechnology

"The feedback between the technological expertise of VIB and the clinical centers that have ample experience with patients and clinical disease progression is a hallmark of this program that provides a tremendous amount of added value."

Sven Francque, UZ Antwerpen

"The ultimate goals of the Grand Challenges Program is to drastically improve both the daily lives and treatment of patients. This combination is quite unique and, indeed, a grand challenge."

Dirk Elewaut, VIB-UGent Center for Inflammation Research

"The added value of the Grand Challenges Program truly lies in the collaboration between us clinicians and VIB researchers. Our clinical questions provide a starting point for VIB research. When they share their findings with us, we can quickly translate those to benefits for our patients."

Sévérine Vermeire, UZ Leuven

VIB SCIENTISTS (DIS)SOLVE A CRYSTAL MYSTERY AND POINT THE WAY TOWARDS NEW ASTHMA TREATMENTS

Researchers from the VIB-UGent Center for Inflammation Research, together with the biotech company argenx have solved a century-long puzzle about the presence of protein crystals in asthma. Normally, proteins do not crystallize in the body, but there are some instances where this process does occur. Charcot-Leyden crystals are made from the protein Galectin-10 and were discovered in the airways of asthmatics as early as 1853. However, the crystals have been largely ignored by scientists, and their actual link to disease remained unknown. Emma Persson, Kenneth Verstraete, and Ines Heyndrickx from the groups of Bart Lambrecht and Savvas Savvides have now established that the crystals are highly abundant in airway mucus, stimulate the immune system and promote the inflammation and altered mucus production that is often seen in the airways of asthmatics. Together with argenx they also developed antibodies that can dissolve these crystals to reduce key asthma features. Bart Lambrecht provides some background on the breakthrough.

Charcot–Leyden crystals

> The collaboration with the Savvides group and argenx is definitely the most pleasant aspect of this project. It feels that all of us own this project. We threw ourselves for 200%, and it worked. The future will be very exciting."
> Bart Lambrecht

Where did the idea for this research come from?
"This work started years ago when we discovered that many adjuvants that we use in vaccines have a crystalline state. We also made the striking observation that uric acid crystals induce allergy. From this, we started reasoning that there might be endogenous crystals in the airways of asthmatics that could boost type 2 immunity. I remembered these old descriptions of Charcot-Leyden crystals from my medical classes and decided to team up with Savvas to start working on this. For me, this project was my introduction to meaningful crystallography. I had never used it before in my research. The collaboration with Savvas, has really improved my understanding of crystallography, and I now see the beauty of protein structures. The project also taught me a lot about how a biotech company works."

Collaboration was key in this project, can you explain?
"This work was only possible because of a deep collaborative effort between the Savvides lab, the Lambrecht/Hammad lab, and argenx, a biotech company in Ghent, which selected this project as one of their innovative access programs. Close collaboration with biotech can really bring a lot to a project. If you're serious about bringing something to the clinic, team up with the experts in drug development.

The core facilities were also continuously in the loop and were key for producing recombinant proteins, performing crucial imaging experiments, flow cytometry, etc. It is fair to say that this project would not have achieved its goals without the core facilities. It was a huge team effort, and everybody is proud of the result."

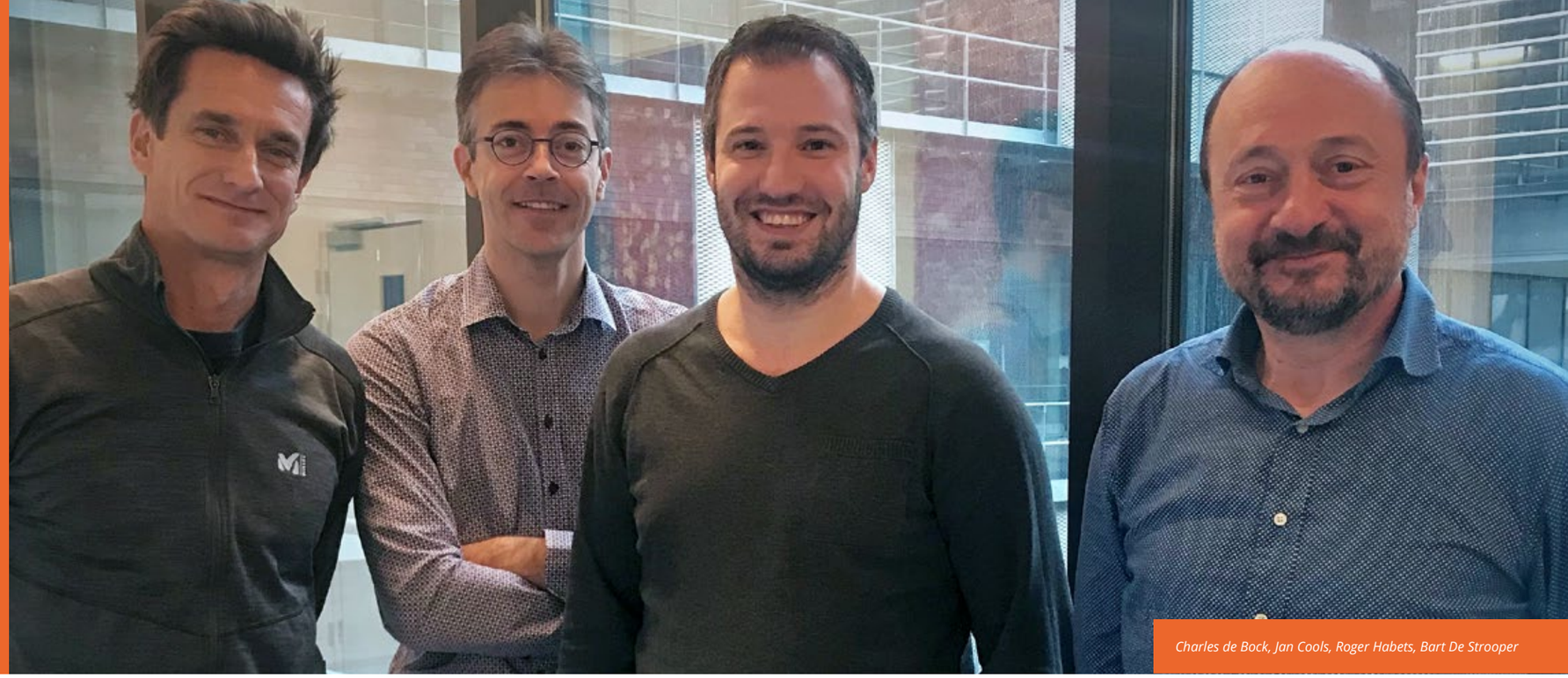
What were the major challenges to overcome?
"The major challenge in this project was that it was a very high-risk project. When I first submitted the work for a grant application, the reviewers at ERC said it was going to be impossible. One year later we got the antibodies that dissolve crystals, this time the reviewers were all positive, and I received an ERC advanced grant. Ghent University believed in it from the start, so luckily we got our key funding early on."

At which moment did you realize that this work was going to be so significant?
"When we saw that we could engineer these protein crystals and observed that we could induce potent features of asthma I knew this was important. But what really convinced me to push this project was the fact that we can dissolve the crystals with antibodies. This was one of the nicest moments in my scientific career. We are very happy that argenx has taken the antibody into the next phase of development and announced it as their ARGX-118 program. In the coming years, we hope to see the further clinical testing of a strategy that dissolves Charcot-Leyden crystals in severe asthmatics."

Where do you personally think the next breakthrough lies in this field?
"Showing that altering these crystals in asthmatics changes the development of the disease and might treat the persistent airway obstruction that is often seen in these patients. This is one of the biggest unmet needs in asthma."

Persson, Verstraete, Heyndrickx *et al.*, Science 2019

TOWARDS A SAFER TREATMENT FOR LEUKEMIA



Charles de Bock, Jan Cools, Roger Habets, Bart De Strooper

A collaboration between the groups of Jan Cools (VIB-KU Leuven Center for Cancer Biology), Bart De Strooper (VIB-KU Leuven Center for Brain & Disease Research), the UK Dementia Institute, and the Children's Cancer Institute (Australia), may lead to a safer treatment for a specific type of leukemia. By refining a therapeutic avenue that was previously abandoned because of its severe side effects, they came up with a targeted approach that was both effective and safe in mice and human cancer cells. The findings revive hope for translation to patients and have been published in Science Translational Medicine. We asked Charles de Bock, one of the two lead authors, some questions about the study and the research behind it.

Where did the idea for this research come from?

"Inhibition of the gamma secretase complex as a therapy for mutant NOTCH-driven T-cell acute lymphoblastic leukemia has been pursued for many years. However, the on-target toxcitiy in normal tissues where normal NOTCH signalling is important has meant this strategy has not been successful in the clinic. From my perspective as a leukemia researcher, I did not realize there were different types of gamma-secretase complexes. So, when the question was posed on which gamma-secretase complex subunits we aimed to study, I replied: what do you mean there are different complexes? This project was certainly not technology-focused but revisiting an old question from a new angle by asking some very fundamental questions again."

Is there a specific person who encouraged or inspired you to pursue this question?

"I think it started off with some corridor conversations between myself and Roger Habets from the Bart De Strooper lab that then quickly turned into a fantastic collaboration. The respective expertise from the two labs was essential. Roger brought his extensive knowledge on Notch signalling, I brought my expertise in T-ALL mouse models and *in vivo* imaging. Bart brought his expertise on the gamma-secretase complex, and Jan brought his knowledge on the genetics and molecular biology of T-ALL. It really was a case of everyone being at the right place at the right time!

On top of that, we could also count on the expertise of the Flow Core run by Pier Andree. We knew that whenever flow cytometry on important mouse samples was required – the machines were ready to go. In fact, the help of all the involved supporting staff was vital, from helping with the preparation of sequencing libraries to ensuring FACS machines were ready."

"THIS FRUITFUL COLLABORATION WAS ONLY REALLY POSSIBLE BECAUSE OF THE WAY VIB ENCOURAGES CROSS COLLABORATION – BOTH THROUGH SCIENCE – FOCUSED EVENTS AND SOCIAL EVENTS WHERE CHANCE CONVERSATIONS CAN OCCUR." - CHARLES DE BOCK

At which moment did you realize that this work was going to be so significant?

"Thé moment for me was when the conditional PSEN1 knock-out mouse model stopped the progression of NOTCH-driven leukemia in a large number of mice. I just was not expecting such an amazing response. Then, as if that was not exciting enough, treating patient-derived xenograft samples *in vivo* with the small molecule MRK560, showed that we could achieve the same result with no toxicity. This was when I realized that this was going to be a really important breakthrough in how we think about gamma-secretase inhibition."

What were the major challenges to overcome?

"Probably the biggest challenge was an intellectual one. The paradigm of gamma-secretase inhibition has been around for some time, so it was a case of trying to convince people again that selective inhibition is possible and effective! This was an important lesson for me as well: even what appears to be very established science can be revisited to make important breakthroughs."

In a hypothetical world where funding and time are not an issue, how would you like to follow up this work?

"We really need to get selective inhibitors of PSEN1 out of our hands and into the clinic where it can make a difference in the kids with T-ALL. Ideally, we need to start clinical trials now! We are really entering the era of personalized medicine. This is the ideal candidate therapy, where in the future patients with mutant NOTCH-driven T-ALL would be able to receive a tailored therapy based on the genetic profile of their cancer."

Any funny anecdotes related to this research?

"When we were analyzing the *in vivo* mouse leukemia models, the response was sometimes so stunning that we kept saying that we must have made a mistake and had forgotten to engraft leukemic cells! Roger and I have had many laughs during the experiments stuck in a hood analyzing mice and blood samples."

Habets, de Bock *et al.*, Science Translational Medicine 2019

WAKING UP SLEEPING BACTERIA TO FIGHT INFECTIONS

Researchers in the group of Jan Michiels (VIB-KU Leuven Center for Microbiology) identified a mechanism of how sleepy bacteria wake up. This finding is important, as sleepy cells are often responsible for the stubbornness of chronic infections. Findings published in Molecular Cell *reveal new perspectives on how to treat chronic infections, for example by forcing bacteria to wake up.*

SLEEPING BACTERIA

Bacteria are able to fall into a deep sleep. These sleeping bacteria are called 'persisters' and they can be found in every type of bacterial population studied so far, including important human pathogens. From a patient's point of view, persisters are unwanted as their sleeping state makes them insensitive to antibiotics.

These sleeping bacteria may wake up spontaneously and colonize the host leading to a return of the infection. Hence, persisters are associated with the failure of antibiotic therapy when they are not killed by the immune system. Until now, it was unknown how these cells were able to revert from dormant to active state. These new results provide insight into how persisters wake up.

BREAKING LINKS TO WAKE UP

To investigate how persisters wake up, the scientists used an E. coli model system based on HokB. HokB is a peptide – a small cousin of proteins – which is known to promote the development of persister cells by forming pores in the bacterial cell membrane. This results into a rapid loss of energy, pushing the bacteria into a low energy state or deep sleep. Importantly, this pore formation is only possible when two HokB peptides are linked together. The awakening of these sleeping bacteria is possible only when the link between the peptides is broken. This in turn breaks up the pore. Only when the pore is degraded, cells are able to energize again by consuming available nutrients.

Lead author Dorien Wilmaerts says: "You can compare this process with a punctured tire: you take out the spike first, and then inflate it again. Doing it the other way around does not make sense."

GETTING RID OF CHRONIC INFECTIONS

Persister cells are responsible for chronic infections that keep returning. Examples are urinary tract infections by Escherichia coli, lung infections in cystic fibrosis patients by Pseudomonas aeruginosa, or tuberculosis by Mycobacterium tuberculosis. How persister cells wake up is a long-standing question in persistence research. This work is the first to provide a detailed mechanistic understanding of an awakening mechanism and opens up new perspectives on how to stimulate awakening of deeply dormant cells.

Jan Michiels says: "Results from this work may help us to discover novel molecules and to design new strategies to eradicate persisters. Combinations of molecules stimulating awakening together with classical antibiotics could eradicate chronic infections."

Wilmaerts *et al.*, Molecular Cell 2019

Jan Michiels

SALTY DIET REDUCES TUMOR GROWTH BY TACKLING IMMUNE CELLS

A study by an international research team led by Markus Kleinewietfeld (VIB Center for Inflammation Research, UHasselt) shows that high salt intake inhibits tumor growth in mice. The effect seems to be due to a change in function of certain immune cells which play a critical role in cancer immunity. The further exploration of this finding might be beneficial for improving anti-cancer immunotherapies.

Markus Kleinewietfeld

SALT IMPACTS EXPERIMENTAL TUMOR MODELS

High salt intake is a known risk factor for high blood pressure and cardiovascular diseases. Recent research has also indicated that too much salt may impact autoimmunity. Studies have shown that a high salt diet could change the immune cell balance towards a more aggressive state and worsen autoimmunity. Interestingly, these shifts in the immune cell balance, though detrimental in autoimmune conditions, could be in theory useful in anti-cancer immune therapies to improve immune attacks against tumor cells.

An international research team led by Markus Kleinewietfeld that included Sven Brandau (University of Duisburg-Essen, Germany), Thomas Kammertöns (Charite & MDC-Berlin, Germany) and Jo Van Ginderachter (VIB Center for Inflammation Research, VUB) have now investigated the impact of high salt intake on tumor growth in mice. They found that a high salt diet inhibited tumor growth in two independent mouse models. The research team further found that this effect seemed to be related to a change in the functions of certain immune cells, so called myeloid-derived suppressor cells (MDSCs). MDSCs are believed to hinder other immune cells to efficiently attack and eliminate tumor cells.

IMMUNE CELLS CHANGING FUNCTION

When the researchers mimicked a salty environment in cell culture, they observed a functional change in MDSCs. The cells were less capable to inhibit other immune cells. A similar modulatory effect of high salt conditions on MDSCs was observed with cells isolated from human cancer patients. Moreover, if these cells were depleted, the effect of a high salt diet on tumor growth in mice was undone.

MDSCs are suspected to be an important mechanism that prevents an efficient immune attack against tumors in anti-cancer immunotherapies. The underlying molecular mechanism that blocks the function of these cells could therefore have therapeutic potential. However, since high salt intake is suspected to be a risk factor for gastric cancer in humans, the findings of this study and molecular mechanisms behind them must be carefully analyzed in future studies.

Markus Kleinewietfeld: "The findings are highly interesting, and we were surprised to see such an effect on tumor growth just by increasing the salt in the diet. However, future studies are needed to fully understand the effect and the detailed underlying molecular mechanisms behind to judge its therapeutic potential for anti-cancer immunotherapies.

Willebrand *et al.*, Frontiers in Immunology 2019

STRIPPING DOWN BACTERIAL ARMOR: A NEW WAY TO FIGHT ANTHRAX

Sander Van Der Verren, Wim Jonckheere, Antonella Fioravanti, Han Remaut

A new study led by Antonella Fioravanti in the lab of Han Remaut (VIB-VUB Center for Structural Biology) has shown that removing the armor of the bacterium that causes anthrax slows its growth and negatively affects its ability to cause disease. This work was published in the prestigious journal Nature Microbiology *can lead the way to new, effective ways of fighting anthrax and various other diseases.*

A DEADLY DISEASE

Anthrax is a deadly and highly resilient disease, caused by the spore-forming bacterium *Bacillus anthracis*. Historically, it was a major cause of death in humans and cattle. Today it is much less prevalent thanks to better hygiene and the immunization of cattle. Nevertheless, anthrax remains a naturally occurring disease that affects wildlife and livestock animals around the world. In humans, it presents a health concern primarily as a skin infection in people handling contaminated animal products, or more rarely as deadly systemic infection when ingested or inhaled.

The toughness of the spores and the lethality of an anthrax infection via inhalation unfortunately spurred its development as biological weapon in the mid-twentieth century. Although the development and stockpiling of anthrax as a bio-weapon has been banned by the international community, these regulations are violated at times. Because treatment options are limited and not effective in most cases, this means anthrax remains a potential bioterrorism threat.

A WEAPON-EVADING ARMOR

As part of its strategy to evade the weapons of the immune system, the anthrax bacterium cloaks itself with a complex, dynamic armor. A poorly understood component of this armor is the Sap S-layer, a single layer of protein that forms a shell around the bacterium. In this study, researchers successfully applied Nanobodies® - small antibody fragments - to control the assembly of the bacterial armor and study its structure. The Nanobodies were not only effective in preventing the armor from forming, but also proved highly efficient in breaking down existing S-layers. When applied to live bacteria, breaking down the armor slowed bacterial growth and led to drastic changes in the surface of the bacterial cell.

Antonella Fioravanti, who led the research, shares her excitement: "I was over the moon. I created these Nanobodies as a tool to study the Sap S-layer, but that they would also inhibit bacterial growth was an unexpected bonus".

The effects were so striking that the Nanobodies were tested as a treatment in mice infected with *B. anthracis*. "The results were amazing, all treated mice recovered from lethal anthrax within days," says Filip Van Hauwermeiren, who performed the infection studies. "We had been studying ways to stop the lethality of anthrax but had never seen such striking effects as with these Nanobodies," adds his supervisor Mohamed Lamkanfi (previously VIB-UGent Center for Inflammation Research, now at Janssen Pharmaceutica and Ghent University).

NEW TARGETS IN AN OLD BATTLE

These findings represent a step forward in a quest that started in the 19th century. When Robert Koch proved in 1876 that bacteria were causal agents of infectious disease, it was *B. anthracis* he was studying. In 1881, Louis Pasteur famously showed the public that exposure to inactivated *B. anthracis* protected livestock against anthrax. Still, a safe anthrax vaccine is not available to the broad public and treating acute infections in non-vaccinated persons is problematic. It requires long treatments with antibiotics which have poor success rates. Therapeutics derived from the Nanobodies discovered in this study may one day fill this treatment gap. Moreover, targeting the S-layer with Nanobodies may be successful in the fight against other bacteria with an S-layer armor. For example, the lab is currently exploring S-layer targeting Nanobodies in *Clostridium difficile* which causes life-threatening colitis.

Finally, the success of the experiments in this study have motivated researchers to look for other vulnerable targets on bacterial cell surfaces. Han Remaut explains: "Proteins on the surface of bacteria are interesting antibacterial targets because they are directly accessible. Targeting these proteins means that we have to worry less about that various ways that bacteria are preventing drugs from getting into the cell."

Fioravanti *et al.*, Nature Microbiology 2019

Peter Carmeliet

USING KETONE BODIES IN THE FIGHT AGAINST LYMPHEDEMA

The administration of ketone bodies, an alternative energy source, stimulates the growth of lymph vessels and has substantial beneficial effects in conditions affecting the lymphatic system. These spectacular positive effects were found by the group of Peter Carmeliet (VIB-KU Leuven Center for Cancer Biology). The team has developed a dietary metabolic approach which will soon be tested in a clinical Phase II trial to treat lymphedema, a condition for which currently no cure exists. The first patients are already enrolled in the study, which is led by Sarah Thomis, vascular surgeon and head of the center for lymphedema in UZ Leuven in collaboration with the Clinical Nutrition Unit, UZ Leuven.

A NETWORK OF LYMPH VESSELS

The lymphatic system consists of a network of lymph vessels that drain tissue fluid (lymph) back to the blood vascular system. Abnormalities in the lymphatic system are associated with the development of several human conditions, including lymphedema (tissue swelling due to failing lymph drainage). Peter Carmeliet's group previously discovered that a molecule called acetyl-CoA is essential for the regulation and growth of lymphatic vessels. The production of acetyl-CoA depends on the availability of substances such as glucose, fatty acids, and acetate. However, it can also be made from ketone bodies.

In this study, the team found that supplementing with ketone bodies to increase the availability of acetyl-CoA, induces lymphatic vessel growth and improves their function in pathological conditions, such as lymphedema. This research has unveiled an entirely innovative therapeutic avenue (changes in diet) to promote the formation of new lymphatic vessels and drainage of lymph fluid in lymphedema.

A KETO DIET FOR MICE AND HUMAN CELLS

To study the role of keto bodies in the lymphatic system, the scientists used two model systems: human cells and mice. First, the pathway that transformed ketone bodies into acetyl-CoA was blocked in human lymphatic cells by stopping a key molecule in this pathway from working. Result? The lymph cells grew and spread less. Then, the researchers added ketone bodies to the cells. The opposite happened. The cells grew and spread with fervor.

But how would lymphatic cells react in living creatures? To find out, the scientists put mice on a keto diet.

Melissa García-Caballero provides some details: "We then studied the impact of the ketone bodies in the lymph system of mice. In adult mice, elevation of ketone body levels in the lymph by feeding a high-fat, low-carbohydrate ketogenic diet, or by administration of ketone bodies, increased the growth and recovery of the lymph system in a mouse version of lymphedema. The ketogenic diet improved lymphatic growth and function, reduced infiltration of immune cells attacking the lymph system, and decreased fluid buildup in the tail."

A POTENTIAL TOOL FOR LYMPHEDEMA AND CANCER RECOVERY

Lymphedema can occur by itself, but it is also a common post-cancer complication. Among cancer patients, 1 in 6 who undergo treatment for breast cancer, melanoma, genito-urinary or gynecological tumors that involves lymph node removal or radiotherapy will develop secondary lymphedema.

Peter Carmeliet explains how their findings can aid patients: "These exciting data suggest that a ketogenic diet could be a novel therapeutic opportunity to stimulate lymph vessel formation, for instance to treat lymphedema. Despite its medical importance, lymphedema is currently incurable, and no approved pharmacological treatment is available, only symptom-controlling physical therapy. The novelty and relevance of our findings triggered great interest from clinicians and has allowed the initiation of a clinical Phase II trial to test a ketogenic diet in lymphedema patients. This is the first diet-based treatment and it represents a milestone in the treatment of lymphedema."

Sarah Thomis coordinates the clinical study: "Together with our dietitian, we have developed our own recipes that lead to a high ketone body production and which are relatively easy to adhere to. The diet consists for more than 90% of fat, with very low levels of carbohydrates and proteins, which will mimic the metabolic effects of a fasting period. Because it can have side effects, it is not recommended to start a ketogenic diet without guidance of an experienced dietitian and doctor."

The clinical team is still looking for participants. "We are currently recruiting patients who have developed secondary lymphedema in the arm after breast cancer treatment. They will be asked to follow the ketogenic diet for 24 weeks and then switch to a modified diet. We will measure changes in the edema volume and in the lymphatic transport. Given the promising findings in the mouse experiments by Peter Carmeliet, we are hopeful to see positive effects of a ketogenic diet also in patients", concludes Sarah.

García-Caballero *et al.*, Nature Metabolism 2019

A SINGLE GUT ENTEROTYPE LINKED TO BOTH INFLAMMATORY BOWEL DISEASE AND DEPRESSION

In 2012, Jeroen Raes (VIB-KU Leuven Center for Microbiology) launched the Flemish Gut Flora Project. Sequencing fecal samples of over 3,000 healthy volunteers, Jeroen and his team defined the boundaries of a normal, health-associated gut microbiota. Next, the team turned to patient groups to identify microbiome alterations associated with diseases. Recently, they described the so-called B2 enterotype, deficient in some anti-inflammatory bacteria. Their results on the high prevalence of this particular enterotype across multiple diagnoses are published in Nature Microbiology.

COMPARING MICROBIOMES

Inflammatory bowel disease (IBD) groups several conditions characterized by chronic inflammation of the intestinal tract, including ulcerative colitis and Crohn's disease. Primary sclerosing cholangitis (PSC) is a chronic liver condition involving inflammation and scarring of the bile duct, often concomitant with IBD. In their new study, the VIB-KU Leuven scientists describe microbiome composition in patients suffering from IBD and PSC.

Jeroen Raes: "Over the years, many research groups worldwide have attempted to describe microbiota alterations associated with diseases. Especially IBD is a hot topic in microbiome research. Our study differs from these previous attempts on three fronts. First, we compared the microbiota of patients with profiles from healthy volunteers from our Flemish Gut Flora Project catalog of over 3,000 microbiomes. Second, in our analyses, we did not only look at the percentages of different bacteria present in the stool samples, but also used a new technique to quantify their abundances. Third, we corrected our results for factors such as loose stools, often symptomatic in the diseases studied, but affecting the outcome of microbiome analyses."

A MICROBIAL FINGERPRINT OF DISEASE

Combining their unique expertise in quantitative microbiome profiling with their knowledge on health-associated microbiota variation, the Leuven scientists identified an altered microbiome configuration – also known as an enterotype – with high prevalence among patient groups. While this enterotype was observed in 13% of healthy volunteers, it could be identified in 38 to 78% of PSC and IBD patients.

Séverine Vermeire, gastroenterologist at UZ Leuven/KU Leuven, who participated in the research, clarifies: "This aberrant microbiome configuration, which we call the B2 enterotype, is characterized by low bacterial abundances and biodiversity. It is notably deficient in some anti-inflammatory bacteria such as Faecalibacterium. In fact, we detect higher levels of intestinal inflammation in patients with the B2 enterotype. Even among healthy individuals, carriers of this enterotype have slightly higher levels of overall low-grade inflammation."

GUT INFLAMMATION, MICROBES, AND DEPRESSION

Surprisingly, only a few months ago, the Raes lab described a similar microbiota alteration to be associated with lower quality of life and even depression.

Jeroen Raes says: "There appears to be a large overlap in microbiome alterations observed across different patient groups. We detected the B2 enterotype in around 26% of depressed individuals. While the gut microbiota has been shown to play a role in disease development in, for example, ulcerative colitis and Crohn's disease, this is far less clear for depression. However, we will explore the association between the B2 enterotype and depression in more detail in future studies."

While around 13% of healthy individuals can be classified as carriers of the B2 enterotype, the researchers stress that this should not be a reason for concern.

Jeroen Raes: "At this point, we cannot make any prediction on disease susceptibility or risk based on a person's enterotype. Moreover, enterotypes are not fixed and can be altered by, for example, changing your diet. The observed associations between diseases and microbiota constellations do not imply that the gut bacteria actually cause the disease. Many personal, lifestyle, and environmental factors are linked to a B2 enterotype. However, as also inflammation turns out to be a B2- associated factor in some individuals, we will most certainly be looking further into potential causality."

Vieira-Silva *et al.*, Nature Microbiology 2019

The interdisciplinary team will translate this knowledge into better IBD treatments in the Mimosa Grand Challenges project (page 9).

Jeroen Raes and Sara Vieira Da Silva

PREVENTING CELL DEATH AS NOVEL THERAPEUTIC STRATEGY FOR RHEUMATOID ARTHRITIS

A collaborative study by research groups from the University of Cologne, VIB, Ghent University, the Biomedical Sciences Research Center 'Alexander Fleming' in Athens and the University of Tokyo identified a new molecular mechanism causing rheumatoid arthritis. The researchers found that death of macrophages, an immune cell type, can trigger the disease. Moreover, they discovered how the protein A20 prevents macrophage death and protects against arthritis. These findings open up new possibilities for the treatment of this debilitating disease.

Geert van Loo

UNDERSTANDING ARTHRITIS

Rheumatoid arthritis (RA) is a chronic and progressive inflammatory disease that affects the joints, causing a painful swelling that eventually results in bone erosion and joint deformity. It affects 1 – 2% of the population, is very painful and severely affects the patients' quality of life. There is no cure for RA, but the disease progression in most patients can be slowed down with anti-inflammatory drugs. The underlying molecular mechanisms that cause the disease have remained largely unclear. Understanding these mechanisms is very important and may help in developing new therapies to treat patients suffering from RA.

CELL DEATH AND INFLAMMATION

A collaboration between Manolis Pasparakis and Apostolos Polykratis (University of Cologne), Marietta Armaka (BSRC 'Alexander Fleming', Athens), Yoshitaka Shirasaki and Yoshifumi Yamaguchi (University of Tokyo), and Geert van Loo and Arne Martens (VIB-UGent Center for Inflammation Research) adds a new piece to the puzzle behind the disease. Their joint effort builds further upon earlier research at the VIB-UGent Center for Inflammation Research, which demonstrated that the protein A20 suppressed arthritis by preventing inflammation. Now the researchers show that the inflammatory response is caused by the fact that a fraction of specialized immune cells, macrophages, die by a specific inflammation-promoting type of cell death called necroptosis. The researchers were able to prevent the development of RA by blocking necroptosis.

Geert van Loo: "We could also identify why these macrophages are dying and could demonstrate the importance of a specific part in the protein A20 for the prevention of cell death and RA development."

Marietta Armaka underlines: "We revealed how the particular type of macrophage demise shapes the activation of synovial fibroblasts, a key cell type that orchestrates the destruction of cartilage and bone tissue in RA".

NEW THERAPIES

This study confirms the crucial importance of A20 in the control of inflammation, but now also shows that preventing cell death is a critical anti-inflammatory function of A20 to protect against arthritis.

Manolis Pasparakis emphasizes: "From a therapeutic perspective, this is a very important finding, since it suggests that drugs inhibiting cell death could be effective in the treatment of RA, at least in a subset of patients where macrophage death could provide the underlying trigger."

Several pharmaceutical companies are developing new drugs to inhibit cell death, which will hopefully help to treat patients suffering from inflammatory diseases, including rheumatoid arthritis.

Polykratis, Martens *et al.*, Nature Cell Biology 2019

CONNECTING NEURONS IN THE BRAIN

Researchers from the VIB-KU Leuven Center for Brain & Disease Research uncover new mechanisms of brain development that determine when, where, and how strongly distinct brain cells interconnect. The brain consists of a large collection of interconnected neurons. How complex patterns of neuronal cells grow into functioning circuits during development has fascinated researchers for decades. Dietmar Schmucker and his team have now uncovered a new signaling mechanism in fruit flies that specifies the formation of neuronal circuits in the brain.

About 100 billion neurons form a complex and interconnected network in our brain, allowing us to generate complex thought patterns and actions. Neurons come in all sizes and shapes, but they mostly have long protrusions that connect to neighboring cells through specialized information-transmission structures called synapses.

How this intricate network takes shape during early development captivates many neuroscientists, including Dietmar Schmucker who has built a career studying neuronal wiring. “Proper brain functioning relies on very controlled branching of neuronal cell-extensions called axons and dendrites, and the correct formation of synapses at precise locations along these branches,” he says. “Specifying synapse formation determines where and how many potential connections a neuronal cell is “allowed” to form. Therefore, controlling synapse numbers at each neuronal branch is essential for the correct formation of complex brain circuits.”

A NEW PLAYER

The Dietmar Schmucker lab turned to the developing fly brain to study which molecular players control synapse formation in specific subcellular compartments. Using a genetic single-cell approach, the researchers could label and manipulate individual neuronal protrusions in the nervous system of the fruit fly, a popular model organism for neuroscientists.

“We found differences in neuronal branching and in synapse numbers at individual protrusions of neurons of the same type,” explains Olivier Urwyler who developed this new experimental system. Urwyler, now a group leader at University Zurich, found that a phosphatase called Prl-1 was decisive for specifying where to form the highest density of synaptic connections on a given neuron.

In fruit flies, loss of Prl-1 led to defects in the formation of neuronal connections in several different circuits, suggesting that this protein phosphatase is of general importance in circuit formation. The team also identified through which signaling pathway Prl-1 exerts its function.

“Surprisingly, it turns out to be one of the most ubiquitously acting signaling pathways, the Insulin receptor/Akt/mTor pathway, required in many physiological responses, cellular growth and cancer, says Urwyler. “Restricting the subcellular protein distribution of Prl-1 to a small compartment results in this potent signaling cascade to locally boost synapse formation.”

FROM FLIES TO HUMANS?

Flies that lack Prl-1 show severe locomotor problems. Interestingly, if Prl-1 is erroneously overexpressed and out of control, it can drive metastatic behavior of cancer cells.

As Prl-1 phosphatases are conserved from invertebrates to mammals, what could this imply for humans? According to Schmucker, their presence in different regions of the human brain means that Prl-1 phosphatases are poised to function in a similar way during vertebrate brain development:

“The compartmentalized restriction of Prl-1 could serve as a specificity factor to control the precise tuning of synaptic connections in human neurons as well, similar to the effects we have shown for the assembly of neuronal circuits and synapses in fruit flies.”

Urwyler *et al.*, Science 2019

Dietmar Schmucker

QUICKSCAN

1

#Pain #TRPA1 #Cholesterol #CellMembrane

The cation channel TRPA1 transduces a myriad of noxious chemical stimuli into pain signals and neurogenic inflammation. Karel Talavera and colleagues in the Thomas Voets Lab (VIB-KU Leuven Center for Brain & Disease Research) found that mouse TRPA1 localizes preferably to cholesterol-rich domains of the cell membrane and that cholesterol depletion decreases the channel's sensitivity to chemical agonists. Understanding the impact of such interactions on TRPA1 gating mechanisms helps to understand the puzzling pharmacology and pathophysiology of this important ion channel.

Startek *et al*., elife 2019

2

#PeptideSignaling #Metacaspase #DAMP #PlantImmunity

As a universal process in all multicellular organisms, damaged cells send out signals to alert the surrounding tissue during wounding. A new discovery, in collaboration with the University of Basel (Switzerland) and led by Simon Stael, a joint postdoc in the labs of Frank Van Breusegem (VIB-UGent Center for Plant Systems Biology) and Kris Gevaert (VIB-UGent Center for Medical Biotechnology), sheds light on the cleavage and release of the damage associated molecular pattern (DAMP) Pep1 peptide upon physical damage to plants. These findings contribute to the understanding of plant immunity and may be used to improve plant breeding and crop immune response.

Hander & Fernández-Fernández *et al.*, Science 2019

3

#NanoporeSequencing #StructuralVariants #Sequencing #Software

Millions of small genetic variants have been identified using short read next-generation sequencing. But the majority of the structural variants which play a role in e.g. dementia and cancer are systematically missed. Wouter De Coster and colleagues from the Christine Van Broeckhoven lab (VIB-UAntwerp Center for Molecular Neurology) showed that per human genome about 27,000 structural variants can be detected using long read sequencing on the Oxford Nanopore PromethION, co-funded by VIB TechWatch. The researchers evaluated software tools and have developed a bioinformatic workflow for efficient and sensitive structural variant calling from long read sequencing, paving the way to reveal missing genetic variation.

De Coster *et al.*, Genome Research 2019

4

#Arabidopsis #Endocytosis #Clathrin #ChemicalGenetics

Through chemical genetics, researchers from the Jenny Russinova lab (VIB-UGent Center for Plant Systems Biology) identified a specific inhibitor of endocytosis in plants. This small molecule binds to clathrin, a protein that plays a major role in the formation of coated vesicles. Such compound offers a new chemical scaffold for designing even more specific and potent endocytosis blockers that can be used in different species.

Dejonghe & Sharma *et al.*, Nature Chemical Biology 2019

5

#Tuberculosis #ImprovedVaccine #ChronicInfection #Mutation

The *Mycobacterium bovis Bacille Calmette Guérin* (BCG) vaccine shows variable efficacy in protection against adult tuberculosis (TB). Nele Festjens and Nico Callewaert (VIB-UGent Center for Medical Biotechnology) show that a live attenuated TB vaccine behaves more like an acute, rapidly immune-controlled infection, rather than the protracted chronic infection caused by the current BCG vaccine. This is likely critical to yield an immune status that affords more prolonged control of a subsequent TB infection.

Festjens *et al.,* Vaccine 2019

6

#BrainAnatomy #Macrophage #Microglia #SingleCell

Even a century after their discovery, brain macrophages continue to spark fascination. Hannah Van Hove, Kiavash Movahedi and colleagues at the Jo Van Ginderachter lab (VIB-VUB Center for Inflammation Research) and the Yvan Saeys lab (VIB-UGent Center for Inflammation Research) combined single-cell transcriptomics with high-dimensional cytometry, fate-mapping and microscopy to reveal the origin and diversity of brain macrophages. This showed that macrophage phenotypes strongly varied depending on their anatomical niche.

Van Hove *et al*., Nature Neuroscience 2019

7

#Alzheimer #γ-Secretase #Nicastrin #AmyloidPrecursor

γ-Secretase complexes are multimeric membrane proteases involved in a variety of physiological processes and linked to Alzheimer's disease. The Lucía Chávez-Gutiérrez lab (VIB-KU Leuven Center for Brain & Disease Research) found that the extracellular interface between the amyloid precursor protein and Nicastrin, one of the gamma-secretase subunits, has an important role in modulating Aβ. These findings may guide future drug discovery efforts.

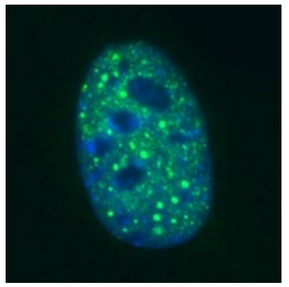
Petit *et al*., EMBO Journal 2019

8

#AntiviralProteins #Influenza #HematopoeticCells #VirusTransmission

Mx proteins are evolutionary conserved dynamin-like GTPases that can suppress the replication of a large number of viruses. The possible contribution of Mx proteins in protecting immune cells against virus infection is largely unknown. Jan Spitaels and colleagues from the Xavier Saelens lab (VIB-UGent Center for Medical Biotechnology) found that Mx in hematopoietic cells plays a crucial role in the control of Thogoto virus, an influenza-like virus that is transmitted by ticks.

Spitaels *et al.*, Journal of Virology 2019



The antiviral protein Mx1 distributes into nuclear specks (green signal). © Judith Verhelst

9

#IntrinsicStructuralDisorder #MultifunctionalProteins #ProteinAbundance #Yeast

Properties of intrinsically disordered regions (IDRs) in *Saccharomyces cerevisiae* have adapted to enable functional diversity while limiting interference from promiscuous interactions in the cellular environment. Results from the Tompa and Wodak labs (VIB-VUB Center for Structural Biology) reveal that the IDR content and the frequency of 'sticky' amino acids (AA) in IDRs decrease with increasing protein cellular concentration. This implies that the IDR content and AA composition experience negative selection as the protein concentration increases.

Macossay-Castillo *et al.*, Journal of Molecular Biology 2019

EU-LIFE, CALLS FOR IMPACTFUL COLLABORATIVE RESEARCH IN EUROPEAN BIOMEDICINE

EU-LIFE points out the increasing lack of opportunities for collaborative research in biomedicine at a European level and highlights how this is endangering long-lasting, positive impact in health research for the benefit of citizens. Based on the analysis on the barriers regarding participation in collaborative health research in Horizon 2020, 6 recommendations aim at contributing to improvement for the upcoming seven-year cycle of Horizon Europe.

"Great discoveries of the past centuries tell us that a short-term vision of impact does not contribute to long-standing, sustainable impact", says Geneviève Almouzni, Chair of EU-LIFE and Head of the Chromatin Dynamics team at Institut Curie, France. Marta Agostinho, EU-LIFE Coordinator, agrees: "The path from discovery to innovation is not linear and includes many feedback loops. Long-lasting innovation requires international research collaborations and without it, we risk losing the scientific foundations of future impact" says.

EUROPEAN SCIENTISTS ASK THE EU PARLIAMENT AND EU COMMISSION TO RECONSIDER GENOME EDITING FOR SUSTAINABLE AGRICULTURE AND FOOD PRODUCTION

One year ago, the ECJ took a very tough stand on genome editing with its strict legal decision. The European scientific community, representing 126 plant research institutes across Europe, recently urged policy makers to reconsider their verdict. In the past year, research has only emphasized the potential of genome editing. As a result, more and more countries across the world are choosing for a rational legislative framework that allows the judicious use of genome editing techniques. Europe cannot stay behind.

European agriculture can make considerable contributions to the UN Sustainable Development Goals. Precision breeding methods like genome editing with CRISPR are innovative tools that have the potential to help reach these goals in a faster and more efficient way.

The European scientific community has written an open statement to urge the European political institutions including the European Council, the new European Parliament and the upcoming European Commission, to take appropriate legal action. This will enable European scientists and breeders to apply genome editing for sustainable agriculture and food. The ability to use genome editing is crucial for the welfare and food security of European citizens.

SINGLE-CELL USER DAY BOOSTS COLLABORATION WITH JANSSEN

The first edition of the Single-Cell User Day at Janssen in Beerse was organized by VIB and Janssen Pharmaceuticals, Inc. as part of the recently established Single-Cell Accelerator program (SCA). This event encouraged interdisciplinary single-cell enthusiasts and business development managers from both VIB and Janssen to share their expertise and discuss recent advancements in single-cell technologies and their research impact.

With a focus on networking in between the different lectures, the event aimed to foster new collaborations in single-cell research to reaffirm the leading role of VIB and Janssen in this fast-evolving field. Over 90 participants joined the event, more than enough to cultivate exciting interdisciplinary cross-talk on research topics ranging from clinical applications to fundamental research and data science.

The event kicked off with a general overview of single-cell research and the available technology platforms at Janssen by Jeroen Van Houdt, Omics Group Leader at Janssen and SCA project manager. This was followed by five in-depth talks by Janssen scientists on single-cell technology developments and applications, from immune repertoire profiling to single-cell applications in Hepatitis B research. Following a networking lunch, VIB took center stage, where the US Janssen departments could join seminars from VIB scientists. The sessions started with presentations by Stein Aerts (VIB-KU Leuven Center for Brain & Disease Research) covering different single-cell technology developments and data analysis tools for single-cell RNA-seq and ATAC-seq, and Martin Guilliams (VIB-UGent Center for Inflammation Research) who shared his experiences and thoughts on the challenges in performing single-cell surface protein profiling by CITE-seq.

"We're very excited about the interest in single-cell genomics within Janssen R&D," Stein explains. "It's a unique opportunity for our students and postdocs to collaborate so closely with Janssen researchers. We experienced a great vibe at the single-cell user event, where researchers from different disciplines presented and discussed upcoming single-cell technologies, bioinformatics challenges, and the progress that is being made to unravel disease progression at single-cell resolution."

Afterwards, eight short presentations from different VIB centers provided a birds-eye view on the VIB single-cell projects. In addition, the aims and initial results in the VIB Janssen SCA collaboration were presented by Jeroen Aerts (VIB Tech Watch), who works closely together with multiple VIB labs. "If we want to stay at the forefront of the single-cell field, VIB and Janssen need to combine their expertise and join forces," Jeroen emphasizes, elaborating on the different single-cell sequencing technologies that are currently being evaluated in the SCA. The fruitful day ended with a networking reception during which topic-focused discussion tables stimulated targeted interactions.

The interdisciplinary discussion about many aspects of the current generation of single-cell applications from the perspective of both basic and preclinical science is a testament to the value of industry-academic collaborations. Therefore, VIB continues to nurture collaborations with Janssen Pharmaceuticals, Inc to maintain its leading role in single-cell research. The single-cell community is looking forward to the second edition of the bi-annual Single-Cell User Day, to be held at VIB.

TOP STORIES FROM THE VIB BUSINESS FRONT

VIB does not only promote world-class science, but also the translation of that science into products and technologies that will have a meaningful beneficial impact on society. One way VIB achieves this is through embarking on business ventures such as the creation of startups and research collaborations with existing companies. Here is the latest news from the business front.

VLAIO grant for Oncurious

Oncurious, an oncology spin-off from Oxurion and VIB, recently announced that it has received a project grant of almost €1 million from VLAIO to support the further pre-clinical development of its pipeline of next generation cancer immunotherapies. The immuno-oncology assets are based on research by the VIB-KU Leuven labs of Massimiliano Mazzone and Gabriele Bergers, and by the VIB-VUB lab of Jo Van Ginderachter. Oncurious will work in close collaboration with VIB Discovery Sciences, guided by the scientific input of the VIB founding labs.

This grant funding will be used to identify a number of multi-specific biologics with distinct modes of action against immunomodulatory targets. These candidates will then be assessed in pre-clinical tumor models, both as monotherapies and in combination with standard of care treatment. The funds will additionally support the further development of its preclinical pipeline, including the recruitment of several scientists.

Confo Therapeutics receives VLAIO grant

Confo Therapeutics develops the innovative CONFO® technology platform based on the use of single-domain antibodies to stabilize G-protein coupled receptors (GPCRs). The technology was developed by Jan Steyaert (VIB-VUB Center for Structural Biology) and is designed to identify drug candidates that target GPCRs. In June, Confo Therapeutics announced that the company was awarded a €1.7 million grant from Flanders Innovation & Entrepreneurship (VLAIO). The grant will support one of the company's proprietary pre-clinical programs, targeting a rare neurological disease. The grant will also support translational biology work by Confo Therapeutics alongside VIB teams.

Biocartis closes deal with BMS based on MSI panel

Recently, Biocartis closed a deal with American pharmaceutical company Bristol-Myers Squibb (BMS). This collaboration of Biocartis and BMS will focus on use of the Idylla™ MSI (Microsatellite Instability) test in connection with immuno-oncology therapies.

Biocartis' Idylla™ MSI Assay includes a set of biomarkers identified at VIB by the team of Diether Lambrechts (VIB-KU Leuven Center for Cancer Biology). In 2019, Biocartis launched the CE-IVD version of the Idylla™ MSI Assay for *in vitro* diagnostic use in colorectal cancer. This rapid a Idylla™ MSI technology will give many more patients access to MSI testing.

Biocartis also collaborates with VIB to investigate MSI signatures in cancers other than colorectal cancers, the predictive nature of MSI markers for immunotherapy response, and mutational load signatures related to cancer immunotherapies.

COMMUNITY BUILDING WITH THE VIB POSTDOC COMMITTEE

Postdoctoral researchers from all disciplines experience many common challenges, both on a scientific and personal level. To support and reinforce the postdocs across the VIB centers, the VIB postdoc committee (PDC) was called into life in 2015. Ever since, the PDC is dedicated towards community building and career development. Driven by their motto 'Connect to Empower', they organize a range of activities for postdocs to meet their peers and provide a platform for discussion and collaboration.

The yearly activities encompass social events like a teambuilding event during spring (such as a visit to the European parliament in 2019; see picture), a postdoc lunch at the VIB seminar, a synchronized postdoc breakfast in the different VIB centers in the autumn, and the yearly VIB postdoc day, which will be organized for the 5th time this year.

Complementary to those activities, a variety of company visits aims to guide the postdocs towards their next career step in a non-academic setting.

In 2018, the PDC organized visits to multinational companies, whereas the 2019 focus is on VIB spin-offs. As such, the VIB postdocs already got a glimpse into Agrosavfe, a VIB start-up that develops biocontrol tools for sustainable agriculture, and argenx, an up-and-coming biotech company that designs therapeutic antibodies against cancer and severe autoimmune diseases. More visits to VIB start-ups have already been scheduled: to Aelin, that develops a new class of antibiotics based on protein aggregates, and to the drug discovery company Confo Therapeutics.

IN MEMORIAM WALTER FIERS

Walter Fiers, one of the founders of VIB and an exceptional scientist, passed away on July 28th, 2019. Since VIB's beginning, Walter Fiers has been heavily involved in the institute, both as founding father and top scientist.

Even following his retirement, Walter Fiers remained active in world-leading science. Together with Xavier Saelens, also a VIB-UGent group leader, he continued to work on their quest to develop a universal flu vaccine.

His work in the early days of genome sequencing is rightfully recognized as one of the major breakthroughs in biology and biotechnology, both in terms of fundamental knowledge and potential application. Walter Fiers received numerous prestigious international awards and was named baron in 1990.

VIB extends its warmest condolences to Walter's family.

Walter Fiers

VIB-alumnus Sara Contreras-Martos with her husband Luis Ferrer Campíns

SARA CONTRERAS-MARTOS

HOW A STRUCTURAL BIOLOGIST CONSCIOUSLY TRANSFORMED INTO A SCIENCE COMMUNICATOR

VIB-alumnus Sara Contreras-Martos met her husband, Luis Ferrer Campíns, when she was studying biology at the University of Barcelona. During her studies, Sara went for a one-year lab training program to the VIB-VUB Center for Structural Biology. One year became six years and resulted in a PhD. In the meantime, Luis became a graphic designer with a strong passion for visual arts and hands-on experience in illustration, branding, animation and video art. Last year, Sara and Luis joined forces when they founded COMSCIOUS, a scientific communication studio. Based in Mallorca, their ambition is to conquer Europe and make science accessible to the broader public.

'Branding' is everything in marketing and communication – so the name of your company must have been a well-considered choice. What is behind COMSCIOUS?
"COMSCIOUS stands for 'conscious science communication'. Scientific texts are often complex, densely written and difficult to understand. They are highly inaccessible for non-scientists, and even for scientists working in other fields. There is a lot of room for improvement in science communication. Secondly, when I was working in the lab, I observed that most senior scientists were working very long hours, had to manage multiple projects and were confronted with piles of paper work and extra duties. With all this pressure on their time schedules and with no experience in communication design, they had a hard time finding the best way to present and disseminate their findings. That is where COMSCIOUS comes in. The company unites our three passions: science, communication, and design."

How do you support your customers in practice? What can they expect from your company? Do you deliver mainly illustrative materials?
"We offer a wide range of services. One is to summarize scientific results in graphical abstracts, figures, graphs, illustrations or posters. A good illustration often says more than a thousand words. But we also do scientific writing: reports, reviews or even articles. We disseminate results through various platforms, including social media. We produce short films and animations to present a lab, a research project, a company or a research team. We set up publicity campaigns or help with the organization of scientific events – and I can certainly recommend Mallorca as a superb location for scientific meetings. In summary, we offer a complete package. But most often, we work on smaller, customized projects tailored to the wishes of the client."

Does being based on the island of Mallorca limit your client base?
"Although we are based in Spain, Europe is really our market. During my PhD, I was able to connect to many people in the scientific world, not only in Spain and Belgium, but all over Europe. Of course, COMSCIOUS has only been active since mid-2018. We have to see how we grow in the years to come and how we can spread our business. We are flexible. We can work from anywhere, as long as there is an internet connection."

In Peter Tompa's lab you characterized 'intrinsically disordered regions' in proteins using nuclear magnetic resonance spectroscopy. Of all the domains in biomedical research, structural biology is probably the hardest to communicate about. The move from structural biology to science communication was not obvious, I presume?
"Actually, the reason that I ended up working in the structural biology field was more by coincidence. When I was about to finish my degree in Barcelona, I still had some credits left which allowed me to study abroad. At that time, I met Jan Steyaert in Barcelona and he suggested for me to come to his lab for a one-year 'lab training program'. The first thing I learned during that year was English!"

But you ended up staying for another five years?
"Yes, Peter Tompa offered me a position as a PhD student after that first year. Another unintentional turn in my life. Or maybe in retrospect, all this was not that coincidental. When I was a kid, I wanted to become an astrophysicist. So somehow, physics and mathematics must have been in my genes. With that in mind, using NMR to study the structure of proteins may have been a natural choice, no?"

During your stay in Brussels, was there anything specific that helped you conceive of and establish your company?
"I really learned a lot when I was at VIB-VUB. Not only technically and scientifically, but also about myself. I realized that my personal goals did not correlate with an academic scientific career. Actually, I resent how the academic scientific system works: the pressure for publications, the aim to publish in the journal with the highest impact factor, the short-term thinking, the fight for funding … this cannot be the aim of research and science."

"Let me be clear: I like doing science. I enjoy learning new things. I am fond of doing experiments … but at the same time, I love art and design. Together with Luis, I reflected a lot upon the graphics and illustrations in my papers. The cover of my PhD thesis had to be a masterpiece. We designed a cover for a journal. And, most importantly, the people in the lab, especially Kris Pauwels and Peter Tompa, supported us in our creative efforts – all the way up to a point where we realized that there might be a business in this. So, in my current job, I combine the best of both worlds: science and design. Come back in five years and see where we stand. I am curious myself."

REPORTER ON THE ROAD: FOREVER YOUNG

Throughout history, humanity has always been obsessed with eternal youth. Alchemists in ancient cultures desperately tried to create the elixir of life, and renaissance explorers scoured the world in search of the fountain of youth. Even today youthfulness dominates pop culture, and billion-dollar industries are thriving on our perpetual quest to look young.

Lifespan vs. healthspan
Today's healthcare system and food security has kept on boosting mean age in Western societies. However, in exactly these relatively affluent countries we are confronted with the real limits of human lifespan. We are slowly realizing that our fixation on lifespan may be unfounded. It is becoming clear we need to focus on healthspan, which is the number of years a person lives disease-free, as the increasing number of debilitated elderly is straining our healthcare and welfare system to unsustainable levels

Living longer, healthier
If we want to prolong human healthspan and fight age-related diseases such as several cancers and neurodegenerative disorders, we need to better understand a universal property of biological systems: aging. The moment an organism hits sexual maturity, things start going downhill. While the biological time frame is relative (compare a mayfly with an elephant, for example), aging is a certainty only a few organisms can escape from. For mammals, it is well-documented that mortality rates increase exponentially after sexual maturity ('Gompertz' law'). From a therapeutic point of view, this seems like an ideal process to target. Indeed, if one could lower the rate of aging, this would affect both the health- and lifespan of individuals. Yet before we can start thinking about ways to slow down this process, we need to understand what determines this intrinsic hastening of aging.

The rodent that defies aging
Only this year researchers documented a fascinating exception to Gompertz' law: the naked mole-rat. Scientists associated with Calico, a Silicon Valley anti-aging company backed by Google and AbbVie, tracked mortality rates in a population of these critters. Interesting fact, while the naked mole-rat is a rodent just like mice, they live for up to 30 years!

Compellingly, the mortality rate for these rodents was constant over time, meaning that a naked mole-rat of 20 years old has the same chance of dying as a one year old. Also, naked mole-rats seem to be virtually immune to cancers and other age-related diseases. All these features put these extraordinary organisms at the forefront of our understanding of aging. It may come as no surprise that Calico is using its $1.5 billion budget to spearhead the use of this novel model organism in their quest to 'cure death'.

The fish that rapidly grows old
We can also learn a lot from organisms that push the balance the other way. Invertebrate models such as *Drosophila* and *C. elegans* have been used extensively in aging research. However, a good vertebrate model of rapid aging was lacking.

In the last few years the Brunet lab at Stanford University has been putting such a novel model organism on the map: the turquoise killifish. These magnificently colored fish live in ephemeral pools in tropical Africa. When the rain season starts, killifish embryos that lay dormant in the mud will rapidly develop and produce sexually mature fish in a matter of just three to four weeks. The fish will then spawn and, as the temporary pools dry up again, the embryos will lay and wait for the next rain season to come by. Given their rapid development to maturity, killifish only have a lifespan of around four to six months. As a comparison, zebrafish which are similar in size can live up to five years.

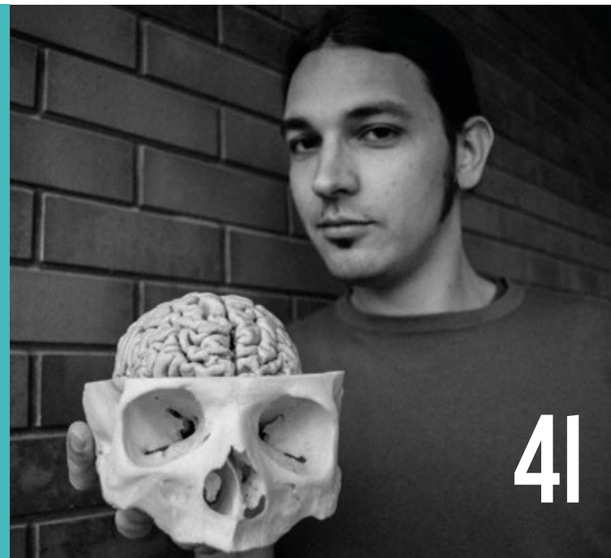
Young blood?
While novel model organisms are part of the way forward, some researchers do not shy away from more unconventional approaches to study aging. Parabiosis may look like the invention of a mad scientist from a Mary Shelley novel, yet has created a big buzz in aging research.

By connecting the vasculature of a young and an old mouse the Villeda and Wyss-Coray labs at UCSF and Stanford found that young blood slowed down aging in the old mouse, while old blood had the opposite effect in young mice. Importantly, the same effects could be replicated by just giving mice plasma transfusions from old or young donors. These findings suggest that there are blood factors that can delay or promote aging, and the hunt is on to identify exactly which ones.

The current advances in aging research will provide food for thought in the years to come. We as a scientific community together with the broader society will need to have a discussion about how far we want our obsession with youth to take us, especially in the light of a growing wealth and therefor health gap. As Alphaville said it best: "Do you really want to live forever?"

Steven Boeynaems is a VIB alumnus who worked at the Kevin Verstrepen Lab (VIB-KU Leuven Center for Microbiology) and the Ludo Van Den Bosch Lab (VIB-KU Leuven Center for Brain & Disease Research). Recently he traded Belgium for the Californian sun. At Stanford University he keeps pursuing his passion for science and science communication.

@steven.boeynaems | @BoeynaemsSteven



AWARDS & RECOGNITION

Dirk Inzé

Each year, European Seed, Europe's most important publication that offers specialized content to the seed industry, selects twenty people who have proven to be very relevant to the seed sector.

This year, **Dirk Inzé**, Science director at the VIB-UGent Center for Plant Systems Biology is one of the honorees.

Aya Takeoka (NERF, empowered by imec, KU Leuven and VIB) has been awarded the Japan Neuroscience Society Young Investigator Award.

Aya Takeoka

Wout Boerjan

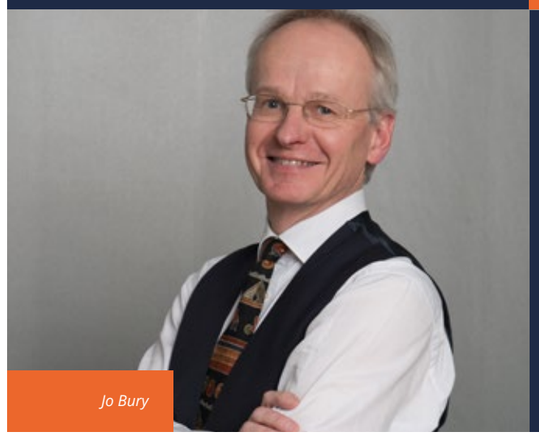
Wout Boerjan (VIB-UGent Center for Plant Systems Biology) was selected for EMBO membership, one of the most highly prized recognitions for excellence in life science.

Thomas Voets

Thomas Voets (VIB-KU Leuven Center for Brain & Disease Research) received the Fonds Elisabeth Vreven award from the Geneeskundige Stichting Koningin Elisabeth for his work in unraveling the role of TRPM3 in neuropathic and inflammatory pain.

Ajit Shetty, chairman of the VIB Board of Directors received an 'Ereteken van de Vlaamse Gemeenschap', a tribute to people who have proven themselves exceptionally serviceable for Flanders, and who have made great contributions to the international prestige of the region.

Ajit Shetty



Jo Bury

Jo Bury, Managing Director of VIB, has been selected to be part of The European Innovation Council (EIC) Taskforce of the European Commission which aims to support researchers, innovators, and entrepreneurs with bright ideas to create societal and economic impact. The goal of the EIC is to turn science into new businesses and to accelerate their scale-up pursuing high-risk high-reward innovations until commercial viability is reached.

MARK YOUR CALENDAR

The Brain Mosaic: Cellular heterogeneity in the CNS (2nd edition)
October 10-11, 2019 - Leuven

Biotech Day
October 20, 2019 - Leuven

Next-Generation Protein Analysis and Detection (3rd edition)
December 2-3, 2019 - Ghent

Applied Bioinformatics in Life Sciences
February 13-14, 2020 - Leuven

Vibes in Biosciences
March 11-13, 2020 - Leuven

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