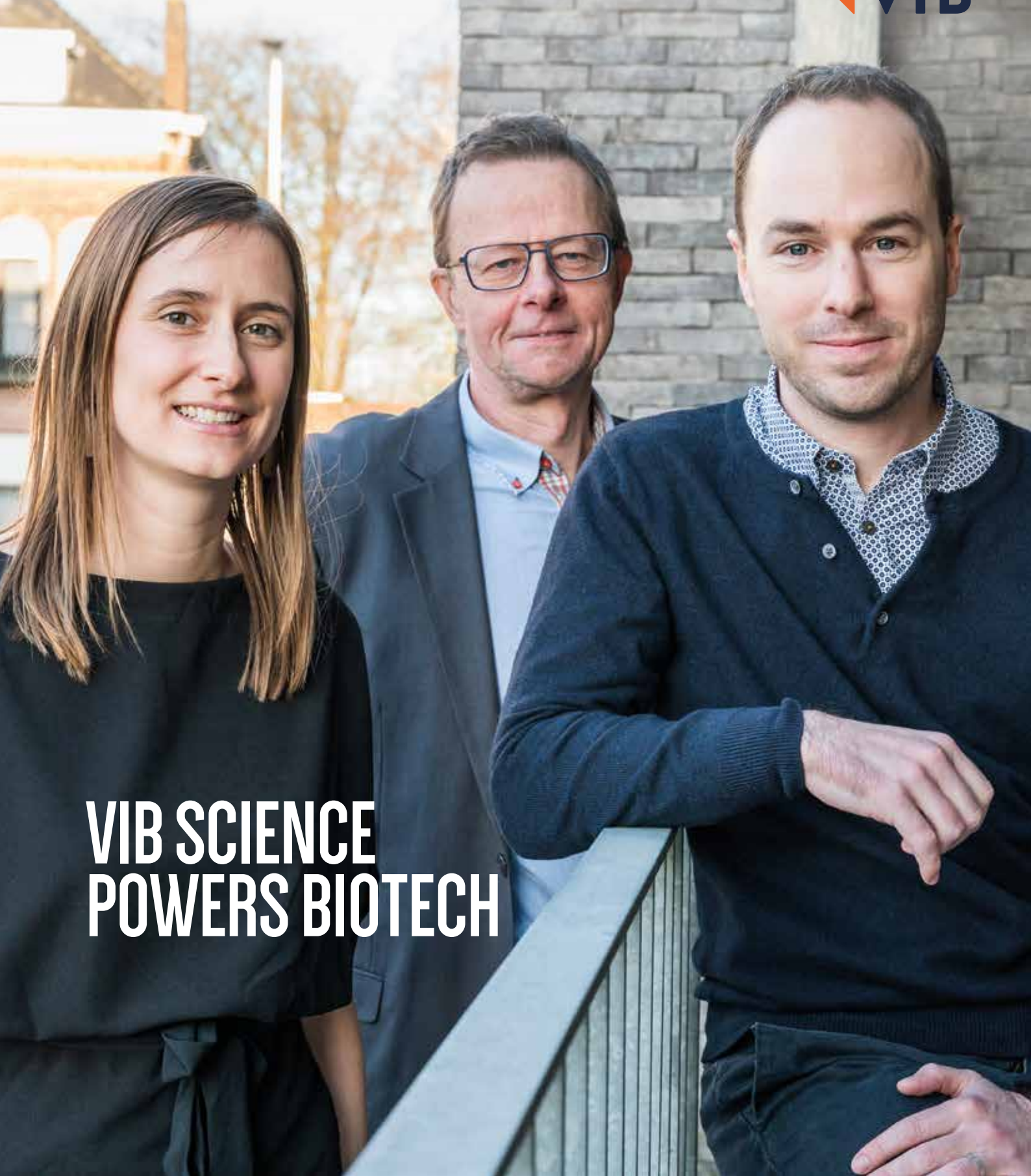


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**VIB SCIENCE
POWERS BIOTECH**

Jan Tavernier and Griet Vanpoucke

FROM BRILLIANT IDEAS TO A SUCCESSFUL BIOTECH COMPANY

What is more satisfying than developing an innovative medication, all the way from your initial basic science to a medical application? Academic discoveries that are translated to the clinic

improve patients' quality of life and add value to healthcare systems around the world. For us, this is the real meaning of 'giving back to society'.



Since the very beginning of VIB, translation of scientific research into benefits for society is one of its foundational pillars. It's VIB's mission to ensure that our discoveries and inventions lead to impactful products and services for the public. VIB encourages its researchers to travel different roads to create value and impact, based on their scientific discoveries. Creating a start-up company is one of them.

In 2015, after a significant period of strategic planning, VIB and Ghent University co-founded the biotech company Orionis Biosciences together with Boston-based scientist and serial entrepreneur Niko Kley. Several scientific innovations made in Jan's lab were fundamental seed technology and intellectual property at the founding stage of Orionis. These included various molecular interaction and AcTakine technologies, with input from Niko Kley and Gilles Uzé (CNRS/Montpellier), respectively. AcTakines, short for Activity-on-Target Cytokines, resemble classical immunocytokines but employ modified cytokines with reduced binding affinity and activity for their cognate receptors, which, however, can be restored upon targeted cell interaction. In this manner off-target cell interactions, and potentially associated systemic toxicities that have hampered clinical applications of cytokines in the past, can be minimized. Realizing the potential of these discoveries and their applications to a broad range of diseases, including cancer, Jan teamed up with Griet and her colleagues from VIB's Innovation & Business team, joined by Niko, to advance translation of these discoveries towards clinical applications.

The creation of Orionis would not have been possible without the experienced support and investor network of VIB's New Venture team. By building trust over the years

and establishing an excellent track record of spin-offs, especially for platform companies, investors see VIB as a reliable and well-respected counterparty that understands the business aspects of investments. Orionis was in this respect a special case as the company has operations in Boston and Ghent and was initially largely financed by US-based investors, complemented with VIB-affiliated V-Bio Ventures.

After four years of taking a somewhat different than traditional approach to company building, Orionis Biosciences has now emerged from stealth mode - along with a major deal announcement (see page 36). We could never have exploited the full potential of our technologies if we had kept them in our academic labs. Orionis refocused, advanced, scaled, further expanded and integrated applications of these and other technologies. Since its inception, Orionis accessed over 20 million euro of venture capital to build a robust technology foundation, enable forging of partnerships and advance its product development efforts. While there was early proof-of-concept for the AcTakine technology back in 2015, since then the technology has further evolved at Orionis and through a productive collaboration between Jan's lab at VIB. An impressive intellectual property portfolio has been created, along with the advancement of preclinical development candidates and a unique pipeline of promising immunotherapy approaches.

Starting and growing a company is a challenging but rewarding long-term endeavor and not for the faint of heart. It requires full commitment, patience and perseverance. It is a fun rollercoaster though. Although the route of a start-up might sound alluring, it also means making sacrifices



Lien Van Hoecke (VIB-UGent Center for Medical Biotechnology), Xavier Saelens (VIB-UGent Center for Medical Biotechnology) and Tim Van Acker (VIB Business Development Manager). Read their article on page 7.

and taking risks. The entrepreneurial route can put you at cross-roads of choices that can impact your academic career: from postponing publications to allow a strong IP portfolio build-up, to turning down certain industrial collaborations early on to not encumber your early product ideas or findings. For a while you might need to combine academic and industrial positions, which requires a good strategy from the very beginning to overcome conflict of interest situations.

Jan's lab has a strong link to Orionis which is formalized under a sponsored R&D agreement, generating significant R&D income for the Center and allowing Orionis to tap into the expertise built over the years in Jan's team, a win-win for both parties. On top of this, it is very rewarding to notice that former lab colleagues find their way to the new venture, bringing honed scientific expertise to the company and gaining valuable industry skills along the way.

Orionis is well underway to bringing the promise of novel therapies, inspired by original discoveries made in Jan's lab, to the clinic. Watch this space for more exciting news in the future.

Jan Tavernier is Principal investigator in the VIB-UGent Center for Medical Biotechnology and full professor at Ghent University. Griet Vanpoucke is Head of VIB's New Ventures team at VIB Headquarters.

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Joana Reis Pedro, Ana Rita Santos, Robert Prior and Michele Curcio

*The new VIB-KU Leuven spin-off
Augustine Therapeutics fights CMT*

SMOOTH SAILING FROM ACADEMIA TO INDUSTRY

VIB's newest spin-off, Augustine Therapeutics, aims to develop therapeutics for patients suffering from Charcot-Marie-Tooth disease and other neuromuscular diseases. CMT is the most common inherited peripheral neuropathy, with high unmet medical needs. The newly formed company is rooted in the research of the VIB-KU Leuven labs of Ludo Van Den Bosch, Joris de Wit, and Bart De Strooper. These scientific teams uncovered several biological pathways in peripheral neuropathies that represent promising therapeutic targets for CMT, including histone deacetylase 6 (HDAC6).

We interviewed four of the scientists driving this project: Robert Prior, working in the Ludo Van Den Bosch lab at the VIB-KU Leuven Center for Brain & Disease Research, and Ana Rita Santos, Joana Reis Pedro, and Michele Curcio, working in the VIB Discovery Sciences team.

Robust results

When did the research on HDAC6 inhibition as a potential therapeutic treatment start?

Robert: "The first HDAC6 project was initiated long before I joined the lab of Ludo Van Den Bosch. Back in 2007-2011, a previous PhD candidate, Constantin d'Ydewalle, was the first one to pioneer HDAC6 inhibition as a therapy for CMT disease type 2 (CMT2) - the axonal form of CMT. Since then, Veronick Benoy and Lawrence Van Helleputte - other lab alumni - have demonstrated HDAC6 inhibition as a strong therapeutic target for other forms of CMT2 and for acquired peripheral neuropathies. My project stemmed from these projects and looked at investigating if the therapeutic effect of HDAC6 inhibition could be extended to demyelinating forms of CMT, as well as modeling the disease, using patient-derived induced pluripotent stem cells. What makes this therapy so robust is that since Constantin's first publication in *Nature Medicine*, several labs across the UK, the US, South Korea, as well as other labs in Belgium, have reproduced the therapeutic effect in the initial findings and the results of subsequent studies."

"Within VIB, we uncovered several biological pathways in peripheral neuropathies that represent promising therapeutic targets for CMT. The validation and in-depth study of the underlying biology of these targets now provides a first-rate foundation for the development of novel therapeutics."

Ludo Van Den Bosch, VIB-KU Leuven Center for Brain & Disease Research

Together with the labs of Ludo Van Den Bosch, Joris de Wit and Bart De Strooper, the VIB Discovery Sciences team is working on the project. How did this cross-team collaboration come about?

Ana: "The close relationship of VIB's Innovation & Business team to the scientists made it possible for VIB Discovery Sciences to be involved early on in this project. We share an ultimate common goal, which is to make a positive impact on patients' quality of life by developing new therapies and treatments. While the originating labs are focused on biological questions and unravelling the (patho)physiology of the protein, the role of VIB Discovery Sciences is to translate such findings

into a final product from which patients can benefit. Our team has an industry mindset focused on optimizing a screening cascade that can drive the optimization of compounds that alter the target's function. We work in close collaboration with the Van Den Bosch and de Wit's laboratories, sharing expertise and network, which has been instrumental to advance the programs."

"Our discovery together with the lab of Bart De Strooper that the amyloid precursor protein APP selectively binds the GABA_B1a receptor and modulates the effects of this receptor served as a basis to start developing compounds that target this receptor as a novel therapeutic strategy for CMT. Current, non-selective drugs have major side effects, and our hope is that we can use our insights to develop more precise therapeutics with fewer side effects."

Joris de Wit, VIB-KU Leuven Center for Brain & Disease Research

Interdisciplinary work is key

What are the major challenges of this CMT drug discovery project?

Joana: "In the early stage of drug discovery programs we face the challenge of developing simple, reproducible and relevant biological assays. One simple assay might be insufficient to answer the biological question, another one may be too complicated to be reproducible and suitable for high throughput screening or hit validation. The best way to overcome this challenge is to read the literature and patents and to work in a multidisciplinary team"

Who is part of that multidisciplinary team?

Michele: "We highly value and rely on the expertise of the VIB Core Facilities: large screenings to identify novel small molecules modulating the activity of a target, proteomics studies to analyze protein modifications, and the imaging facility for unbiased and deep biological high-content analysis. We are extremely lucky in having such a specialized in-house support in a wide array of research fields at VIB. On top of that, Ana and I would like to highlight the key contributions made by Inge Van Molle from the VIB-VUB Center for Structural Biology."

Creating a new company

When did you realize that this work was going to be significant - eventually even leading to a spin-off?

Robert: "I knew HDAC6 inhibition was going to be a huge therapy in CMT before I started my PhD. It's actually the reason why I'm in Belgium. While I was doing my Bachelors and then subsequently my Masters in Ireland, I had scanned every CMT lab in Europe and the US for nearly two years! There were no breakthrough studies in CMT research on the horizon in any of the labs - until I came across Ludo's lab. You see, certain members of my family have CMT1X, which is a milder demyelinating, X-linked form of CMT. Although it's milder, my mother is in a wheelchair from the disease. So really, for years I had been keeping an eye on the CMT research field and when I finally found Constantine's and Ludo's paper, I knew this was where I needed to be. Since then, there has been a lot of progress in the lab with identifying HDAC6 inhibition as a therapeutic target in other forms of CMT and ultimately, the launch of Augustine Therapeutics. These are exciting times for the whole CMT research and patient community!"

"We launched Augustine Therapeutics to start the journey of bringing truly innovative products to patients suffering from serious neuropathies. The scientific discoveries of the VIB-KU Leuven scientists provide an ideal starting point for the pipeline of the new company. From here on, the senior, industry-trained team of VIB Discovery Sciences brings the required deep expertise in drug discovery for early-stage drug development."

Jérôme Van Biervliet, head of VIB Discovery Sciences

Indeed, last December, Augustine Therapeutics was officially launched. How did you experience the company creation process that preceded this exciting event?

Ana: "The creation of a company is not something you usually get to witness while you are being trained as an academic scientist, so to me this project represented a unique opportunity to experience that process. I found it very interesting to participate in the many discussions that took place, on the scientific, financial as well as legal level."

Joana: "During a process like this, you learn many lessons from both successes and failures. This definitely helps me grow as a scientist. Moreover, it is very rewarding to see that our business partners were attracted by the science we gradually produced."

A spin-off project typically involves multiple stakeholders. How do you manage their demands?

Michele: "For Augustine Therapeutics, we do not only interact with our team manager Laurent Galibert, the PI's teams, VIB's Innovation & Business team, and VIB Core Facilities, we also cooperate with external parties including CROs, the company's investors and other business partners. It helps to put in the effort to personally get to know these different stakeholders. In my opinion, establishing regular communication, setting clear timelines, deliverables and milestones, and realistic expectations are the right mix to avoid frustrations and concerns and the best way to success."

Augustine Therapeutics completed a seed financing round of 4.2 million euro. The company is the result of a collaborative effort of VIB, KU Leuven, V-Bio Ventures and PMV, joined by Advent France Biotechnology and Gemma Frisius Fund. Augustine Therapeutics is a great example of VIB's approach to company co-creation with business partners and investors: in addition to providing capital, the investors remain involved in the startup's day to day management.

Ward Capoen, Principal at V-Bio Ventures: "We are proud to have built an international syndicate of renowned investors for Augustine Therapeutics together with VIB. We intend to help grow the company and prepare Augustine for a bright future in search of novel treatment options that will benefit patients suffering from neuromuscular diseases."



Tim Van Acker, Xavier Saelens, Lien Van Hoecke, Kenny Roose and Sandra Van Lint

The Saelens group teams up with eTheRNA to develop

NEW STRATEGIES IN CANCER IMMUNOTHERAPY

The team of Xavier Saelens in the VIB-UGent Center for Medical Biotechnology has been working on enhancing immunotherapy approaches in an inventive way by provoking a certain type of cell death, called necroptosis, in cancer cells. Previous research had demonstrated that when cells die from necroptosis, the immune system is alarmed. Building on that knowledge, the team went looking for a way to provoke necroptosis in cancer cells and thus awaken an anti-tumor immune response. The researchers explored properties of MLKL, a protein that plays a crucial role in necroptosis. An important question remained however: how to deliver MLKL in the tumor tissue? Xavier Saelens and PhD student Lien Van Hoecke saw an ideal opportunity in recent advances in synthetic mRNA design and production. Recently, they teamed up with eTheRNA Immunotherapies, a Belgian company specialized in mRNA technology with R&D programs in immune-oncology. The fruitful collaboration was facilitated by VIB's Innovation & Business team.

Synthetic mRNA

What was the initial drive of the lab researchers to explore MLKL?

Xavier: The fact that it is possible to turn a tumor from its stealth mode into a visible target for the immune system by provoking so-called immunogenic cell-death, had been around in the scientific literature for years. However, the approaches to induce such type of cell death in the tumor mostly relied on poorly targeted chemotherapeutic approaches. The identification of MLKL as a key player in necroptosis induction provided an opportunity to explore a way of inducing immunogenic cell death in a much more controlled way.

Lien: An important question that had to be answered was how to deliver MLKL in the tumor tissue. Recent advances in synthetic mRNA design and production offered an ideal opportunity here. Over the past decade, mRNA-based drugs have emerged as a highly appealing new class of biologics that can be used to encode any protein of interest directly in vivo. The mRNA macromolecule can instruct the protein synthesis machinery of the patient's cells to express the encoded protein in the body itself. Problems such as complex production and purification processes and, in some cases, undesired post-translational modifications that may become part of the eventual protein drug are thus avoided. Furthermore, preclinical and clinical studies in different application fields have generated great optimism about the prospects and advantages of mRNA-based vaccines.

Xavier: Actually, we were inspired by Johan Grooten at Ghent University, who retired a few years ago. Grooten had already been exploring synthetic mRNA to deliver T-cell epitopes in vivo. So the delivery technology was close by.

What are the major findings of your research on MLKL and synthetic mRNA?

Xavier: That transient expression of exogenously applied MLKL encoding synthetic mRNA in tumor tissue can induce a curative immune response in experimental cancer models.

Lien: We obtained proof-of-concept results with this new MLKL-mRNA based antitumor treatment in experimental mouse models of melanoma, colon carcinoma and in mice with a humanized immune system that were challenged with a human lymphoma tumor. Moreover, our developed mRNA-based anticancer approach can elicit curative T cell-dependent immunity and profound neo-antigen-specific cellular immune responses. MLKL-mRNA treatment combined with immune checkpoint blockade even further improves the antitumor activity.

Personalized cancer vaccine

When did you realize the proof-of-concept results were meaningful?

Xavier: For me this was definitely the moment when Lien showed me the tumor neo-antigen-specific responses: they were massive.

Lien: Indeed, the induction of T-cell specifically against neo-antigens, without active vaccination against those neo-antigens, is the biggest advantage of this treatment strategy. It is clear that the inter-individual heterogeneity between cancer patients is enormous. Therefore, immunotherapy strategies are moving towards a more individualized approach where custom-tailored medicines are designed for individual patients. The use of autologous CAR T-cell therapies is an example of successful personalized cancer therapy. Unfortunately, the identification of a patient-specific mutanome is time consuming and expensive. The MLKL-mRNA treatment, can potentially bypass the expensive and time consuming step of mutanome identification. The tumor, if accessible for MLKL-mRNA treatment, may be regarded as its own personalized vaccine.

Specialists up close

Did you rely on contributions of other VIB-specialists and supporting staff in achieving this breakthrough?

Xavier: My group has a tradition in developing immune protection against viral infections, not against malignant cells. Luckily, we had very productive interactions with specialists from the VIB-UGent Center for Inflammation Research, including Geert Berx (a cancer biology specialist) and Peter Vandenabeele (an authority in cell death research). Furthermore, the team of animal care takers at VIB-IRC is outstanding.

Lien: The people of the VIB Flow Core were also a huge help for the design and analysis of flow cytometry experiments. The flow cytometry experiments were key to show the involvement of the immune system in the protection mechanism induced by the MLKL-mRNA treatment.

Xavier: Our collaboration with Jan Tavernier's lab at the VIB-UGent Center for Medical Biotechnology was especially significant: Jan's group had just established humanized mouse tumor models in which we could confirm that the MLKL-based anti-tumor immunity worked as well against a human-derived lymphoma.

"The technology developed in the Saelens Lab was clearly quite "hot" as several companies expressed their interest. When we initiated the discussions with eTheRNA, it was clear from the start that eTheRNA and VIB were on the same page: both parties want to advance the technology developed in the Saelens Lab and bring it to the clinic as soon as possible. The negotiations with eTheRNA were very constructive and VIB is delighted that this license agreement will both take the Saelens Lab's technology to the next level and further support the local biotech ecosystem."

Tim Van Acker, Business Development Manager at VIB

Obvious match

When did the expertise of the VIB's Innovation & Business team come in?

Xavier: Our findings had clear application potential, so we contacted VIB's IP team in the first place to learn if there was substantial ground for an IP filing. There clearly was and in no time a patent application was filed on the findings. The collaboration with eTheRNA Immunotherapies, a Belgian company specialized in mRNA technology with programs in immune-oncology, was facilitated by VIB's Business Development managers. The match was obvious. Although we also received interest from American, Israeli and Dutch companies, eTheRNA was the quickest on the draw.

What is the aim of the research collaboration with eTheRNA at the moment?

Xavier: One aim of the research collaboration is to demonstrate that MLKL encoding mRNA generated in a scalable and cGMP-compliant platform at eTheRNA works equally well as lab-produced mRNA.

Lien: We will provide advice and assist with eTheRNA's experimental tumor models whenever needed. We are also trying to work out alternative delivery routes for MLKL, which could be of interest to our industrial partner.

How do you see the future of this project? Any challenges ahead?

Xavier: We will hopefully observe a clear clinical benefit for cancer patients that are treated with MLKL-mRNA. Such a trial is part of the eTheRNA programme once non-clinical and manufacturing challenges are complete. A limitation for now could be the topical application of the MLKL-based anti-tumor treatment, which also requires a short electro-pulse. Clinical grade electroporation devices are available though, and the technology is becoming more mature allowing to reach internal tissue. However a number of routes for delivery of this therapy are possible and eTheRNA is actively exploring several of them.

INTERNSHIP PROGRAM

in VIB's Innovation & Business team

"I was pushed out of the comfort zone of my PhD and was challenged by real life tech transfer cases." *Frederik Van Leemputte* is completing his internship at VIB's Innovation & Business team and is a brisk campaigner of the program. "The installation of an internship program has been a great asset for our team and it creates an excellent opportunity for young and dynamic researchers to broaden their skills as well." *Els Hermans*, Business Development manager at VIB, confirms the added value of their recently launched internship program.



Frederik Van Leemputte and Els Hermans

Broadening skills

When did the idea of an internship at VIB's Innovation & Business team arise?

Els: "In clinically oriented life sciences, such as veterinary medicine and animal health, the concept of an internship has been implemented for many years, giving young clinicians the possibility to enroll in a rotating program at different medical units for a limited time. I have a

background as a Doctor of Veterinary Medicine and am quite familiar with the idea of an internship program and its potential benefits. Within VIB's tech transfer unit, we anticipated that an internship program could be a great asset too, and a splendid opportunity for young and dynamic researchers with an interest in business."

How is the internship organized?

Els: "We want to offer a great experience within the relatively short time frame of one year, while maintaining a balance between the requisites of a specific field and the capacities of the young applicants. The Innovation & Business team at VIB consists of four different units: Intellectual Property, Business Development, New Ventures and VIB Discovery Sciences. Therefore, we opted for a 3-month period at each unit. In each 3-month period, we alternate theoretical courses with a variety of practical exercises, supervised by the head of the unit and her/his team. The time periods are too short to acquire all the specific knowledge and know-how, but at least in one year our interns get to flavor different fields of tech transfer."

The bigger picture

Frederik, why did you apply for an internship at the VIB Innovation & Business team?

Frederik: "When I was writing my PhD thesis, I was given the opportunity to temporarily step in for a Business Developer at VIB HQ. That way, I came in touch with both the people and the activities of VIB's Innovation & Business team, which was definitely an eye opener for me as a PhD student. I applied for the first internship program to deepen my business development skills and to experience other aspects of tech transfer such as spin-off creation, drug discovery, and IP."

In what way did the internship differ from your PhD-work?

Frederik: "During my PhD I had to remain laser-focused on my research topic in the lab, while at VIB HQ I was exposed to a broad range of biotech valorization routes. That exposure heavily changed my perspective. On top of that, it was exciting for me to be able to develop totally new skillsets. The internship strikes the perfect balance between theoretical study and real-life cases."

Any personal highlights so far?

Frederik: "I was able to work on a variety of scientific topics. At the IP team, I came into contact with PIs and researchers of six different VIB centers. Under the guidance of the IP managers, I've helped with patentability and Freedom to Operate (FTO) analyses, IP landscaping, drafted the claims for a new patent, and completed a Patent Cooperation Treaty (PCT) application. I arrived at the New Ventures team just when a really interesting project gained traction. There, I was involved in activities ranging from scientific due diligence to term sheet negotiations. It was genuinely interesting to meet with different stakeholders, such as scientific founders

and researchers, business partners, and investors. Next up is Business Development, and I really look forward to join the VIB Discovery Science team! Overall, I greatly appreciate the flexibility of the team. Their openness is absolutely key to the success of the internship."

Out of the comfort zone

In what way are the internships an asset for VIB and the VIB community?

Els: "By offering the possibility of an internship to young researchers and opening up our in-house expertise to others, we believe we can further contribute to the ecosystem in Belgium and abroad. We thus generate a pool of highly qualified scientists with a clear notice of tech transfer and a better understanding of the field. Some of them will be involved in valorization projects and/or join our team as future colleagues. In sum, we create champion ambassadors of VIB, spreading the legacy of VIB and expanding the network."

Frederik, which skills did you acquire that could be valuable for your future career?

Frederik: "The program definitely pushed me to step out of the comfort zone of my PhD project. During the internship at the VIB Innovation & Business Team, you really are submerged into all aspects of tech transfer, closely interacting with the biotech ecosystem, which is great for your network. VIB takes up a central position in the local life sciences ecosystem and is a perfect representative of the biotech industry. On top of that you acquire soft skills, such as negotiating and stakeholder management. Skills that you would not necessarily develop in a lab-setting."

"One of the key roles of VIB is to train and provide a dynamic and highly qualified talent pool for local life sciences companies and organizations. Via this internship program, we offer business experience to young scientists, which can help them to get their foot in the door of industry."

Johan Cardoen, Managing Director

A new call for interns will open this month. Keep an eye on the VIB jobs website!

Advice from

VIB ALUMNI IN INDUSTRY

Many former VIB members have successfully switched to a fulfilling career in industry. We asked some of them about the lessons they learned along the way, and advice they might want to give others who are seeking to pursue a similar path.



Emma Persson

"During my postdoc at VIB I attended several events on switching to industry as well as company visits organized by the VIB postdoc committee. This is just one way in which VIB stimulates the step to industry. Also important is the fact that many VIB research groups have agreements with industrial partners. This makes it easier to get in contact with companies. Moreover, as a postdoc or a PhD student at VIB, you are actively encouraged to look into a career in industry.

In my current job, my actual scientific work and day to day problem-solving is not so different. Of course, in industry you work towards a clearer goal (a product) and timelines may be stricter. In academia, you may have more scientific freedom but also more pressure to publish your results."

- Emma Persson - argenx (previously postdoc in the lab of Bart Lambrechts and Hamida Hammad, VIB-UGent Center for Inflammation Research)

"As a researcher at VIB I learned how to work in a scientific way: being critical, implementing a good experimental design and thinking out of the box. My years at VIB also showed me the added value of collaborations, also across your field of expertise, and the importance of building a scientific network.

After several years of conducting fundamental research, I felt the urge of translating some of this fundamental knowledge into something practical. I believe industry is the most appropriate place for this. As I have a more pragmatic or 'applied' mindset, I had realized that continuing with fundamental research would not give me the satisfaction I was looking for.

As an R&D scientist, I am still involved in research. This is for me an important aspect of my job as it keeps me sharp and challenged. When developing innovative products, you encounter problems and difficulties that no one has ever met before. In industry, there are more strict rules towards documenting the work you are doing. But the general rules towards safety and work ethics are the same for both the academic world and industry, as it should be."

- Jan Geerinck - Biotalys (previously PhD student at the labs of Alain Goossens, Dirk Inzé & Geert De Jaeger, and postdoc in the lab of Wout Boerjan, VIB-UGent Center for Plant Systems Biology)



Jan Geerinck



Sandra Schoors

ALL VIB ALUMNI ARE INVITED TO JOIN THE VIB ALUMNI GROUP ON LINKEDIN.

"By being trained in a VIB lab, I had the opportunity to participate to different trainings and became skilled in a broad range of specific types of technologies. Several VIB training courses are designed to broaden the mind-set of researchers about transferable skills such as science ethics, technology transfer, business models, management, grant writing, etc. By developing those skills, I can perform multidisciplinary research and deal much better with unforeseen circumstances.

They say that the big advantage of academia is the intellectual satisfaction and freedom to investigate whatever you like. However, at a certain point I preferred to go beyond the pure science and see how the work I did could pertain to the clinical reality. Since the cancer field tries to address big questions, it's an ideal environment to go for direct impact. My drive to perform 'true' translational science was my main reason to move to industry. Conducting innovative science in a biotech company is not just possible but even required to achieve our ultimate goal: help patients."

- Sandra Schoors - DROIA Oncology Venture (previously PhD student and postdoc in the lab of Peter Carmeliet, VIB-KU Leuven Center for Cancer Biology)



Sofie Van Landeghem

"While I have never been the kind of person who needs to be micromanaged, during my PhD at VIB I definitely learned to take responsibility for my projects and to manage my time properly. These are important skills: you need to be able to work independently and set reasonable intermediate goals to keep pushing yourself to reach your final objective.

These skills have greatly helped me set up as a freelancer after my time at VIB. I am a technical person by education and by heart, and I felt like academia was pushing me too much towards additional administrative tasks such as writing papers, teaching, and applying for grants (including all the politics that comes with that). Instead, I wanted to further strengthen my technical skills in new domains. As a freelancer, you have much more uncertainty about what your next job or project will be, which means it's difficult to plan things for a longer term. The upside is that you learn and maintain a more diverse set of tools and skills, because you're often engaging with different clients and different projects. It is a great way to learn a lot in a short amount of time!

Freelancing can also lead to opportunities. For example, I am currently working as a Machine Learning and NLP engineer at Explosion, a software company specialized in developer tools for Natural Language Processing (NLP). I started working with Explosion as a freelancer, and I'm currently transitioning to a full-time employee."

- Sofie Van Landeghem - Explosion (previously PhD student and postdoc in the lab of Yves Van de Peer, VIB-UGent Center for Plant Systems Biology)

A MYSTERIOUS PROTEIN TAG, DEMYSTIFIED



Lia Martina, Caroline Asselman, Francis Impens, Rupert Mayer, Denzel Eggermont, Fabien Thery and Katie Boucher

To keep control of expressed proteins, cells can attach a chemical 'tag' onto a protein to modify its activity. One of the most well-known protein modifications is a small protein, called ubiquitin. First discovered as a label to tag a protein for degradation, ubiquitin is now known to have various functions.

The labs of Francis Impens (VIB-UGent Center for Medical Biotechnology) and Lilliana Radoshevich (University of Iowa, USA) investigated a ubiquitin-like modification called ISG15. ISG15 has a broad antimicrobial function, but the underlying molecular mechanisms remain elusive since the identity of the modified proteins and their exact sites of modification are still unknown. Taking advantage of technology developed to identify ubiquitin modification sites and an animal model for infection, the labs report for the first time the discovery of nearly thousand ISG15 sites on more than four hundred protein targets during bacterial infection.

Francis Impens and Fabien Thery (co-first author) answered some questions about their work, published in *Nature Communications*.

What led to this research?

Francis: "The idea stems from my postdoc in the Pasteur Institute. I got interested and 'dragged' into ISG15 research when I contributed to the first paper describing an antibacterial role for this modification. At that time, we tried several approaches to map ISG15 sites, but none of them worked. We could only identify ISG15 substrates, but without knowledge on the exact site of the modification. Now, we could implement a technology in the lab developed to map ubiquitin sites. Once this method was up and running, we used it to identify ISG15 sites."

"The moment we obtained the first lists with modification sites, we realized the potential impact of the project. While previous studies have mapped ubiquitin and SUMO sites by MS, our study is the first to report on the systematic identification of ISG15 sites."

As a child, could you have imagined doing something like this?

Francis: "Not at all. I had no idea I would become a scientist. As a teenager, I wanted to become a musician. But my postdoc supervisor at the Pasteur Institute, Pascale Cossart is a truly inspiring and charismatic scientist. She retired last autumn and has a nose for novel research topics and areas where breakthroughs can occur. It was for instance her idea to check for a potential antibacterial role for ISG15, next to its well-documented antiviral function. She inspired both me and our collaborator Lilliana Radoshevich (also former postdoc in the Cossart lab) to keep working on ISG15 in our present research groups."

A lot of people contributed to this study.

How important was this?

Francis: "The collaboration with the Radoshevich lab in Iowa was essential. While we took care of the MS analysis and biochemical validation in the paper, the Radoshevich lab was responsible for the animal work, cell biology and imaging. The complementary expertise of both laboratories is extremely powerful and makes it possible to advance rapidly. We really divided the work and discussed progress very regularly, almost daily at certain points."

"The VIB Proteomics Core was also crucial since all mass spec runs were carried out in this facility. Together with the other proteomics research lab in the Center for Medical Biotechnology, we are the first layer of users of this core. The mass spec analysis of our samples was tricky for the Proteomics Core staff. They only had two shots and the instrument needed to be freshly cleaned and in top condition to identify as many sites as possible in our samples."

Fabien: "This work is the result of the contribution of several people in the lab. While I took the lead for the data analysis of the proteomics part, the biochemical validations were carried out by Kevin Leandro, our former Erasmus+ Master student from Portugal. In addition, our staff scientist Katie Boucher, originating from USA, generated

the genetic constructs needed for the biochemical validations. The contribution of several people, with their own expertise and focus, was key to the success and speed of execution in this project."

Fifty years from now, this work will be the basis for...?

Francis: "We currently follow-up on the most modified protein, containing more than twenty ISG15 modification sites. In an independent screen, we identified this protein as a potential receptor or binding platform for ISGylated proteins, a finding that we are most excited about and hope to publish soon."

"In fifty years, this will hopefully lead to new host-directed therapies and drugs against infectious diseases. ISG15 and underlying pathways are underexplored and most likely harbor undiscovered drug targets. Compounds against its specific deconjugase are being developed and also the aforementioned receptor might be a future drug target."

What was the most pleasant aspect of the entire process from study design to publication?

Francis: "The enthusiasm of the PhD students and researchers involved in the project. Thirty years after its discovery, we finally start to understand the molecular mechanisms behind the antimicrobial function of ISG15. As often, this is driven by new technologies, in this case mass spectrometry. You can feel that people realize that breakthrough discoveries lie ahead and that ISG15 might become a hot topic soon. Together with a network of ISG15 researchers, we just started organizing the first international conference on ISG15."

What is the main lesson you learned during the years you dedicated yourself to this research?

Francis: "Sometimes things are almost too simple to be true. For years, ISGylation was considered as a low abundant, obscure modification, only occurring under specific conditions in immune cells. For that reason, many people including myself did not believe that by using antibodies to map ubiquitin sites, we would be able to identify ISG15 sites. Our data shows that this is not true, and that under conditions of infection ISG15 modification of proteins can increase significantly. To me the abundance of the modification was the biggest surprise. It also means that some of the ubiquitin sites identified before in high-throughput MS studies might actually be ISG15 sites."

Which questions will herald the next breakthrough in the field?

Francis: "Figuring out what happens with all those ISGylated proteins that we identified. What is their fate in the cell? Sending them for degradation by the proteasome or the lysosome? While many proteins are known that bind to ubiquitin or SUMO, none have been described for ISG15. Since now we know the position of nearly thousand modification sites, we can make mutants and design experiments to answer these questions."

DOPAMINE NEURONS



Sebastian Haesler

Dopamine neurons play a key role in associative learning. When sensory cues are associated with reward, these neurons respond to unexpected reward by an increase in their firing rate. Some theoretical models suggest learning is also influenced by the salience or associability of the stimulus. A hallmark of these models is that they can explain latent inhibition, or the observation that novel stimuli are more effectively learned than familiar ones.

Here, the team of Sebastian Haesler (NERF, empowered by imec, KU Leuven and VIB) used fiber photometry to measure the response of dopamine neurons to stimuli of varying familiarity. Using optogenetic modulation during conditioning, they show that stimulus-evoked dopamine promotes conditioned responses. Selectively increasing or decreasing dopamine recapitulated the different learning rates observed for novel or pre-exposed stimuli. This suggests that it is their cue-related activity by which dopamine neurons contribute to latent inhibition.

We spoke to Sebastian, senior author of the paper published in *Neuron*.

Where did the idea for this research come from?

Sebastian: "During my postdoctoral work, I studied the mechanisms of associative learning. This type of learning is extremely common in all animals, including humans, as it allows to quickly form a relationship between a stimulus and an outcome. Essentially, it enables you to do more of the things that are good for you and avoid those that lead to negative outcomes. For a long time, it has been known that the dopamine system in the brain is involved in associative learning. Essentially, dopamine neurons signal to the rest of the brain whether something was better or worse than expected. But some data suggested that dopamine neurons also get activated by novel stimuli, which did not fit the model, as for novel stimuli you cannot make any predictions. How can the neurons then signal that something was better or worse than expected?"

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

Sebastian: "Not really a specific person, but when I started my lab, I received a highly competitive career development award from the Human Frontier Science Program for my research on novelty and dopamine. This strongly encouraged me to pursue the project and continue when I received negative feedback from other funding sources, indicating the work might be too far out and risky."

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

Sebastian: "When we received the first behavioral results from mice, that demonstrated that highly specific stimulation of dopamine neurons in only a few trials can accelerate learning, I thought 'cool, our hypothesis might actually be correct'."

How important was collaboration?

Sebastian: "Collaboration is the key to success. I have a small team and without the dedication of everyone involved it would not be possible to move forward. Importantly, we work together so that everyone can contribute their strengths. We really share the workload."

"The hard part in research is that you have to overcome an almost endless number of small challenges until the work gets published. For PhD students this long process can be really tough. You have to be there for the students and keep motivating them so they can continue to give their best."

"If you have an interesting research question as well as the experimental tools and an excellent team to study it – don't give up, it will pay off, although maybe later than you might have hoped for."

How would you like to follow up this work?

Sebastian: "Our work offers an extremely simple explanation for latent inhibition. We suggest novel stimuli are conditioned more rapidly because they directly

activate dopamine and other neuromodulatory systems. However, this study was not designed to test this specific hypothesis, so we cannot rule out any other mechanism at this point. It would be interesting to study this further in the future."

Where do you personally think the next breakthrough lies in this field?

Sebastian: "In associative learning involving dopaminergic error signals, learning progresses gradually over many instances of trial and error. However, many real-world learning situations involve learning in only very few trials. Animals and humans are extremely good at that this – we do not need to see someone 100 or 1,000 times in order to be able to recognize that person. We have established a great system to study such rapid sensory learning and I am excited to continue this research."

"Most machine learning algorithms operate similarly to the brain, using error signals which gradually improve performance based on extensive training data. However, sometimes large training sets are not available, and rapid learning from few examples would also be far more efficient. Therefore, few-shot learning is currently receiving much attention in the field of artificial intelligence. We are excited to find out if the biological system of the brain can inspire new algorithms or maybe the other way around, machine learning algorithms give us some clues to understand the amazing learning capacity of the brain."



Christian Maueroeder, Geert van Loo and Esther Hoste

LINKING WOUND HEALING AND CANCER RISK

When our skin is damaged, a whole set of biological processes springs into action to heal the wound. Now, researchers from the VIB-UGent Center for Inflammation Research have shown that one of the molecules involved in this, HMGB1, slows down wound healing. It is, however, also essential for tumor formation at sites of previous injury. The researchers found that HMGB1 controls the actions of neutrophils in skin wounds and that this is crucial for cancer initiation. Targeting this pathway could be beneficial in diabetic wound care and in patients suffering from skin blistering diseases.

NETting wounds and cancer risk

Wounding initiates a complex repair mechanism that is aimed at fast regeneration of the injured tissue. Chronic inflammation or previous injury can predispose tissues to tumor formation. However, it is still not fully understood what the molecular mechanisms are that link injury repair to cancer. The first immune cells that enter the skin after injury are neutrophils that form specialized structures termed NETs (neutrophil extracellular traps) in skin wounds.

Esther Hoste, first author of the study, and colleagues in the group of Geert van Loo (VIB-UGent Center for Inflammation Research) investigated

the role of the molecule HMGB1, a molecule that is secreted by damaged tissue and activates the immune system. The scientists genetically deleted HMGB1 from skin cells in mice and showed that their wounds healed faster than normal mice and that they are completely protected from wound-induced tumor formation.

The harmful NETs that link wound repair to tumor formation were also observed in patients suffering from the severe blistering disease Recessive Dystrophic Epidermolysis Bullosa. These patients undergo repetitive cycles of injury and repair and are at high risk to develop skin cancer.

Mapping the RELAY NETWORKS OF OUR BRAIN



Karl Farrow

A team of scientists led by Karl Farrow at NeuroElectronics Research Flanders (NERF, empowered by imec, KU Leuven and VIB) is unraveling how our brain processes visual information. They identified specific roles for distinct neuronal cell types in passing on information from the eye to downstream brain regions that guide behavior. Such knowledge is essential to understand how sensory information guides our actions and decisions.

We use information about the world around us to guide our behavior. While the fluttering wings of a butterfly or a quickly approaching predator can both catch our attention, they trigger a very different behavioral response.

To get from detection to action, visual information is passed from the retina in our eye to different downstream brain regions. The nervous system consists of many different cells that work together in circuits and understanding how these circuits relay information has puzzled researchers for decades.

“The first stage of visual processing, the transfer of information from the retina, happens through a wide range of retinal cell types, each with their own typical shapes and responses,” explains Chen Li, a PhD student in Karl’s lab at NERF. “One major target of these cells is the superior colliculus, a brain area that receives approximately 85% of the retinal outputs in rodents.”

Mapping networks

“The aim was to decipher the wiring rules that enable the brain to integrate the behaviorally relevant visual information from the retina,” says Katja Reinhard, a postdoctoral researcher in Karl’s lab. To this end, the team traced the connections of >30 retinal cell types in mice, each informing one or several brain areas about a certain feature of the visual world.

“We compared the shape, molecular properties and visual response of different retinal cells innervating two pathways that pass through the superior colliculus. By tracing circuits and examining neuronal activity, we found that there is a clear preference in which retinal cell types provide input to a given circuit.”

As such, the researchers deciphered a projection-specific logic where each output pathway from the superior colliculus sampled a distinct and limited set of retinal inputs. These findings suggest a mechanistic

basis for the selective triggering of behaviors by the superior colliculus.

Highly specific inputs and outputs

“Earlier studies suggested that there is a large degree of fuzziness in the information each neuron receives from the retina,” says Karl. “Our data suggests there are strict limits on the degree of mixing of retinal inputs that occurs in the superior colliculus, where each output pathway has access to a distinct, only partially overlapping, set of visual information encoded by the retina.”

Understanding the specific network structure in this context will greatly enhance our ability to create mechanistic models of how sensory information triggers behaviors and informs decision-making.

Essential oil components can be

TESTED AS DRUG CANDIDATES



Patrick Van Dijck and Adam Feyaerts

A research team at the VIB-KU Leuven Center for Microbiology and the KU Leuven Department of Biology showed that, contrary to generally held belief, most components of essential oils could meet the criteria set for drug candidates. Essential oil components are the constituents of essential oils, which are complex mixtures of plant metabolites obtained by dry or steam distillation, or by citrus peel pressing.

Revisiting essential oils

The research project, supervised by Patrick Van Dijck (VIB-KU Leuven Center for Microbiology) and Walter Luyten (KU Leuven Department of Biology), is rooted in the observation that in the past decades, drug discovery has mainly shifted to high-throughput screening of large, synthetically produced chemical libraries, while natural product drug research has diminished.

Patrick: "Natural products such as essential oils and their components are often avoided in drug discovery, for example, because they are relatively hydrophobic and volatile. This can cause interference during (high throughput) screening."

However, recent technical developments combined with restrictions on the use of chemicals led to a renewed interest in natural product drug discovery. Some of the new methods to study essential oils and their components were developed in the laboratory of Walter Van Dijck under the

coordination of Adam Feyaerts, mainly with the aim of finding new antimicrobials, for example antifungal drugs.

Adam: "Nowadays, a relatively large number of essential oils and their components are already available as dietary supplements, but only a few have made the transition to drugs. As most technical barriers were removed, I wondered whether avoiding essential oils and their components in drug discovery was still justified. So, we evaluated certain parameters used in conventional drug discovery for more than 600 essential oil components to assess their potential as drug candidates."

Walter adds: "The discovery and development of a new drug takes a long time and is very expensive, not in the least because so many initial candidates turn out not to be suitable. In other words, the earlier in the drug discovery process non-promising molecules can be eliminated, the better. Many

candidate drug molecules fail when they are tested in animals."

A treasure trove of potential drugs?

Fortunately, in silico drug discovery filters have been developed that can predict drug disposition based on combinations of specific calculated parameters, which reduced the rate at which potential drugs failed later in the drug development pipeline. This study shows that essential oil components can be assessed using the filters implemented by the pharmaceutical industry.

Adam: "Our findings suggest that essential oil components can be promising sources of new drugs and deserve more attention, especially if they originate from essential oils that have already shown clinical benefits. Essential oil components also have unique properties that might be useful for some therapeutic applications, such as for lung or airway diseases, for transdermal administration, and for diseases of the central nervous system."



Martin Guilliams

Scientists develop

'TWITTER' FOR CELLS

Computational biologists led by Yvan Saeys (VIB-UGent Center for Inflammation Research) developed a new bioinformatics method to better study communication between cells. This method, called NicheNet, helps researchers to gain insight into how the gene expression of cells is regulated by interacting cells.

NicheNet and a test case

In multicellular organisms cells don't function on their own, but they produce signaling molecules that influence gene expression in interacting cells. This intercellular communication plays an important role in many biological processes, such as the development and functioning of cells.

Guided by post-doc Wouter Saelens and Yvan, PhD student Robin Browaeys developed a new method to analyze how cells might signal each other. The newly developed method, NicheNet, can be compared with a hypothetical biologist who not only knows everything that is already published about intercellular communication, but who can also apply all this knowledge on complex, big datasets.

A first test case for NicheNet was Kupffer cell niche data generated by Martin Guilliam's lab. Researchers from that lab were able to experimentally validate some of the signals that NicheNet predicted.

The value of NicheNet for generating novel hypotheses about how cells communicate in fundamental biological processes and diseases can hardly be overstated.



Yvan Saeys

Revealing the

LANDSCAPE OF BLOOD VESSELS

Recent work by the team of Peter Carmeliet (VIB-KU Leuven Center for Cancer Biology) has pushed the boundaries of cancer research forward. They expanded their pioneering work on endothelial cells by providing an even more detailed, single-cell look at the cells and the blood vessels they line. The team used an array of high-end technologies, single-cell and bulk RNA sequencing, mass cytometry, proteomics, big data analysis, as well as functional testing of identified targets. Their description of distinct subsets of endothelial cells and blood vessels is an important addition to our understanding of the vasculature's functions in health and disease, especially considering the changes in blood circulation in and around tumors. Their work has already resulted in four papers in top journals. We spoke to Peter about the accomplishments of his team.

Where did the idea for this research come from?

Peter: "As every organ resides in a specific micro-environment carefully adapted to meet the organ's physiological needs, it is widely accepted that blood vessels are also phenotypically adapted accordingly. However, exactly how extensive these tissue-specific adaptations are has remained largely in the dark. Therefore, we aimed to categorize the vasculature on a cell-to-cell basis."

"Research from our group previously showed that tumor vessels differ from vessels in healthy tissue, but it was unknown up to now which phenotypes constitute the tumor endothelium, what their distribution

is, and how this differs when compared to the endothelium in healthy surrounding tissue."

Your team generated incredible amounts of data. How do you deal with this 'data torrent'?

Peter: "The amount of biological data, generated with (single-cell) omics technologies, is rapidly increasing, thereby exacerbating bottlenecks in the data analysis and interpretation of omics experiments. Data mining platforms that facilitate non-bioinformatician scientists to analyze a wide range of experimental designs and data types can aid the exploration of omics datasets. Therefore, our lab developed BIOMEX, a browser-based user-

friendly software suite, designed to facilitate the Biological Interpretation Of Multi-omics EXperiments by bench scientists. BIOMEX is open source and freely available."

It's an incredible piece of work. How important were the Core Facilities/ supporting staff?

Peter: "Immensely important! This kind of huge data generation and switch of research field is impossible without the efforts of a whole team. It was truly a joint effort, the structural changes, reorganization, and support of the entire lab was needed to achieve these findings."

"The Single Cell Core facility of Diether Lambrechts supported us,



also Bernard Thienpont's expertise was invaluable to develop the correct skills and knowledge in our team. We are truly grateful for their invaluable contribution. Our team progressively acquired know-how in data analysis, 10X Genomics GemCode technology, scRNA-sequencing, bioinformatics analysis, etc. Combining the expertise of biologists and bioinformaticians not only led to a descriptive cell atlas but also to novel biological insights."

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

Peter: "The difficulty is no longer to generate a cell atlas; the challenge is to prioritize from large lists the targets that hold potential for drug development. If funding would be unlimited, I would use these resources to develop new drugs, or at least perform additional functional validation studies to expedite bridging the gap between a top publication and licensing patents to big pharma."

"An impactful follow-up of this work would be the creation of a human tumor endothelial cell atlas. In fact, efforts are undertaken to start-up this project. Such data would create opportunities to further advance cancer treatment by tailoring the anti-angiogenic therapy to the tumor type-specific endothelial properties. These findings will form the basis

of new drugs and personalized medicine. There is a pile of targets that could be validated, which potentially could create spin-off activities. A good example hereof is the recent creation of the spin-off company Montis BioSciences, based on scRNA-sequencing data from our lab and the input of Massimiliano Mazzone. Montis will investigate the interaction between immune and endothelial cells, it is the step forward to translate research findings into therapeutic applications."

Any pleasant surprises along the way?

Peter: "Getting a paper accepted in JASN within 55 days after initial submission on a fast track, after getting glowingly positive reports from six reviewers, or receiving highly enthusiastic feedback from the *Cell* editor (even before all reviewers had sent in their comments) with the request to resubmit as soon as possible with guided advice on how to revise our paper. Or the multiple spontaneous positive comments and congratulations by email and social media on the publications, as evidence of their impact in the field."

Any lessons or envisioned breakthroughs?

Peter: "Biology is even much more complex than we ever thought! The vasculature is known to play a critical role in a wide range of pathologies.

Despite vast technological advances and the rise of single-cell compendia, blood vessels were somewhat overlooked until now, hampering detailed analyses of the importance of endothelial variety for blood vessel biology."

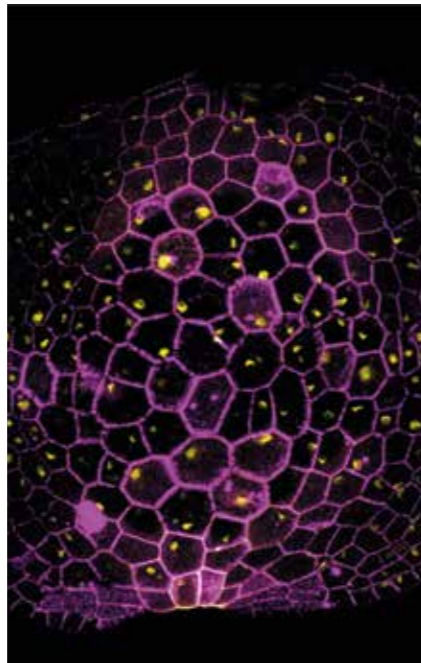
"New tools will enable more single-cell studies, providing insight at a more detailed level. However, the bottleneck in omics approaches is becoming less and less about data generation, but more and more about data analysis, interpretation, and integration. The challenge will be to select and prioritize those candidate genes that are true targets for drug development. For instance, together with Max Mazzone, we are developing new CRISPR-based transgenic technologies to generate many more endothelial cell-specific conditional knockout mice much faster. Similar and alternative techniques will be needed to mine the large amounts of data for further translation."

Rohlenova, Goveia, Garcia Caballero, Subramanian *et al.* (in press). *Cell Metabolism*
Kalucka, de Rooij, Goveia *et al.* (2020). *Cell*
Goveia, Rohlenova, Taverna, Treps *et al.* (2020). *Cancer Cell*
Dumas, Meta, Borri *et al.* (2020). *Journal of the American Society of Nephrology*

QUICKSCAN

Fighting Flu

Influenza A virus infections are a major recurrent cause of seasonal respiratory tract infections. The best way to prevent influenza disease is vaccination. However due to the accumulation of point, human influenza vaccines need to be reformulated and administered regularly. Here, the teams of Xavier Saelens (VIB-UGent Center for Medical Biotechnology) and Han Remaut (VIB-VUB Center for Structural Biology) developed a novel anti-influenza A virus approach based on an engineered single-domain antibody construct that can selectively recruit innate immune cells to the sites of virus replication.



Handling Big Data in proteomics

The field of computational proteomics is approaching the age of big data age. But most proteomics tools are unable to operate directly on the formats generated by mass spectrometers. Here, the Lennart Martens team (VIB-UGent Center for Medical Biotechnology) presents ThermoRawFileParser, an open-source, cross-platform tool with a user-friendly interface that converts Thermo RAW files into open file formats. Here are some Twitter impressions:

@lgatt0: "Very first time I converted a Thermo raw binary file to mzML on a Linux computer. Did it using ThermoRawFileParser from @compomics - very neat!"

@UCDProteomics: "Just tried it and it worked the first time! This almost never happens with proteomics software."

@drupad_t: "So much progress. Vendor locked formats might be history soon. Need this blessing for Waters files with a way to re-bin data so that files aren't humongous."

@byu_sam: "Game changer for grid computing"
Hulstaert *et al.*, *Journal of Proteome Research* 2020

The development of plant vascularity

Vascular plants contribute to most of the food and feed production on earth and deliver heating and construction materials in the form of wood. Yet, we know very little about how non-vascular plants acquired vascular tissues during evolution. Here, the teams of Klaas Vandepoole and Bert De Rybel (VIB-UGent Center for Plant Systems Biology) provide the first example of a developmental regulator for which the innovations leading to a vascular function are clearly correlated with the emergence of vascular plants.

Lu *et al.*, *PNAS* 2020

Designed cytokines that fight tumors

The clinical application of many cytokines, including TNF and IFN- γ , is severely hampered by their often dangerous side-effects. Jan Tavernier's lab (VIB-UGent Center for Medical Biotechnology) has developed 'designer' cytokines (AcTakines) that reduce undesired side-effects. Depending on the strategy, these AcTakines either increased the efficacy of immune therapies or induced selective destruction of tumor neovasculature, leading to complete tumor elimination without toxicity.

Huyghe *et al.*,
EMBO Molecular Medicine 2020

Sequencing the water lily genome

Biologists are always learning new information about the genetic makeup of different species. Here the Yves Van de Peer team (VIB-UGent Center for Plant Systems Biology) announced that they have sequenced the genome of the blue-petal water lily (*Nymphaea colorata*). The DNA of a water lily holds information about water lilies themselves, such as a whole-genome duplication event, but it also paints a bigger picture in the context of all angiosperms.

Zhang *et al.*, *Nature* 2020



The optimal length to identify structural variants

Long-read sequencing has substantial advantages, but the required and optimal read length has not been assessed. In this work, scientists from the VIB-UAntwerp Center for Molecular Neurology used the Oxford Nanopore PromethION for human whole-genome sequencing and structural variant detection. They determined the optimal and sufficient read length for the identification of most structural variants to be 20 kb through an in-silico simulation study for multiple read lengths. These findings crucially guide our future experimental design aiming for population-scale structural variant identification in the context of neurodegeneration.

De Coster *et al.*, *NAR Genomics and Bioinformatics* 2020

The Hippo pathway in tumor growth

The Hippo signaling pathway has been implicated in tumor growth, sparking interest in the pathway as a potential therapeutic target. In a study of liver cancer in genetically manipulated mice, the Georg Halder team (VIB-KU Leuven Center for Cancer Biology) discovered that the role of this pathway in tumorigenesis is more complex than previously appreciated. They found that whether tumor cells survive or are eliminated depends on competing signals produced by the tumor and surrounding tissue.

Moya *et al.*, *Science* 2019

NanoSatellite surveys the genome for signs of Alzheimer's

The lab of Kristel Slegers (VIB-UAntwerp Center for Molecular Neurology) investigates a Variable Number of Tandem Repeats (VNTR) expansion as the functional variant in the ABCA7 locus associated with Alzheimer's Disease. For this purpose, they used Oxford Nanopore PromethION whole-genome sequencing and developed NanoSatellite, a tool based on dynamic time warping of the raw current signal. Using nanopore sequencing and this algorithm they can identify repeat expansions on a genome-wide scale and identify their length, repeat unit interruptions, and nucleotide modifications.

De Roeck *et al.*, *Genome Biology* 2019

The many faces of endothelial tumor cells

Heterogeneity of lung tumor endothelial cell phenotypes across patients, species, and models remains poorly inventoried at the single-cell level. The team of Peter Carmeliet (VIB-KU Leuven Center for Cancer Biology) single-cell RNA (scRNA)-sequenced 56,771 endothelial cells from human/mouse (peri)-tumoral lung and cultured human lung TECs and detected 17 known and 16 previously unrecognized phenotypes. Integrated analysis identified collagen modification as an angiogenic pathway.

Goveia *et al.*, *Cancer Cell* 2020

An implant for long-term brain monitoring

To advance our understanding of complex brain function, long-term electrophysiological recordings of neural activity in freely behaving animals are powerful – but technically challenging – tools. Now, the Kloosterman lab (NERF, empowered by imec, KU Leuven and VIB) presents a new implant for inserting multiple probes that allow free behavior in rats. This enables the monitoring of brain activity over a long time period. The probes are micromachined and the positioning mechanism is 3D-printed using stereolithography. These probes can be assembled in only a single day.

Van Daal *et al.*,
Journal of Neural Engineering 2019

Removing the armor of anthrax

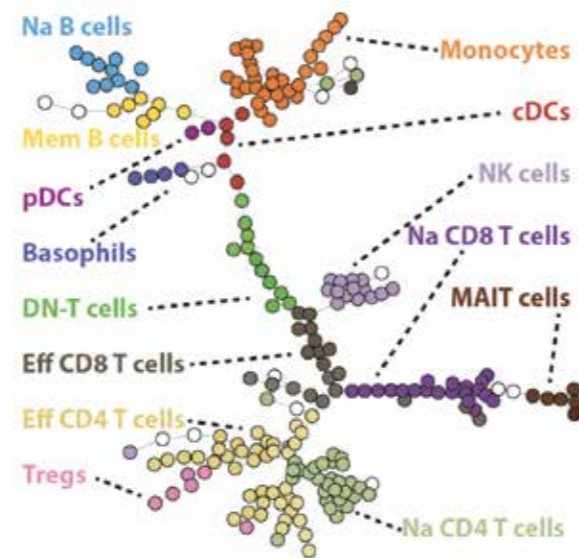
Anthrax is a deadly and highly resilient disease, caused by the spore-forming bacterium *Bacillus anthracis*. The lab of Han Remaut (VIB-VUB Center for Structural Biology) has shown that removing the armor of the bacterium that causes anthrax slows its growth and negatively affects its ability to cause disease. A poorly understood component of this armor is the Sap S-layer, a layer of protein that forms a shell around the bacterium. In this study, researchers successfully applied Nanobodies® to control the assembly of the bacterial armor and study its structure.

Floravanti *et al.*, *Nature Microbiology* 2019

Finding TRPM3 in human neurons

The TRPM3 ion channel functions as a noxious heat sensor and plays a key role in acute pain sensation. Despite its potential as novel analgesic drug target, little is known about the expression, function and modulation of TRPM3. The Voets lab (VIB-KU Leuven Center for Brain & Disease Research) studied TRPM3 in human dorsal root ganglion neurons and in human stem cell-derived sensory neurons at the mRNA level. They detected TRPM3 channels in both neuron types, and provide the first direct evidence of functional expression of the pain receptor TRPM3 in human sensory neurons.

Vangeel *et al.*, *British Journal of Pharmacology* 2020



Representative image of the unsupervised FlowSOM analyses applied on patient samples to gain novel insights into the immunopathology.

The genetics of hyperinflammation

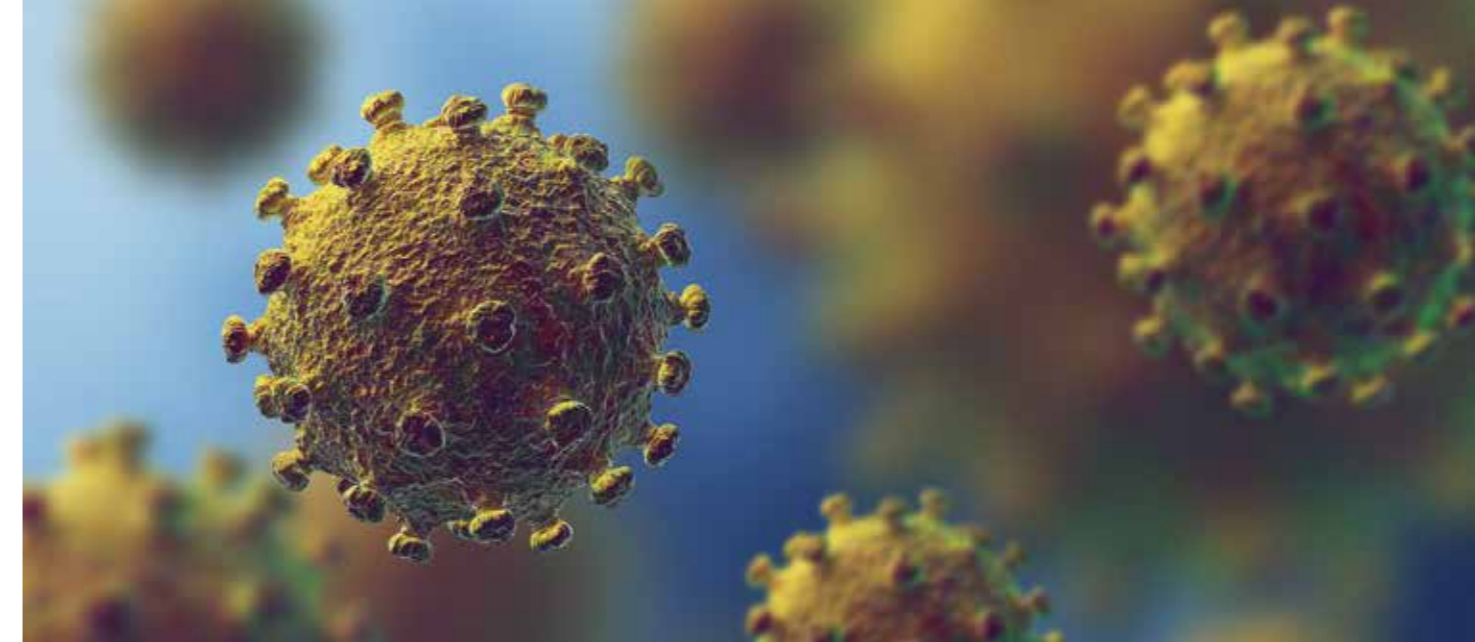
Hemophagocytic Lymphohistiocytosis (HLH) is a rare but deadly disease and is caused by the uncontrolled release of cytokines by an overactivated immune system. In a number of children suffering from HLH, genetic mutations have been identified that impair the natural breaks built in the human immune system. Here, Filomeen Haerynck (UZGent) and Simon Tavernier (VIB-UGent Center for Inflammation Research), in collaboration with the research groups of Vigo Heissmeyer (Ludwig Maximilian University of Munich) and Carola Vinuesa (Australian National University), identified a new genetic variant in the gene RC3H1 in a patient with relapsing HLH. RC3H1 encodes for Roquin-1, a posttranscriptional repressor of mRNA and an important regulator of the immune system. This report establishes a novel link between Roquin-1 and human immune disease.

Tavernier *et al.*, *Nature Communications* 2019

Alzheimer risk genes determine microglia response

The De Strooper lab (VIB-KU Leuven Center for Brain & Disease Research) investigated how genetic risk of Alzheimer's disease manifests itself at the molecular and the cellular level in the brain. Analysis of different transgenic mouse models showed that the genetic risk is mainly reflected in the transcriptional responses of microglia to amyloid- β pathology. Single microglia sequencing confirmed the expression of 15 risk genes in microglia and confirms that many more microglia adopt an activated phenotype when facing amyloid- β than when facing TAU pathology.

Sierksma *et al.*, *EMBO Mol Med* 2020



Collaborating

AGAINST CORONA

As the outbreak of the new coronavirus (2019-nCoV) continues to spread, VIB scientists are quickly mobilizing to try to find a potential treatment for the viral infection. The lab of professor Xavier Saelens (VIB-Ghent University), with its long-standing expertise in developing vaccines and antivirals against respiratory viruses, is well positioned to help mitigate this crisis.

Since the coronavirus outbreak was reported by China in December 2019, the number of confirmed cases of the virus is increasing rapidly. All over the world, scientists are rushing to develop vaccines or treatments.

Research from the lab of professor Xavier Saelens (VIB-UGent Center for Medical Biotechnology) has already resulted in novel vaccines and antivirals against influenza and RSV that are currently in or making their way to the clinic. In view of the urgency of the matter, the Center quickly added additional staff to the team and VIB's Discovery Sciences unit is providing advice. In a collaboration with Dr. Barney Graham at NIAID and Dr. Jason

McLellan, associate professor of the College of Natural Sciences at the University of Texas at Austin, the Saelens lab is now making significant progress in developing a therapeutic antibody against the novel virus.

"The growing crisis requires all hands on deck," Xavier Saelens comments. "Our team is working as fast as possible to develop a protective drug capable of stopping the coronavirus." The scientists already succeeded in identifying a single-domain antibody with high binding affinity to a unique, conserved conformational epitope present on the receptor-binding domain of SARS-CoV and 2019-nCoV. Bert Schepens, staff scientist in the group of Xavier Saelens, explains:

"Antibodies are usually extremely effective in defending the body against very specific viral intruders. But coronaviruses come in different shapes. This new coronavirus illustrates the need to develop antiviral antibodies that can tackle a very broad range of these viruses."

Currently, the VIB researchers are preparing the preclinical test phase for a coronavirus treatment. Although the first results are highly promising, further research is necessary to confirm the full potential of this antibody-based drug against 2019-nCoV.

Confirmed - VIB core facilities:

A LEADING EXAMPLE IN EUROPE

Geert Van Minnebruggen



Every five years, the quality of the services of VIB's core facility program is evaluated by an international, interdisciplinary panel of technology experts. At the end of November 2019, seven of our cores received high praise – and future-focused recommendations – from nine of the world's top experts. Geert Van Minnebruggen, head of core facilities at VIB, tells us what these results mean for the program's roadmap.

Why is the TEB – the Thematic Evaluation Board – so crucial for VIB cores?

Geert: "Our cores and groups are subject to regular evaluations not only as part of our drive for excellence, but because of a management agreement we have with the government. They set the key performance indicators for the respective units and it's serious business: if a group leader or core facility head fails to meet expectations, actions are taken to get them back up to standards. Even discontinuing the activities of a core or its head is not excluded. As you can imagine, we invest huge amounts of time and energy in preparing for TEBs."

"TEBs are important for another reason: the board's recommendations are very valuable for further improvement. There's always a next goal to aim for, and the life sciences are a dynamic domain. This means that our cores must continuously evolve to stay at the top of their game. Based on the review of the technologies and techniques applied at each core, the panel issues an assessment of the program's activities and recommendations for the next five-year cycle. We use this as momentum for future developments."

And as for the 2019 assessment: what stands out as a key highlight for you?

Geert: "It's a fact that collaboration and partnerships are the keys to boundary-pushing life sciences. Group leaders who drive science forward work much more closely with core facilities because science and technology are interconnected. The future will happen at the intersection of disciplines and core facility services."

"As the head of this program, I strive to invest in a spirit of unity to enable all cores to work as one. Our team spirit takes the level of the core program to new heights, and our efforts were truly recognized by the TEB panel this year. When it comes to the professionalization of the services, technologies and activities of each core, the panel acknowledged our enormous progress since 2014. As our international peers, these experts rate us as acting at the highest-possible level in Europe. We can be very proud that the value we generate for our community of scientists has been recognized and lauded."

"The panel achieved full consensus in their opinion that overall, the VIB core facility program is a major driver of research excellence within VIB and in Belgium (and Europe). VIB is recognized for its core facility program and is a gold standard in Europe for how cores should be implemented and operated. Indeed, the panel would like to congratulate and commend the VIB leadership for the extraordinary success and importance of the core facility program."

TEB panel, 2019 assessment executive summary

Do you feel that the panel's recommendations will prove important for the future of VIB core facilities?

Geert: "Absolutely, the panel was spot-on in its guidance. Two recommendations are especially interesting to highlight today, and these are investment in infrastructure and data management."

"Over the last evaluation cycle, we set up an earmarked fund for infrastructure investments, and this is an enabler for our program. Infrastructure is expensive, especially for all of these domains, and a top-notch device can be outdated in only a couple of years. We must prepare for these expenses, carefully mapping out the devices we have in operation to understand the dynamics between them. In addition, we have developed a co-investment strategy in which we work with VIB centers and partner universities to jointly fund the infrastructure that will allow us to maximally benefit all parties. The aim is to further capitalize on this co-strategy."

"And as for the second recommendation, data management is becoming exponentially more important. As scientists, data is the most important asset. That's what we do – generate and learn from data. We also started to work with artificial intelligence-based and deep-learning techniques for data analysis. Within this context, the panel issued a powerful statement: 'if you don't establish an institutional data policy at VIB within the next five years, your rank at the top will be challenged.'"

"This may hamper the cores as data-producing units. Therefore, it's important for us to handle vast quantities of data correctly by modernizing our IT structure, better documenting our data, metadata, and establishing a policy that makes data available for both the scientific community and the general public."

In addition to responding to these recommendations, do you have specific ambitions for the core facility program that you'd like to share?

Geert: "There's a topic that I recently covered in an opinion paper and which VIB is currently pioneering in the EU: innovation in core facilities (Lippens *et al.*, EMBO Rep. 2019). To ensure innovation that doesn't interfere with our key service activities, we need to attract staff members with other skillsets and an entrepreneurial mindset. We also need another set of metrics for innovation activities. Real innovation requires freedom. It's high risk, but it's also high gain."

"Another ambition is to continue acting as enablers, working ever more closely with VIB research centers to develop our activities starting from the needs of our scientists. One of the main realizations after the 2019 TEB is that it's now very clear that the cores, together with our eight research centers, are part of the overarching strategic roadmap of VIB."

Congratulations to Geert, the core facility heads and all our core colleagues on this achievement. Each of the seven core facilities evaluated received targeted recommendations as well.

A TECH WATCH SUCCESS STORY

Nanopore sequencing at the VIB-UAntwerp Center for Molecular Neurology



Standing (from left to right): Wouter De Coster, Svenn D'Hert, Tim De Pooter and Peter De Rijk. Sitting (from left to right): Jasper Van Dongen, Mojca Strazisar and Geert Joris.

The value of early access

Getting early access to novel technologies through the VIB Tech Watch program can be very valuable to derisk and facilitate their adoption. One of the recent success stories of this initiative is nanopore sequencing at the VIB-UAntwerp Center for Molecular Neurology.

We started using this technology in 2014 with the Oxford Nanopore Technologies MinION early access project co-funded by Tech Watch. Early on we recognized that a novel technology requires not just rounds of optimizations of the wet-lab protocols but also the development of new bioinformatics approaches. This led to the development of NanoPlot and the NanoPack package, the current standard tools for nanopore sequencing quality assessment.

At the center, we initially used nanopore sequencing for targeted transcript sequencing to look at alternative splicing of *ABCA7*, a gene associated with Alzheimer's Disease. A MinION run will nowadays give you reads of up to 30 gigabases but human genome sequencing only became tractable with the high-throughput PromethION sequencer, also obtained with the help of Tech Watch co-funding. Outside of the company itself, we held the global record of the highest yield obtained on a single flow cell for months by optimization of our wet-lab protocols.

Enter the nanopore

Using a nanopore for sequencing is a relatively old idea, initially conceptualized by David Deamer (University of California, Santa Cruz, US) in 1989. The technology is based on the principle that molecules

passing through biological pores anchored in a membrane across which a voltage is applied will disturb the current signal in a structure-specific manner. This allows the identification of nucleotides – the building blocks of DNA – and potentially other molecules.

Some key characteristics differentiate nanopore sequencing from the more commonly used Illumina sequencing: longer reads (10,000 up to the current record of 2 million bases), lower per nucleotide accuracy (90-95%), and direct observation of modified nucleotides, for example methylcytosine.

Detecting elusive variants

The long read lengths enable detection of an elusive type of genomic variants: structural variations, defined as locations in the

genome of at least 50 bases with a change in copy number or location. Short read sequencing leads to many false positives and false negatives and is therefore inadequate.

We evaluated PromethION human genome sequencing for two repeat expansions: one in *ABCA7* contributing to Alzheimer's disease and another in *C9orf72* underlying frontotemporal dementia.

Traditionally only labor-intensive and low-resolution methods such as Southern blotting and repeat-primed PCR can be used for this type of variant, but long read sequencing enables detection, sizing and evaluation of repeat motif interruptions. In the past year, multiple groups have identified novel repeat expansions, suggesting that this class of mutations is underappreciated.

We evaluated genome-wide structural variant identification with PromethION and compared the available software tools.

We established that long-read sequencing can identify more than 25,000 structural variants per human genome with an unprecedented resolution. PromethION genome sequencing also confirmed a challenging four megabase inversion associated with dementia. Through a simulation experiment, we determined that reads of 20-25 thousand bases are optimal and sufficient for structural variant identification. Further applications we now have experience with are the identification of small variants, targeted transcript sequencing, and sequencing cell-free DNA.

Taking nanopore sequencing forward

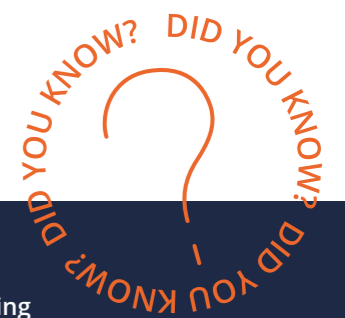
The presence of a modified nucleotide, such as methylcytosine, will have an influence on the current signal. Several computational methods have been developed for the detection of nucleotide modifications, for which we developed methplotlib, software for visualization and further analysis. These methods will have a large

impact on our understanding of epigenetic regulation and its role in health and disease.

In our current projects, we will sequence DNA extracted from the brain from a large cohort of dementia patients, hunting for structural variants and aberrant nucleotide modifications involved in neurodegenerative disorders. We are always open to collaborations, so reach out to us if you believe nanopore sequencing could help your research (Mojca.Strazisar@uantwerpen.vib.be). The future of genomics definitely looks bright using direct long-read sequencing.

By Wouter De Coster (VIB-UAntwerp Center for Molecular Neurology)

- ...that Flemish minister for Innovation Hilde Crevits provided additional funding for ELIXIR Belgium? These additional funds will allow further activities on the FAIRification of research data and the facilitation of reproducible analysis.





From left to right: Yvan Saeys, Saskia Lippens, Frank Vernailen, Anneke Kremer, Amanda Gonçalves, Joris Roels and Alexander Botzki

KEEPING HUMANS IN THE LOOP

for large-scale bioimage analysis

In a unique collaboration between the VIB Biomaging Core facility, the VIB Bioinformatics Core facility and the Yvan Saeys lab (VIB-UGent Center for Inflammation Research), scientists have developed a new, user-friendly tool for interactive image analysis of microscopy data. Based on a human-in-the-loop model, state-of-the-art image analysis techniques developed in the Saeys lab were translated into an interactive and GPU-accelerated tool for practical use by the scientists.

Tools of the trade

A technology is only as useful as the tools that exist to interpret the data being generated. This is especially true in the field of 3D electron microscopy (3D-EM) where the tools to analyze these huge volumes of data are lagging.

“In the field of bioimage analysis, large amounts of data are generated, but not for all state-of-the-art imaging technologies are ready-made solutions to perform analysis available. This especially the case for 3D-EM techniques,” explains Saskia Lippens, who led the study together with Prof. Yvan Saeys.

“Although this technology has proven its potential for many areas within life sciences, there is still a bottleneck at the level of image reconstruction and analysis,” adds Yvan Saeys. “For such applications, analysis solutions need to be tweaked, and that’s where the

expertise of bioinformaticians and computer scientists comes in.”

Removing noise

The novel tool was jointly developed by Joris Roels and Frank Vernailen. Already during his PhD in the Saeys lab, Roels had been developing novel tools for image restoration and segmentation in a close collaboration with the VIB Biomaging Core. In order to bring these new solutions to the microscopy users, Roels joined forces with Frank Vernailen, a developer at the VIB Bioinformatics Core who specializes in imaging tool development.

“This successful collaboration resulted in DenoisEM, a new tool for denoising big 3D-EM datasets and segmentation, available as a plugin for Fiji. Since we wanted to optimally combine human and computational power, DenoisEM uses a human-in-the-loop model, where the scientist has several

‘checkpoints’ to interact with the data,” Roels explains.

Vernailen further highlights the importance of the interaction with the user: “The scientist can determine the specific parameters for image analysis so that the interpretation of data does not happen in a black box but under supervision of the experts.”

The researchers’ next aim is to continue developing solutions, including (semi)-automated segmentation, in order to speed up this process, avoid long manual work and bias. The collaboration between the Saeys lab, BioImaging Core and Bioinformatics Core is a prime example that shows how research can be translated into a tool for practical use. They are convinced that the interaction between research labs and core facilities regarding data analysis and novel tool development has yet to reach its full potential.



Sebastian Munck

Opening up

THE CORES

Core facilities are unique repositories of technology and know-how. They are often vital ingredients for successful science in top life sciences institutes. However, they also offer great potential for use by external users, something many core facilities promote. Writing in *EMBO Reports*, Sebastian Munck (VIB Bio Imaging Core and VIB-KU Leuven Center for Brain & Disease Research) and colleagues discuss access models and outline a gated process for interacting with external collaborators over distance.

“Shipping samples,” they write, “has the potential to enrich service portfolios, accelerate discoveries, and contribute to the facility’s success, ultimately benefitting the host institution.”

They illustrate their proposal with a recent study that developed a new method for imaging axon regeneration with synthetic nerve conduits. Despite being almost 750 km apart, the core facility and external research group collaborated successfully for over two years, shipping samples the entire time. Interacting remotely did not hinder the process, in fact, it might have made it more efficient, both in terms of time and resources — resulting in less scheduling conflicts, less travel time, and as a corollary, a lower carbon footprint.

The keys to success, according to the authors, were that: “The respective scientific interests of the core facility as well as the center that they are embedded in and the external research group had been aligned, and clear expectations and milestones were formulated.”

With this example in mind, the researchers propose that their new access model for core facilities “...has the potential to become the most suitable access model for some imaging facilities, allowing them to carry out projects and long-term strategic interactions that otherwise could not be done via short term visits. In any case, the overall objective, regardless of the access model, should be to enable the best science.”

JAN TAVERNIER LISTED

in Top 20 translational researchers



Jan Tavernier

Moving from scientific insights to innovative applications is not always an easy road to travel. Each year, *Nature Biotechnology* compiles a list of twenty researchers who excel in navigating this challenging path. Jan Tavernier (VIB-UGent Center for Medical Biotechnology) is only the second Belgian ever (following Nico Callewaert from the VIB-UGent Center for Medical Biotechnology), and one of the very few Europeans, to make it onto this US-dominated list. The list is an aggregate score of number of patents granted in that year, patent citations and h-index.

With his inclusion on the list, Jan Tavernier follows in the footsteps of Nico Callewaert (VIB-UGent Center for Medical Biotechnology) as internationally recognized top translational researcher. They are the only Belgians ever to be included, which is a great recognition of VIB's technology transfer policy that aims to directly translate groundbreaking science into societal benefits.

From receptor to start-up

The lab of Jan Tavernier specializes in unraveling the fundamental functioning of cytokines and their receptors that drive a wide variety of biological mechanisms underlying health and disease. Complementing this basic research, Jan's team focuses on manipulating receptor signaling, which has numerous potential applications.

A recent example is the development of AcTakines, cytokine fusion proteins that bind to a receptor but only induce receptor signaling in selected cell types. These can be used in the development of new drugs for the treatment of certain autoimmune diseases and pathologies linked to specific types of cancer.

In order to achieve this, VIB safeguards its inventions with patents through the work of the dedicated Innovation & Business team in close collaboration with the researchers. These patents rights are actively licensed to national and international companies or can be retained to support the inception of novel spin-offs. Tavernier's patent portfolio has been instrumental in VIB's value creation for its start-up Orionis Biosciences.

Two new VIB spin-offs announced

MONTIS BIOSCIENCES AND MRM HEALTH

Montis Biosciences launched and locked on (tumor) target

Montis Biosciences, founded by VIB, KU Leuven and Droia Ventures, is based on the science from the labs of Peter Carmeliet and Massimiliano Mazzone (both VIB-KU Leuven Center for Cancer Biology). The novel spin-off's mission is to investigate and therapeutically exploit interactions between perivascular macrophages and tumor vasculature, in order to drive and sustain immune reactions against solid tumors.

Seed funding of €8,4 million allows Montis Biosciences to progress towards clinical studies and expand its screening and assay platform to identify and validate additional promising targets. For the seed financing, the founders were joined by new investors Polaris Partners, ALSA Ventures and Pfizer Ventures.

"It is becoming increasingly clear that endothelial cells in the tumor vasculature play a major role in immune reactions to cancer. Historical therapies targeting the tumor vasculature largely ignored this role," says Peter Carmeliet. "Our research shows that we can use blood vessels to herd the correct immune cells towards the tumor and get much more potent and sustainable effects."

"Our approach with single-cell RNA-sequence data allows us to investigate the communication between immune

cells and the tumor vasculature," adds Massimiliano Mazzone. "Montis is the step forward to translate this concept into therapeutic applications."

Johan Cardoen, managing director, says: "Montis is a prime example of how scientific excellence complemented with an entrepreneurial mindset and early stage investors can result in a promising new venture."

MRM Health ready to leverage microbiome knowledge

Together with KU Leuven and Ghent University, VIB announced another spin-off last February: MRM Health, a biopharmaceutical company focused on the discovery and development of innovative therapeutics based on the human microbiome. MRM Health will leverage the extensive microbiome and bioinformatics capabilities of the lab of Jeroen Raes (VIB-KU Leuven Center for Microbiology) and the multidisciplinary know-how in arthritis and inflammatory diseases of Dirk Elewaut (VIB-UGent Center for Inflammation Research) and his team.

The new company debuted by announcing a collaboration with DuPont Nutrition & Biosciences and the successful completion of its first external investment round of €14 million with the participation of Ackermans & van Haaren, DuPont Nutrition & Biosciences, MRM Technologies, Qbic II and VIB.

Jeroen Raes says: "I'm excited by MRM Health's expertise in microbiome product development. Our know-how perfectly matches their platform to develop new treatments for a wide range of conditions."

Dirk Elewaut adds: "My team has a longstanding interest in studying the links between gut and joint inflammation observed in rheumatic diseases. This new venture is a big step forward in accelerating the development of treatments for patients with arthritis or other inflammatory diseases."

The investment round provides MRM Health with the resources to advance its lead program in Inflammatory Bowel Disease to clinical studies in different patient populations, and to progress its ongoing programs towards delivering potential treatments for spondyloarthritis and other conditions.

Johan Cardoen comments: "This new venture represents a unique opportunity to make the scientific discoveries made in the labs of Jeroen Raes and Dirk Elewaut available to the pharmaceutical and life science industry. We are pleased to continue our collaboration in the microbiome field with MRM Health and invest in the company."

VIB spin-off

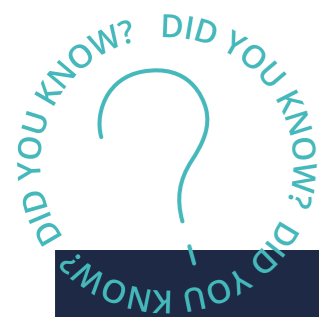
ORIONIS BIOSCIENCES ENTERS COLLABORATION WITH NOVARTIS

Orionis Biosciences announced a major drug discovery collaboration with Novartis. Orionis has developed innovative technologies in genome-scale drug discovery and tunable molecular design of novel therapeutic drug modalities to tackle the industry's most intractable disease targets.

Orionis Biosciences, named for the Orion star system, is a unique constellation of people, technology platforms and drug modalities. The company was founded by VIB and drug discovery and technology pioneers Niko Kley and Jan Tavernier (VIB-UGent Center for Medical Biotechnology). Riccardo Sabatini joined the company as architect and leader of Orionis' computational science platform.

"The opportunity behind the forming of Orionis was that existing drugs reflect relatively few disease targets being addressed with too many similar drugs. We have been steadily executing our mission to bring together an array of technological innovations to enable discovery of a diversity of new drug candidates that act with high therapeutic target-focused precision," commented Prof. Jan Tavernier.

The four-year collaboration with Novartis will leverage Orionis' ALLO-GLUE™ technology platform in the discovery and design of novel small molecule therapeutics, including different classes of protein degraders, across various therapeutic areas.



- ...that Confo Therapeutics has won the Most Innovative European Biotech SME Award in the category 'healthcare', awarded by EuropaBio?
- ...that Confo Therapeutics has been granted two key ConfoBody™ patents derived from the patent estate known as the 'Steyaert patents'?
- ...that AgroSavfe has changed its name to Biotalys and incorporated the US subsidiary, Biotalys, Inc.?
- ...that VIB will again be strongly represented at Knowledge for Growth 2020 with multiple VIB colleagues in the program? You can join them by registering on the Knowledge for Growth website.

AWARDS & RECOGNITION

DIRK INZÉ WAS NAMED AAAS FELLOW



Dirk Inzé

The American Association for the Advancement of Science (AAAS) is the world's largest general scientific society. Each year, certain AAAS Fellows are elected, an honor bestowed upon AAAS members by their peers. Dirk Inzé (VIB-UGent Center for Plant Systems Biology) was named AAAS Fellow for 2019.

Dirk receives the fellowship for his lifelong dedication to plant science, and the translation of basic research on cell biology and stress biology into crop improvement in wheat and maize. He is only the second VIB member and Flemish scientist ever to have been named AAAS Fellow, a testament to his unwavering dedication to excellent science with societal impact.

AWARDS FROM THE QUEEN ELISABETH MEDICAL FOUNDATION

The Queen Elisabeth Medical Foundation (Geneeskundige Stichting Koningin Elisabeth) awards funding to trailblazing neuroscientific research.

Thomas Voets and Pierre Vanderhaeghen

(both VIB-KU Leuven Center for Brain & Disease Research) have been awarded project grants. Thomas will investigate noxious cold sensing and Pierre will explore cellular modelling of intellectual deficiency and autism spectrum disorders using human neurons *in vivo*.



Pierre Vanderhaeghen

Thomas Voets



Valerie Uytterhoeven

Valerie Uytterhoeven

(VIB-KU Leuven Center for Brain & Disease Research) received a young investigator project grant for her work on the molecular mechanisms and inducers of chaperone-mediated Tau autophagy in Alzheimer's disease.

Aya Takeoka

(NERF, empowered by imec, KU Leuven and VIB) also received a young investigator grant to determine cellular signatures underlying age-dependent spinal cord plasticity.



Aya Takeoka



VIB Alumna Els Beirnaert

CEO OF AELIN THERAPEUTICS

Els Beirnaert

Every day brings a new challenge; every week we push our boundaries

Els Beirnaert pioneered for nine years at Ablynx. In 2010 she joined VIB, first as Business Development Manager, later as Head of New Ventures. Els was involved in the creation of Confo Therapeutics, Multiplicom and Q-Biologicals, to name a few. At the beginning of 2018, she took the lead of Aelin Therapeutics.

At the beginning of your research career you focused on infectious diseases. Was that a deliberate choice?

Els: "Absolutely, I was especially intrigued by the interplay between viruses and their host cells. After my master's degree in Ghent on influenza, I got the opportunity to work on HIV with Guido van der Groen at the Institute of Tropical Medicine (ITM) in Antwerp. At that time HIV and AIDS were tremendously important research topics. The virus was still considered a global threat and there was still a lot to be discovered. At the same time new diagnostics and therapeutics were on the brink of breaking through. The HIV research community was a very dynamic and exciting group at that time, and with ITM we were right in the middle of this community."

Did you also do field work in Africa?

Els: "All the samples processed at ITM came from Africa. At some point Guido van der Groen sent me to a scientific meeting in Ivory Coast to present some results. It became a very interesting experience. Not that the conference itself was so inspiring, but I was taken to underprivileged neighborhoods where HIV was only one of the problems people were facing. HIV was maybe not even the worst of those problems. There was also malaria, dengue, and many other infectious diseases that we in the Western world were not confronted with.

I got a second eye-opener during an internship at food giant Unilever. I suddenly realized that research in an industrial context can lead to concrete products. This objective-oriented approach suited me more than the exploratory *modus operandi* in academia. This insight completely changed my professional career path. The moment I finished my PhD, I applied for a job at Ablynx, at that time an early start-up. The rest is history ... the next 18 years I would be hooked up to biotech start-ups."

What is so different to work in a start-up compared to academia besides the goal-oriented approach?

Els: "There is more teamwork in industry, especially at early start-ups. Everyone has to adopt the same line towards a common goal, while in academia most people are mainly focused on their PhD, their publication, their grant, their project... At a start-up you *have* to function as a team, otherwise you will not reach your goals.

Even if that team consists of a mix of chemists, biologists, pharmacists and physicians... They have to overcome the boundaries of their own expertise and knowledge. They have to leave their comfort zones and function together towards the next phase, the next common milestone.

And at the end of the day, things need to be done at a start-up, a problem has to be solved, the next hurdle has to be taken; very often without immediate access to experts or specialists and with limited resources. This demands a pioneering spirit, out of the box thinking, flexibility, and commitment. Building these kinds of

pioneering teams is really what I have always loved to do."

But if the team gets the credits, how can you build a personal career in biotech?

Els: "By seizing the opportunities. And there are many opportunities in start-ups, believe me. Every day brings a new challenge, and thus a new opportunity. Every week we push our own limits. Without exception, each employee in a start-up has to tap into his full potential. If you want to know for yourself what you really have to offer, I advise people to join a start-up like Aelin Therapeutics. You will come into an environment where all your competences and talents – including the hidden ones – will be harnessed."

Aelin Therapeutics secured a 27M€ series A financing in December 2017. One of the largest series A financing rounds in Belgium ever. Can you explain the technology platform behind the company?

Els: "The science behind Aelin is the pioneering work of structural biologists Joost Schymkowitz and Frederic Rousseau of the Switch Lab (VIB-KU Leuven Center for Brain & Disease Research). They investigated the aggregation of beta-amyloid in Alzheimer's disease. Frederic and Joost discovered that nearly all proteins contain short sequences promoting aggregation, even those without any natural tendency to aggregate. They also realized the potential of protein aggregation in clinical applications by inducing the process with synthetic peptides containing aggregation-prone regions. This technology, coined Pept-Ins™, is able to knockout nearly any protein, independent of structural or functional protein class.

In reality, Joost and Frederic were turning the world upside down. They were using the mechanism causing Alzheimer's disease to create a completely novel modality in drug development. Few people believed them. It took Joost and Frederic a painstaking 10 years to proof their concept. They had to swim against the tide. They rearranged their research priorities and resources, stubborn as they were. But it all paid off. Their famous 2016 paper in *Science* entitled 'The *de novo* design of a biologically active amyloid' created a dam burst. Suddenly the whole world was interested in this novel approach. The proof of concept was the final boost towards the foundation of Aelin Therapeutics. Frederic and Joost are still involved in the company as scientific advisors. In addition, the Aelin staff – 16 people in the meantime – collaborates very intensely with the Switch Lab. The work of Joost and Frederic form the fundamentals behind Aelin Therapeutics and their insights are still very precious to us. It is now our task to turn these fundamentals and insights into products to treat unmet medical needs."

The life of

A NEUROSCIENTIST IN HOLLYWOOD



Every postdoc has heard this a million times: “Well, if you can’t get a faculty position, you can still go to industry”. This sentence haunts us wherever we go, whether we are talking to colleagues, our mentors, or even our parents. Moreover, we all hear it so much that at times we even start to believe it ourselves, as if we are being brainwashed into thinking that a career beyond academia is a mere participation prize. Plenty of examples, however, illustrate that this is far from the truth. One such example is Kim Staats.



Kim Staats

City of Angels

“Steven, I just landed a new client!” I am on the phone with Kim Staats. In the background I hear a barista calling for someone to pick up their almond milk chai latte. While I am sitting at my bench between stacks of plates with smelly yeast and bacteria, Kim is in her office, aka a trendy coffee shop in downtown LA. The contrast could not be starker.

I met Kim as a fellow PhD student during my years in the Van Den Bosch lab at VIB. I was new to the neurodegeneration field, and vividly remember her talking with such passion about what motivated her to study amyotrophic lateral sclerosis, or ALS: “While growing up, my neighbor was diagnosed with ALS. It turned out to be a familial form, meaning that his son would have a 50% chance of getting the disease as well.” This triggered a drive in Kim to understand the disease

thoroughly, with the hope of one day contributing to a meaningful benefit for ALS patients.

Right on track

After being exposed to this devastating condition, each of Kim’s career choices were made to understand another facet of the disease: While working on ALS mouse models during her PhD, she first collaborated with and then moved to the Liston lab (ex-VIB; currently Babraham Institute, Cambridge) to explore the role of inflammation in the disease process. After five years at VIB, Kim traded Leuven for Los Angeles. She pursued a first postdoc in ALS genetics at UCLA, after which she made another switch to USC to model the disease using stem cell technology. Saying this academic rollercoaster was a fruitful endeavor would be an understatement. Kim co-authored a whopping 25+ papers, 10+ of which she is first author, amassing 1000+ citations. Moreover, she has shown herself to be a prolific grant writer, and has been a key contributor in acquiring a total of 1.5M+ USD in academic funding. Someone with Kim’s profile must be set for the academic job market, right?

Closing the lab’s door

“I used to enjoy academia. I led a wonderful team of talented students, I was successful in publishing and obtaining funding, but I felt that I hit a plateau. Everything I was already doing during my postdoc, I would just keep doing as a PI.” She continues, “I wanted more. More challenge, more independence, but moreover I wanted to contribute in a more impactful way to patients.” At an ALS conference, Kim met a businessman, who coincidentally used to work at a VIB spin-off, and who was launching a start-up focusing on developing ALS therapeutics. “The company’s purpose-driven focus resonated with me, but it was their strategy to bring new therapeutics to ALS patients quickly that made me want to contribute, a lot. While they had a unique strategy, they needed someone with strong expertise in ALS research. That is when I started consulting for them.”

What started as a freelance consultancy side gig, led Kim to quit her postdoc six months later. “I wrapped up my experiments, and ensured my students were in good hands. The initial freelancing taught me that there was indeed a need, and thus a market, for my expertise and skillset beyond academia. This was initially very surprising to me, as I had somehow erroneously adopted the mindset that being successful in academia, was useless beyond academia.”

Leap into the unknown

Currently, Kim is running her brand new consultancy firm out of various LA coffee shops. She tells me “I absolutely adore working with exciting biotech companies, and, at current, I’m happily maxed out. That being said, I just gained access to my first freelance consultant to potentially expand operations”. However, not everything has been easy. “It was certainly a leap into the unknown. For me, as I love science and have identified for more than 10 years as a scientist, I needed to give myself permission to reinvent myself, and to try something unknown again. I think that the American culture is very supportive of that. In addition, starting a company, especially abroad, comes with a fair amount stress, only because I want to do it all right,” she laughs. “It’s risky, but it’s also exhilarating.”

When in Hollywood

When I ask her about the future, besides telling me about the exciting work she is doing in the biotech space, she tells me about a new movie project: “I consulted on a short film about ALS and clinical trials, which was conceived by two passionate and talented women. It is called ‘The First Color’, and is now being submitted to film festivals across the globe.” Kim ends with: “I do not consider myself an artistic person at all. Even then, I found myself giving ‘notes’ on a script! I guess, when living in LA, even if you do not go looking for Hollywood, it somehow will find you all the same.”



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.



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A conference report by An Staes
(VIB-UGent Center for Medical Biotechnology)

LOOKING BACK AT NGAPAI9



When one thinks of protein sequencing, mass spectrometry is the first thing that comes to mind. At the third Next-Generation Protein Analysis and Detection meeting that took place at the beginning of December in wintery Ghent, several skilled speakers showed the 270 participants that other methods are gaining traction.

By adapting the method for DNA sequencing, it is not only possible to sequence proteins, but also to detect and analyze them at a single molecule level. The technology for protein analysis on this single molecule level is still very preliminary in mass spectrometry-driven proteomics. However, keeping in mind that tumors contain an array of cell types, single molecule detection will show more differences compared to healthy tissue. Will this development shift the technology to analyze the proteome away from mass spectrometry? Or will both fields merge and will new technologies like mass photometry take over?

DNA sequencing technology has evolved to the point where it can be applied in the field and is no longer bound to the lab environment. Transposing the technology to protein sequencing would enable taking protein sequencing to the field as well with the help of small devices, as opposed to more high-end proteomics which is still very lab restricted.

Next, biological questions were addressed through the use of novel and clever mass spectrometry-based technologies, for example through digging into the waste bin of the cell aka the proteasome or the surfaceome instead of the regular cytosolic shotgun proteome. This led to some new insights. Moreover, the results can be more easily implemented as part of treatments and diagnostics.

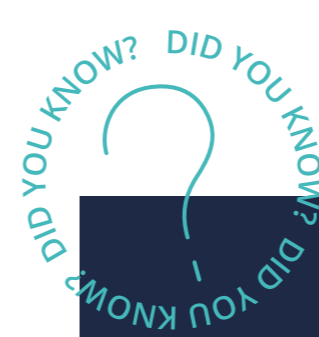
The work presented at the conference makes it clear that mass spectrometry is still evolving extensively, and that new technologies are coming that elevate mass spectrometry proteomics to the

next level.

Not only a shift in analysis was proposed, even moving away from the well-established use of antibodies for diagnostic tools was addressed. Furthermore, on the level of detection, bioluminescence was proposed as a powerful alternative for fluorescence, again a well-established and widely used technique. Since bioluminescence does not have a background problem in plasma as fluorescence has, it is of high interest for diagnostic tools.

Last but not least, artificial intelligence is taking its first steps into the world of proteomics, revealing insights and tendencies in the data that no human brain could ever cover. Using the already extensive data that is present, a lot can be uncovered through machine learning.

The Next-Generation Protein Analysis and Detection meeting opened the world and minds of genomics and proteomics experts to look past the borders of their field and join forces in the fight against diseases.



- ...that Moritz Nowack (VIB-UGent Center for Plant Systems Biology) received an ERC Consolidator Grant and Diether Lambrechts (VIB-KU Leuven Center for Cancer Biology) an ERC Proof of Concept Grant. Congratulations both!
- ...that Annelies Emmaneel (VIB-UGent Center for Inflammation Research) was selected for the 'Wetenschapsbattle'? She'll present her research to an auditorium packed with children in the week of March 16th. Good luck, Annelies!
- ...that Caroline Van Cauwenberghe (VIB-UGent Center for Inflammation Research) received a grant from Stichting Alzheimer Onderzoek? On top of that, her project is ranked first for funding by the Fund J. Delière, the Fund Steldust and the Fund M. Waeyenborghs managed by the King Baudouin Foundation.
- ...that Roos Vandenbroucke (VIB-UGent Center for Inflammation Research) and Tom Vanden Berghe are laureates of the Charcot research fund 2020? Roos will decipher the role of extracellular vesicles in multiple sclerosis, and Tom will tackle the therapeutic study of ferroptosis inhibitors for the same condition.
- ...that Barbara Möller (VIB-UGent Center for Plant Systems Biology) was invited to the French embassy to present the research done as part of the TOURNESOL France-Belgium scientific exchange program. Très intéressant, quoi?
- ...that Inge De Clercq (VIB-UGent Center for Plant Systems Biology) received an FWO grant for a research stay in Australia. Enjoy, mate.
- ...that 18 VIB scientists are represented in the 2019 Clarivate highly cited researches list. Immortal fame awaits.
- ...that Stefanie Smolders (VIB-UAntwerp Center for Molecular Neurology) won the European Academy of Neurology (EAN) Investigator Award 2019.
- ...that Rita Cacace and Eline Wauters (VIB-UAntwerp Center for Molecular Neurology) were selected for additional research funding by the 'Stichting Alzheimer Onderzoek' and the 'Geneeskundige Stichting Koningin Elisabeth'.
- ...that Rosa Rademakers (VIB-UAntwerp Center for Molecular Neurology) and Damya Laoui (VIB Center for Inflammation Research) were interviewed by VRT as part of a series where Belgian top scientists look ahead to 2030. Here's to a better future.
- ...that Frederic Rousseau and Joris de Wit (VIB-KU Leuven Center for Brain & Disease Research) obtained grants from the Stichting Alzheimer Onderzoek for their projects on Tau amyloid-like protein aggregation and altered neuron excitability in Alzheimer's disease.
- ... that Katarzyna Zoltowska and Emanuela Pasciuto (VIB-KU Leuven Center for Brain & Disease Research) have been awarded pilot grants for their projects on the molecular determinants of Alzheimer's disease onset and the protective role of brain regulatory T-cells in Alzheimer's disease.

MARK YOUR CALENDAR

Translational Immunology

March 26-27, 2020 - Ghent

14th International Trends in Brewing

April 5-8, 2020 - Leuven

Tumor Heterogeneity, Plasticity and Therapy

May 14-15, 2020 - Leuven

State of the Union

May 27, 2020 - Ghent

Knowledge for Growth

May 28, 2020 - Ghent

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