VBTIMES

QUARTERLY NEWSLETTER OF VIB. JUNE 2018



YEARS OF VALUE CREATION

BASIC SCIENCE AND BUSINESS: How big is the gap?

I think it was 2014 when VIB's Innovation & Business Team initiated the talks with our lab and research center. Just like us, they saw the business potential in the field of plant-protecting and plant-stimulating microorganisms. Of course, that didn't come out of nowhere: we had the expertise, biological agricultural products were becoming a hot topic, and the technology was finally ready. All the pieces of the puzzle were present to sketch out what would later become Aphea.Bio.

Witnessing our company's launch last year felt a bit like seeing the birth of my own (brain)child. And looking back on the last four years, I remember mainly positive and exciting moments. What I did – developing the proof of concept, contributing to the business plan, giving scientific advice, etc. – was not a huge stretch for me as a basic scientist. That's because there's one constant factor in starting a VIB spin-off: you're surrounded by professionals with complementary skills. For example, I was happy to see Isabel Vercauteren and Steven Vandenabeele, two very nice people I was already acquainted with, take on the management responsibilities. That match is very important, because they're the ones who put your idea to the economic test. This means that, in some cases, the final business plan will differ slightly from what you had in mind. Aphea.Bio, too, had a broad theoretical basis but is now focusing on applications in nutrient stress and diseases. As scientists, we have no choice but to have flexible mindsets.

So, if you think about it, basic science and business are actually the two sides of the same coin. This is especially true at VIB, an institute with a strong focus on the translational value of research. In that respect, one thing I learned to do in the last couple of years is to be a bit more realistic in terms of feasibility or economic value of a research project. Sometimes, scientists tend to be a bit too idealistic about the potential applications of their findings. Then again, I also believe that idealism and curiosity are still indispensable forces that propel science forward. It's our job to ask fundamental questions, even if it will take decades to translate the answers into applications. Both drivers curiosity and business potential - are imperative to conducting leading-edge science with long-term societal impacts.

Sofie Goormachtig Group Leader at the VIB-UGent Center for Plant Systems Biology Co-founder and Scientific advisor Aphea.Bio



20 YEARS OF VALUE CREATION

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SCIENCE MEETS SCIENCE

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20 YEARS INFRASTRUCTURE CREAT **BIO-INCUBATOR LEUVEN BIO-ACCELERATOR GHENT BIO-INCUBATOR GHENT** 9.000 M 6.500 M **18,000** M² **15** COMPANIES/TENANTS COMPANIES/TENANTS 4 COMPANIES/TENANTS **START-UPS** 225 EMPLOYEES 550 EMPLOYEES 280 EMPLOYEES **I.17 B** CAPITAL INVESTMENT **823** DIRECT EMPLOYMENT INTELLECTUAL SUPPOR' 588 TENT APPLICATIONS **253** TOTAL NUMBER OF ACTIVE PATENT FAMILIES ECOSYSTEM FLANDERS.BIO / VIB MBI Life sciences & health INTERNATIONAL SCHOOLS IDUSTRIAL **9**2 20 \bigcirc 70 LEUVEN PUPILS 90₀ 4M © TOTAL OVER LAST 5 YEARS ACCESS TO TALENT 5 4 INWARD INVESTMENTS 900M 650 EMPLOYMENT

WORKING IN A VIB START-UP





Orionis Biosciences

"After years of tweaking and validating our technology within VIB, it's been a great experience scaling the platform to industrial level and seeing that there's broad interest among potential biotech and pharma partners."

r t c l



Multiplicom/Agilent

"Translating academic research into commercial products that directly impact the lives of patients is one of the most rewarding experiences of my life. Achieving this together with a multidisciplinary, dedicated team is an unprecedented and addictive experience."

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Aphea.bio

"It's amazing how such a small team made up of people with different areas of expertise can come together and help build a well-running laboratory and greenhouse in a short amount of time. It creates a unique atmosphere in the company."



ActoBio Therapeutics (former ActoGeniX)

"I am proud to have contributed from the start in developing Lactococcus as a delivery vehicle for human, animal and plant applications. This required a lot of patience, perseverance and a great team."



Aelin Therapeutics

"Helping set up Aelin Therapeutics allows me to do something new and exciting every day on every level imaginable, with the goal of making a real difference for the patient. This is truly a once-in-a-lifetime opportunity."



AgroSavfe

"It has always been a great experience to bring fundamental research results into practice through a spin-off company. Working in a young, dynamic environment like AgroSavfe is very challenging, but also exciting. Witnessing the company grow from four people to twenty-two motivated colleagues in 5 years is especially rewarding."



Ablynx

20 Years of Value Creation

"The 15 years I've been with Ablynx has been a lot like mountaineering. We were in steep ascent mode, particularly during the first few years, and the small, energized and engaged team excelled at getting things done in good spirits and trust. That's how something 'Nano' can become 'Titan-ic'.



CropDesign

"Joining CropDesign was a very challenging experience. I became part of a hard-working team that believed the sky was the limit, and in which every member worked together towards one goal. It was, and still is, a very strong and positive feeling."



Christine Labeur – Business Unit Director Drug Development and Manufacturing at Ardena

Pronota

"Building a new biotech company is an amazing and stimulating experience. The buzz, the dynamics of a new team and creating value for a new technology: it all adds up to a unique momentum. Belgian Biotech rocks! The biotech community is alive and kicking."

"Our job? Working together with world class scientists, seasoned managers and blue chip investors to bring value to society."

A splendid idea with high social impact and an attractive business model, conceived by some of the world's brightest minds? Check. A great team to back the invention with legal, financial and business expertise? Double check! Can we speak of the birth of another VIB spin-off then? Reality check: biotech requires money. A lot of money. This is how our New Ventures team clears the path for the key ingredients of a successful VIB spin-off.

Building a company from scratch requires many different skills, and thus, people. Griet Vanpoucke, Carla Snoeck and Katrien Swerts, VIB's New Ventures team, are strategically embedded within the VIB Innovation & Business team, featuring critical intellectual property expertise, business development experience, and, last but not least, a vast network of entrepreneurs, business angels and investors alike.

FROM IDEA TO SPIN-OFF

Carla, after a pivotal discovery, there's a critical choice between starting a new venture or partnering up with an existing one. How do you make that decision?

Carla: "It's a common question, but one without a black or white answer. The first thing we do after

STARTING A NEW BIOTECH VENTURE: MBARKING ON A LONG-TERM ADVENTURE

such a breakthrough is build a solid data package, obtain proof of concept (PoC) and define a solid IP strategy. This is vital: since there's no product yet, the idea's value is determined by proprietary knowhow, PoC data and intellectual property. Together with the scientists and supported by our IP colleagues, we aim to de-risk and make the invention commercially relevant and applicable - and thus more marketable. Inventions offering many applications or product opportunities (e.g. platform technology) are usually piloted to the new venture option. Ablynx with its Nanobodies[®] and our recent spin-off Aelin Therapeutics with its Pept-in® technology are good examples. For single assets, we often choose to explore licensing options with existing pharma or biotech companies but we may also build a company based on such single assets,

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and bring these to the next level. Or, when the idea needs more development, we set up partnerships with companies, both local and international. The key message is that we create several options to bring VIB's inventions to market; there is no onesolution that fits all."

Katrien, when the choice for a start-up has been made, what are the next stages?

Katrien: "Then it's time to draft a tangible business plan. This is where targets, timings and cost estimates come in. Sometimes we do this inhouse, like with Aelin Therapeutics, but we prefer involving entrepreneurs early-on in this process. They can help make the plan and eventually become part of the start-up's management team. These 'entrepreneurs in residence' are usually seasoned professionals in biotech or pharma, who we convince to take a leap into a new adventure. In some cases, this means moving to Flanders."

Griet: "We're looking for white ravens here; compiling the management team is a critical step in the process: the technology or the invention is the foundation for a new venture but it's the team that needs to run with it and turn it into a success. We also strive for a good match with the scientists. A great management team is also the living proof that we've done our homework properly! It's our job to strike a balance and keep everybody happy – including the people who come in the next stage: funders."

ALL 'BOUT THE MONEY

Elvis was right: only fools rush in. Big investors will rarely engage in projects that haven't been backed properly by data or have been sufficiently derisked. Though they are called venture capitalists, they are often pretty risk averse.

We have sufficiently de-risked a project, built a comprehensive data-package. How do we look for bigger funders?

Carla: "Developing a new drug costs a lot of money, you will never raise this amount all at once – too risky for the funders, too much dilution for the founders. The crux is to build your business plan stepwise and define different value inflection points: each time you hit a major milestone, you further de-risked your project and increased the value of your business. As such, new money

becomes cheaper as funders will pay more to get a share of your company. This is the point where bigger investors will step in."

Griet: "For Aelin Therapeutics, we were able to raise a record amount of 27 million euros, sufficient to bring a first candidate drug to the clinic and test its safety in humans. This will be a major milestone for the new company: are Pept-ins safe to use in humans?"

"Over the past 20 years, VIB managed to build a solid reputation in the investment world because of its successful start-up track record. That network is invaluable: raising funds is all about networking and connecting to the right people at the right time. There is no textbook protocol for this, you start with your close network, the "friendly" investors, because they are great sounding boards we can use to fine-tune our pitch."

Katrien: "Raising money takes time, form first pitch to closing the financing round takes on average 6-12 months. During this time you need to make sure your story stays a priority for the investor: you should know that an average VC receives ~300 investment proposals per year and will invest in only 3-5. It involves a lot of talking, pitching, reshaping and improving plans and hopefully add more convincing data as you move along."

Johan, what is the role of V-Bio Ventures, the VIB affiliated venture fund?

Johan Cardoen: "V-Bio Ventures was launched as an early stage life sciences investment fund in 2015. VIB is an investor (LP) into the fund and VIB has a preferred Dealflow arrangement with V-Bio



Ventures. The relationship with V-Bio Ventures proved to be very valuable as the fund acts as a sounding board and brings the VC-perspective when we discuss early-stage start-up opportunities. Furthermore, investment of V-Bio Ventures in our start-up projects is a further sign of endorsement and convinces others to also invest in the project."

Are VIB start-ups also capable of attracting foreign capital?

Johan: "After the financial crisis in 2008, it was hard to find foreign investors unless the project was











already seeded thanks to Flemish capital. But since 2014-15, we're seeing a positive shift: even in early stages (series A), foreign investors tend to take the lead and these days, international well-renowned funds approach us and scout for opportunities to work with VIB. Even more, we've observed a spillover effect: they discover other interesting investment opportunities in Belgium or Flanders thanks to our initial project. While perhaps less known, this is another good example of the importance of biotech for the Flemish economy!"

ALL VIB Alumni are invited to Join the Vib Alumni Group on Linkedin.

Luc Maertens

PIONEER OR PHD: The spin-off success story of luc maertens

Becoming a pioneer or getting a PhD: that was the choice that Luc Maertens had to make in 1997 when Thierry Bogaert founded biotech company Devgen. Luc, currently CEO of agro-biotech firm AgroSavfe, followed Thierry to Devgen and became a pioneer in turning disruptive technologies into innovative products and bringing them to the market.

You were in your early twenties, freshly graduated from university, when Thierry gave you this choice. It must have been a difficult decision, yes?

"The original plan was indeed to obtain a PhD in one of the labs of Joël Vandekerckhove (VIB-UGent). Thierry Bogaert would be my supervisor. I had just submitted my IWT application when Thierry revealed his plan to spin off the *C. elegans*-based platform for identifying novel druggable targets into a biotech start-up. Suddenly, my PhD topic was gone. But Thierry offered me an alternative: he had managed to get funding for his idea and Devgen was born: VIB's first spin-off. In those early days, we were a group of six or seven people. As a rookie scientist, I suddenly had to deal with all kinds of problems that were completely new: buying equipment, installing labs, getting things rolling... Remember, this was 20 years ago. There were no bio-incubators or other facilities to support start-ups."

Did you ever regret this choice? A PhD is seen as a necessary stepping stone to building a career in science and technology, even in industry. "Being at Devgen from the start was a great opportunity for me. I got the chance to combine top-notch science with daily management, mentoring responsibilities, and supplier and client negotiation. On top of that, in industry, science is the starting point. True innovation is about doing something beneficial for society with that science by bringing products to the market. Having people like Thierry, Hilde Windels and Bob Ackerson as bosses and mentors was priceless! Over the years, we saw Devgen grow into an established company. Several successful financing

rounds were followed by an IPO on Euronext in 2005, another first for a VIB start-up. Most remarkable was the broadening and scaling up of the science and the product pipeline. The company started with a nematode/RNAi screening platform, but eventually brought its own nematicides to the European, African and US markets.

It also turned into a seed company: Thierry's brilliant move to use RNAi for applications in agriculture allowed us to sign a major deal with Monsanto, leading us to develop traits and take over the rice business of Monsanto. We pioneered in redesigned hybrid rice, delivering a pipeline of high-yielding products for the Indian and Southeast Asian markets."

From one of the most junior employees at the start, you became responsible for regulatory affairs and built Devgen's rice business in Indonesia. When Syngenta took over Devgen, you even became Thierry's successor.

"Thierry has always been the driving force behind Devgen, but when Swiss-based Syngenta acquired Devgen in 2012, Thierry decided not to join. So, I accepted the task of integrating the team and Devgen's knowledge and capabilities into the business model of Syngenta, a multinational with 27,000 employees. We successfully safeguarded and even expanded the Ghent R&D site by building on our unique position, turning it into Syngenta's center of excellence for RNA-based biocontrols."

After four years at Syngenta, you joined AgroSavfe, one of VIB's latest spin-offs, as CEO. Back into pioneering mode, I presume?

"I have always been a very strong believer in AgroSavfe's Agrobody[®] Technology Platform. These antibodies have fundamentally changed approaches in other industries and will also lead to a revolution in the way pests and plant pathogens are handled in the agricultural sector. Being able to turn this disruptive technology into innovative products is a bonus for me. I've embraced the 200% entrepreneurial mindset again, something that goes along with a start-up."

What would you describe as the key selling proposition of AgroSavfe?

"As is apparent from its name, AgroSavfe has the ambition to contribute to safer agriculture production and healthier food. Agrobodies[®] fragments derived from camelid binding domains will allow substantial reduction in the level of chemical residues in fruit and vegetables, and at the same time provide farmers with very effective solutions to protect their crops and maximize yield and quality."

Biological pesticides have been on the market for decades. Why is their success limited?

"The market of biological crop protection products is growing, but most of the existing products are based on (living) microorganisms. They show inconsistent performance in different environmental contexts and are based on a limited number of microorganisms, increasing the risk of resistance development. Agrobodies[®] are designed and formulated to bind essential molecules of crop pests and pathogens. They offer consistent performance in the field and have the advantage of acting directly and uniquely on the target organisms, minimizing the risks for wildlife, bees, farmers and consumers. Agrobodies[®] can be produced in a cost-effective manner using industrial-scale fermentation."

How ambitious is AgroSavfe?

"We are pursuing an ambitious product development program using the platform approach. We are on track to introduce our first product to the US market early in the next decade, followed by Europe and other regions. AgroSavfe is poised to be the next VIB agro-biotech success story!"

GEERT NOELS: "Unlock flanders' biotech potential by investing in the very young"

What if ... VIB hadn't been founded more than 20 years ago? According to economist and author Geert Noels, the answer is simple: we probably wouldn't have the thriving biotech ecosystem we know today. But that's no reason to rest on our laurels. To keep our competitive edge, we must strengthen VIB's building blocks: focus on excellence in science, translation of science and education.

On April 18, VIB organized a networking event revolving around creating value in the biotech sector in Flanders. Various biotech stakeholders discussed topics such as VIB spin-offs, financing, co-development collaborations and the importance of the Flemish ecosystem. Geert Noels shared his opinions from an outsider's and economist's point of view.

Biotech seems to have gained momentum lately. We're seeing new spin-offs, successful funding and significant acquisition bids. How much credit can VIB take for that?

"If visionary people like former Minister-President Gaston Geens and Luc Van den Brande hadn't made such a bold move in launching VIB, we probably wouldn't have a biotech hub. And we cannot underestimate the importance of this ecosystem: it's probably the only Belgian one that is recognized as having a worldwide importance. Look at research reports all over the world, ask the brightest minds in Silicon Valley: Flemish biotech is considered world-class.

That being said, VIB alone was not enough. We already had a couple of biotech companies like Innogenetics and Plant Genetic Systems, our government was committed to a long-term investment, there were strong chemical and pharmaceutical companies, and let's not forget our top-notch universities. These elements have been instrumental in helping develop our ecosystem. And once it was in place, financing followed a bit later. Right now, we are harvesting the fruits of all these seed efforts."

What makes Flanders such an interesting place for foreign investors?

"The plusses are clearly our thriving ecosystem and our knowhow. Add to that good financing and the vicinity of research institutes, and we get great staying power, meaning that a decent percentage of new ventures succeed. That, of course, attracts the attention of foreign investors, especially when venture capital is thriving."

In terms of collaborations with the broader science and technology sectors, what is the role of our hub?

"Well, first of all you see that big pharma is looking at smaller biotech players to form new alliances, because they are logically afraid of disruption and they need new products. This is also a form of value creation. A relatively new trend is the formation of partnerships with the IT sector. Because the boundaries between biology and IT are fading, VIB will have to link up increasingly with that sector in the future. Economically, that would be a logical move. After all, great science as an economic asset transcends a specific sector."



Christina Takke (V-Bio Ventures), Cedric Ververken (Confo Therapeutics) and Geert Noels (Econopolis)

How can we remain competitive and attractive as an area for innovation in the next 20 years as well?

"I'm optimistic, as a consequence I see much more potential in biotech - it could be the engine of our prosperity. More efforts and funds could enable our companies to become a bit larger, giving more returns to our society. I'm also concerned about the quality of our education, especially the number of STEM-degrees being issued. That's why companies, knowledge institutions like VIB and federations should raise more awareness with our youngest people, and ensure that science is attractive to even the very young people. In Switzerland, sector federations are spending 25% of their budgets to help 4-year-olds get acquainted with science. If we start investing in the very young right now, we could double the potential for biotech in Flanders. If we don't, the future of our beautiful ecosystem is at stake."

IOCKS (CUTTING-ED BIOTECH HOW INFRASTRUCTURE DRIVES VIB RESEARCHERS AND ENTREPRENEURS FORWARD

HE BUILDING

Though it may seem self-evident, access to adequate infrastructure plays a crucial part in VIB's impact and stature. In recent years, modern facilities that are fully-equipped for top-notch science have allowed our researchers to advance their fields with international acclaim. And because leading-edge biotech is not just about science, we have also supported the creation of optimal environments for entrepreneurs. Despite these efforts, the need for additional infrastructure remains. That's why multiple building projects are currently in the works.

On February 19 of this year, Flemish Minister for Work, Economy, Innovation and Sport Philippe Muyters laid the first stone of FSVM II, the new research facility that VIB and Ghent University are building at the Tech Lane Ghent Science Park in Zwijnaarde. Named after the Ghent biotech pioneers Fiers, Schell and Van Montagu, it will be connected to the existing FSVM I research building, bringing the total area of adapted infrastructure to 40,000 m².

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"We're not just building new facilities, we're working on a thriving ecosystem. Wim Goemaere, COO VIB

FSVM II will host the VIB-UGent Center for Medical Biotechnology under the guidance of Nico Callewaert, which currently operates at various locations across the city of Ghent. VIB's COO Wim Goemaere confirms the enormous potential of FSVM II: "Obviously, it will be much more efficient to work in one building equipped with all the necessary topquality infrastructure. Both buildings will be interconnected to facilitate smooth interaction between the various research centers. We're not just building a new facility, we're working on a thriving ecosystem."

"By investing in state-of-the-art infrastructure, VIB and Ghent University ensure that our researchers can continue to make important breakthroughs," said Minister Muyters. "Their achievements are, after all, the reason that Flanders is internationally recognized for high-quality biotech research and a proactive approach to translating research results into economic and social added value."

BUILDING A THRIVING ECOSYSTEM

Apart from direct investments such as FSVM II, VIB also supports its other partner universities indirectly by contributing funds for state of the art infrastructure. On the campuses in Leuven, Antwerp and Brussels, these resources have enabled construction projects that house the VIB research centers. Several new projects are under construction or in the pipe-line currently to ensure the infrastructure remains up-to-date to allow our researchers to stay in the front-line in their specific fields.

FUELING ENTREPRENEURSHIP

Because the creation of added value for the economy and society requires more than just scientific infrastructure, VIB has also made considerable investments to meet the needs of starting biotech companies and spin-offs.

"At the Tech Lane Ghent science park in Ghent, VIB has set up a bio-incubator and expanded it over the years," VIB's CFO Rik Audenaert explains. "Today, more than 6,000 m² are available for biotech entrepreneurs taking their first steps. More importantly, the bio-incubator is in the immediate vicinity of our own research departments, enabling close collaboration. In Leuven as well, a bioincubator with a total usable area of 9,000 m² was built together with KU Leuven and two industrial partners."

MORE SPACE NEEDED

As both incubators are now fully occupied by young entrepreneurs, even more infrastructure will be needed in the coming years.

"Our long-term solution has to be twofold," Rik Audenaert comments. "On the one hand, startups that have made considerable progress should be able to move on to other locations that offer more space, or even the equipment to start pilot production. In Ghent, several initiatives have already been kick-started by private investors. The biotech accelerator offers 18,000 m² and the recently developed Bioscape project adds another 10,000 m². But despite these initiatives that help biotech companies grow, we also need more space for start-ups."

PROJECTS IN THE PIPELINE

Luckily, VIB isn't wasting any time responding to this need. In Leuven, plans are being worked out to provide another 3,000 m² to start-ups. But perhaps the most ambitious project in VIB's pipeline is the brand-new headquarters that will be integrated in a soon-to-be constructed bio-incubator. The building, which is financed by VIB and the Flemish investment company PMV, will have a floor area of 12,000 m² and will be realized in the Tech Lane Ghent Science Park in Zwijnaarde on a site known as 'Eiland'. Construction will start in 2019 and should be finished by 2022, first half.

Mathias De Clercq, first alderman in Ghent and chairman for NV Eiland Zwijnaarde: "VIB's decision to build an additional incubator and to establish its headquarters at Tech Lane Ghent Science Park is of inestimable value to the Ghent region. VIB is a world-renowned research institute that has been the driving force for the development of an internationally renowned ecosystem for biotech and life sciences in Ghent and in Flanders over the past two decades."

"VIB's decision to build an additional incubator and to establish its headquarters at Tech Lane Ghent Science Park is of inestimable value to the Ghent region."

Mathias De Clercq, first alderman Ghent

EYE-CATCHER ALONG THE MOTORWAY

Together with the recently announced bio-incubator of 10,000 m² at Tech Lane Ghent Science Park campus in Zwijnaarde, a total of almost 20,000 m² of extra space will be provided for start-up biotech companies. "This meets the large demand for adapted lab infrastructure in the Ghent region and enables the expansion of the life sciences cluster in Ghent," CFO Rik Audenaert concludes. "Last but not least: the incubator that is to house our new head office will be a 10-story building at a strategic location along the E40 motorway. As a result, our new HQ is destined to be a real eye-catcher, thus making the importance of biotech in Ghent even more visible. "

VIB COLLABORATES WITH GENECORNER ON PLASMID MANAGEMENT – AND MUCH MORE

After spending the last few decades under the name LMBP, the plasmid collection service of the VIB-UGent Center for Inflammation Research has now changed its name to GeneCorner.

GeneCorner has been embedded within VIB for quite some time and is led by Rudi Beyaert and Martine Vanhoucke. Thanks to VIB's recent decision to collaborate even more closely with GeneCorner, existing ties will now be further strengthened.

GeneCorner is funded by the Belgian Science Policy (Belspo) as part of the Belgian Coordinated Collections of Microorganisms (BCCM). The plasmid collection began in 1977 under the supervision of Walter Fiers, one of the founding fathers of VIB, and has evolved since then into the most active plasmid repository in Europe.

GREAT AT SMALL THINGS

HOW GENECORNER SUPPORTS VIB SCIENTISTS

Easy access. GeneCorner distributes a wide variety of expression plasmids, with and without inserts, as well as several plasmids for mouse engineering and other gene technological applications. GeneCorner also provides easy access to genome-wide human and mouse shRNA libraries and to the human ORFeome library. Since GeneCorner also manages a transit collection, it's always interesting to contact GeneCorner if you're unable to quickly find what you are looking for in the online catalog.

Open science. The rapid turnover of scientists implies a high risk of losing plasmids and associated information. Many journals make the deposit of plasmids in a public repository mandatory, and accession codes for deposits need to be provided in the paper upon submission. A public deposit at GeneCorner provides a pragmatic solution to the challenge of safeguarding and sharing valuable constructs with other scientists worldwide, a process covered by a standard MTA agreed upon by VIB. Even more, forwarding plasmid requests to GeneCorner saves time.

Data management. Scientific integrity and excellent data management practices are crucial in scientific research. More, funding agencies (ERC, FWO) require a detailed data management plan that covers plasmids and related data. GeneCorner not only safeguards your plasmids, it also subjects the biological material to stringent quality controls and processes the associated data to European norms. Most of its services are carried out in accordance with the internationally recognized ISO9001:2015 quality norm.

Visibility. GeneCorner refers to the depositor and the original publication in the online record, increasing the visibility of your research and your team.

Confidential storage and intellectual property. With GeneCorner, you can also deposit plasmids, cell lines (including hybridomas) and other genetic resources in the confidential safe deposit or patent deposit collection or make use of the storage of third party biological material (STPM) service.

Other services. GeneCorner can help you with other plasmid-related services, such as plasmid profile analysis of non-pathogenic bacterial strains and sequence analysis of noncharacterized plasmids.

Info and contact: www.genecorner.ugent.be bccm.genecorner@ugent.be

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THE BIG IMPACTS OF VIB'S **HIGHLY CITED PAPERS:** 2012-2017 ANALYSIS

For several years in a row, the number of highly cited papers (>100 citations in a five-year window) published by VIB scientists has been rising. When VIB started out, about 4% of the papers written by our scientists achieved the highly cited label. Twenty years later, the proportion of VIB's highly cited papers has more than doubled, reaching 10% in recent years.

ONLY THE BEST FOR VIB SCIENTISTS

During the 2012-2017 window, a total of 161 papers were cited more than 100 times. In this list, 111 new papers crossed the 100-citation line. Many of these newcomers offer a better understanding of the molecular mechanisms of health and disease (66%) or present insights into the mechanisms governing the biology of plants and microbiota (11%). Even more, the number of metagenomics consortia is on an upward trend, with over 14% papers linked to consortia papers in the field of microbiomes, whole genome analysis and GWAS studies. Finally, 6% of highly cited papers present new bioinformatics tools or life sciences guidelines.

Almost all highly cited papers (96%) were published in the best quarter of life sciences journals (Tier25 journals), and most of them (82%) were even published in the best 5% journals in our fields (Tier5 journals).

CURIOUS TO LEARN MORE?

Have a look at the 6-year list of VIB highly-cited papers on the VIB website. Based on an analysis

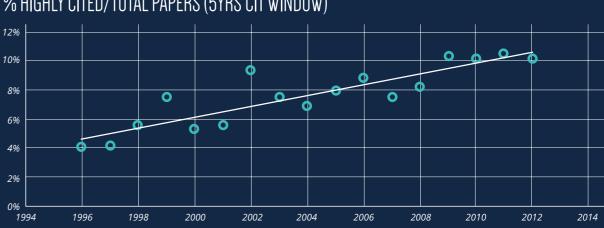
of the senior and corresponding authorship of these highly cited papers, we can see that almost half (43%) of these papers are initiated and lead in VIB laboratories (so-called 'own' papers). Another clear indication that VIB scientists are playing an important role in pushing the frontiers of life science research forward.

ACHIEVING AN EXCEPTIONAL I,000 CITATIONS

We're extremely proud of the fact that 35 VIB papers – 12 of which are new – have made the phenomenal 1,000-citation shortlist. In addition to papers on GWAS and metagenomics (#4), new bioinformatics tools (#3) and guidelines (#1), publications concerning basic life sciences mechanisms also make a great showing: VEGF and PIGF synergies, auxin gradients, membrane traffic modeling and the use of nanobodies to describe GPCR structure are topics in the 1,000-citation spotlight!

Heartfelt congratulations to all researchers who have contributed to these highly cited papers.

% HIGHLY CITED/TOTAL PAPERS (5YRS CIT WINDOW)



INSTITUTIONAL RANKINGS: MEDICINE

Institution
Broad Institute of MIT and Harvard
Howard Hughes Medical Institute
The Rockefeller University
VIB
Dana Farber Cancer Institute
Harvard-MIT Division of Health Sciences and Technology
Wellcome Trust Sanger Institute
Cardiovascular Research Foundation
American Cancer Society
Centro Nacional de Investigaciones Oncologicas
Institute of Cancer Research
Cardiovascular Research Foundation American Cancer Society Centro Nacional de Investigaciones Oncologicas

INSTITUTIONAL RANKINGS: AGRICULTURAL SCIENCES

Institution
Carnegie Institution for Science
VIB
Lawrence Berkeley National Laboratory
Howard Hughes Medical Institute
Centro Internacional de Mejoramiento de Maiz y Trigo
Biotechnology and Biological Sciences Research Council
National Center for Atmospheric Research
Massachusetts Institute of Technology
Universite de Savoie
University of East Anglia
Max Planck Gesellschaft

Country	Papers	Indicator value
USA	1314	49.2%
USA	3732	47.2%
USA	1174	39.5%
BEL	947	39.4%
USA	5565	39.2%
USA	743	38.5%
GBR	1081	38.5%
USA	510	38.5%
USA	617	38.3%
ESP	677	37.8%
GBR	1785	37.8%
	USA USA USA USA USA USA USA USA USA ESP	USA 1314 USA 3732 USA 1174 BEL 947 USA 5565 USA 743 GBR 1081 USA 510 USA 617 ESP 677

Country	Papers	Indicator value
USA	519	46.4%
BEL	505	45.3%
USA	674	42.7%
USA	1277	42.7%
MEX	515	38.5%
GBR	2332	37.6%
USA	566	37.5%
USA	1244	35.5%
FRA	586	35.4%
GBR	1072	34.9%
DEU	5736	33.5%

VIB LAUNCHES AN INTERNATIONAL GRANTS OFFICE

VIB researchers rely heavily on competitive grants for funding, and each grant comes with its own requirements, eligibility criteria, reporting aspects and more. Competition is fierce – European Research Council grant success rates, for example, are as low as 13% – and high-quality help is an absolute must to give VIB scientists a head start to increase their chances on success. Therefore, VIB is currently setting up an International Grants Office: a 'onestop shop' for international grants support.

"When I first arrived at VIB, one of my first priorities was to find information about grant support. Since I'd spent the previous 24 years in the United States, I was no longer familiar with the EU grant system," explains Gabrielle Bergers (VIB-KU Leuven Center for Cancer Biology) when asked about her own funding search at VIB. "Most institutions have central grants offices – a central repository for grant-related information and a source of help with the application process. Instituting one here at VIB would be a huge relief and help ensure that scientists don't miss out on important funding opportunities."



THE BENEFITS OF A UNIFIED APPROACH

Right now, grant support is distributed throughout VIB, with each center and each PI working independently. Unfortunately, this can lead to duplication of efforts, inefficiency, inconsistent communication, missing out on expertise and a lack of transparency. As the organization grows and evolves, it becomes clear that specialized grant support is an important element of VIB's strategic focus.

"A central grants support office would drive visibility and transparency, offer dedicated assistance, reduce internal competition and manage the development of overarching processes to improve grant development. It would also free up our scientists' precious time allowing them to focus less on formal grant requirements and more on their innovative research ideas," says Lieve Ongena, who will be heading the International Grants Office. "With these goals in mind, we're proud to share our plans to create a central International Grants Office, that began with the start of our first International Grants Officer Elien Vandermarliere in May. We will kick off by focusing on two very relevant funding sources: European MSCA fellowships to attract postdocs to the labs and ERC, the most coveted grant for group leaders in Europe these days."

Elien Vandermarliere: "I am looking forward to start at this brand new International Grants Office and be at the service of VIB scientists in multiple ways: to find grants that fit their needs; to help them to conceptualize and pre-review grant applications; to be involved in training our scientists; to help them out with grant negotiations, etc. In summary: to take some work out of their hands and increase success rates."

DRIVING EFFICIENCY, BOOSTING GRANT SUCCESS RATE

The new International Grants Office will consolidate VIB's grants expertise at HQ with the local expertise available at our research centers in a common 'grants pilot team', joining forces and sharing knowledge towards one main goal: increase success rate and embark on the higher hanging fruits.

The feedback on some initial pilot work has been overwhelmingly positive:

"I needed feedback that covers the many different aspects of an ERC proposal from somebody that is experienced with the program. The office delivered the expertise I was looking for." Andy Wullaert, VIB-UGent Center for Inflammation Research

"The Grants Office's feedback on the conceptual elements and the structure of my research proposal was very helpful. I really appreciated their availability and quick responses." Ive De Smet, VIB-UGent Center for Plant Systems Biology

"The support enabled me to make my abstract much less technical, and the comments were very useful." Sophie Janssens, VIB-UGent Center for Inflammation Research

"Pilot Grants team members kindly helped me preparing a key overview figure for my proposal. I'm convinced that having this support is highly beneficial to researchers all over VIB." Lucía Chávez Gutiérrez, VIB-KU Leuven Center for Brain & Disease Research

PARTNERING WITH VIB SCIENTISTS AT EVERY STEP

In addition to providing dedicated assistance and expertise, the Grants Office aims to develop a training package for VIB people only occasionally involved in grant management. A grant application software package to automate administrative processes and a centralized database for management reporting and statistics will be developed.

The Office will create overarching policies that cover all centers to make it easier to submit joint applications, reduce internal competition and boost success rates. Grant meetings, scientific workshops and advisory boards will play important roles in keeping everybody on the same page.

"These activities cover every stage of the grant application process, from training, eligibility advice, administrative issues as well as pre-application peer review. Upon success, they will coordinate negotiation with the funding body and coordinate final signatures," says Lieve Ongena. "Finance staff will also be invited to these international grants meetings which will allow us to increase our understanding of the needs in the reporting process in order to develop additional tools and support processes for this part of the grant."



A STUDY BY THOMAS VOETS AND HIS TEAM HEATS UP OUR UNDERSTANDING OF ION CHANNELS

After years of ongoing experiments and an extended review process, the teams of Thomas Voets (VIB-KU Leuven Center for Brain & Disease Research) and Joris Vriens (KU Leuven) have successfully published a boundary-pushing paper on mammalian heat-sensing channels in the high-impact journal Nature. The researchers are credited with a hot discovery: the presence of three redundant ion channels in neurons, forming a fail-safe heat-sensing mechanism for extra burn protection. It took plenty of commitment – and sometimes 80 behavioral mouse experiments per day – but all the hard work has paid off for Thomas and team members Ine Vandewauw, Katrien De Clercq and Marie Mulier.

Despite the fact that pain signaling neurons in mammals have been identified for more than a century, the molecular mechanisms that make them work are poorly understood. Using mouse models, the team successfully deactivated several known molecular heat sensors, but there was no loss in heat-sensing ability.

It was only by creating a triple knockout mouse strain lacking three specific ion channels that a complete lack of response to pain was shown. This observation demonstrates just how important heatsensing is in mammals, with this triple-redundancy system ensuring that we avoid potential burn sources even if two of our heat-sensing ion channels fail.

Thomas, has anything changed as you finish up your first year at VIB? Any surprises?

Thomas:"The VIB experience has been very positive for me and the lab throughout the year. Although it is only fair to say that my years as a researcher at KU Leuven and the university's continuous investment in our research has given us a head start. But VIB offers many new opportunities for scientific collaborations and training, direct access to 8

advanced technologies – not to mention a significant increase in the number of emails in my inbox..."

Did publishing in Nature pose any obstacles?

Thomas: "The publishing process was quite a struggle. Although we were confident that we had fully established the central findings of the paper more than two years ago, it took an additional 18 months to convince the referees. As a result, the paper contains an extended supplementary online section – and enough material for one or two more papers. But considering the many positive reactions to our paper from colleagues and the coverage in the press, it was certainly worth it."

To the rest of the team, what were the most important experiences for you during this project?

Katrien: "I started on this project at the beginning of my PhD. As a result, I learned quite a bit about animal handling and experiments – knowledge that I now use daily."

Ine: "On my side, this research represents most of my PhD work. In fact, I presented the results of our study during my defense – naturally a key life experience for me!"

Marie: "I came later to the project, and the story of the triple knockout mice had already been shaped. Together with Ine, I worked on a protocol to retrain a specific ion channel in our mouse model. I knew up

Science meets science



From left to right: Silvia Pinto, Katrien De Clerq, Andrei Segal, Ine Vandewauw, Thomas Voets, Rudi Vennekens, Joris Vriens, Marie Mulier

front that it would be a challenge, but we succeeded!"

Any key challenges that you'd like to mention?

Ine: "For me, the biggest challenge had to do with the skin-nerve recordings. It took me quite some time to set up this technique in our lab, and it took even more time – and a lot of patience – to get good single-fiber recordings.

As Thomas mentioned, getting the paper published was a long process, but it was worth it in the end. I learned that patience and perseverance are important for excellent research."

Katrien: "I completely agree. It takes a huge amount of dedication to publish in a high-impact journal."

Finally, are there any key takeaways that you'd like to mention?

Marie: "I loved the excitement of successful experiments! The more the reviewers asked for, the more well-documented our story became, and the better we could prove our hypotheses. A few months after publication, I attended an ion channel congress abroad where several keynote speakers mentioned the importance of our paper in their presentations. It's fulfilling to hear how our story completes the work of other researchers in this field."

Vandewauw et al., Nature 2018



Acute lymphoblastic leukemia, known as ALL, is one of the most common cancers occurring in childhood. Even though chemotherapy is very effective in treating the disease, it leads to significant side effects that impact children later in life. As a result, the need for an alternative therapy is pressing – and Jan Cools (VIB-KU Leuven Center for Cancer Biology) accepted the challenge, with high-impact results published in Cancer Discovery. We asked Jan and team members Charles de Bock and Sofie Demeyer, both Postdocs, for more details.

ALL develops when gene mutations cause bloodborne immune cells to transform into aggressive leukemia cells. However, many of the mutations seen in the disease occur in specific gene pathways, called JAK3/STAT5 and HOXA9. Jan and his international team of researchers used multiple sequencing technologies to observe the interaction between these two genes, discovering that HOXA9 boosts the effects of JAK3/STAT5 mutations, which in turn causes leukemia to develop even more rapidly and aggressively in patients with both mutations.

Sofie, can you describe the biggest challenges you ran into while performing this research?

Sofie: "There were some big computational challenges that came with this project. We had to combine different types of sequencing data, and linking RNA-seq, ChIP-seq and ATAC-seq data was not as straightforward as we expected. Even more, we had data from different models and conditions, and it was tough to ensure that we were comparing the data correctly.

Moreover, optimizing the ChIP-seq protocol and finding the right antibodies required a lot of analyses. I think we analyzed about twice as much sequencing data than was actually described in the paper to get to ChIP signals that we were convinced could be trusted."

Charles, in your opinion, what was the fulfilling aspect of this study?

Charles: "This research highlights the power of using genomic sequencing data from patients to identify potentially cooperating mutations and then functionally testing them using in vivo mouse models. On that note, one of the interesting aspects of this project was to creatively find a novel solution to limit transgene expression within a specific blood lineage. We tested a few different

FRESH FROM THE JAN COOLS LAB: 2 GENES COOPERATE TO DRIVE LEUKEMIA DEVELOPMENT

Jan Cools

published strategies, but it was our own method that worked the best, which was very fulfilling. This new method is now being used in several ongoing projects.

It was also inspiring to witness the great teamwork executed by a dedicated group of postdocs, PhD students and technicians to overcome numerous technical challenges. As Sofie said, generating informative ChIP-seq data from patient samples took a lot of effort."

Jan, how has your leukemia research evolved over the years?

Jan: "Fifteen years ago, our team identified and characterized a specific kinase as the cause of chronic eosinophilic leukemia – a generally long-term and subacute cancer. Today, patients suffering from this type of leukemia can be cured using the inhibitor of the kinase that we identified."

Why do you undertake this research, and what do you think are the future next steps to better target ALL with new therapies?

"It's extremely rewarding to work on research questions that can lead to the development of new therapies for important diseases such as cancer. Acute lymphoblastic leukemia is rare, but it's important to me, since it severely affects the lives of children and young adults. It's also a much more complicated cancer than chronic eosinophilic leukemia and involves many different mutations.

That being said, I'm convinced that by making better mouse models that we can use to study the cooperation between different oncogenic events, we will find a way to target these leukemia cells."

De Bock et al, Cancer Discovery 2018



Jean-Christophe Marine

Stein Aerts

EUROPEAN SCIENTISTS UNITE TO TRACK ALL CELLS IN THE HUMAN BODY

A large consortium of European researchers will develop and apply new technologies to profile virtually all individual cells within the human body, and track how they change during ageing and disease. Stein Aerts (VIB-KU Leuven Center for Brain & Disease Research) and Jean-Christophe Marine (VIB-KU Leuven Center for Cancer Biology) are two Belgian partners in this very ambitious project. The FET-Flag LifeTime project is an unprecedented European scientific endeavor launched by a consortium of 60 scientists from all across the continent. Their goal is to track, understand and predict how the molecular make-up of cells changes during human diseases, and ultimately, how to intervene.

NEW TECHNIQUES

The success of the project relies heavily on technology development. The scientists need new ways to extract DNA, RNA, and proteins from individual cells, at high-throughput scale. They are working on lab-ona-chip and microfluidic devices that can generate nanoliter droplets to capture a single cell, barcode it, and amplify its DNA and RNA.

Recording the spatial location and all biological parameters of each individual cell within a tissue will generate a gigantic amount of multidimensional data. It is up to creative bioinformaticians such as Stein Aerts and his team to develop novel approaches to extract useful information from this avalanche of data.

Stein: "We are keen on inventing new bioinformatics and machine learning algorithms to analyse and model which genes are active in individual cells. A variety of genome-wide information layers or "omics" data will be generated for millions, perhaps even billions of single cells. We'll need smart ways of making sense of this data if we want to use it to make valuable predictions for patients, including disease outcome, therapy choice, or prognosis."

NEW INSIGHTS

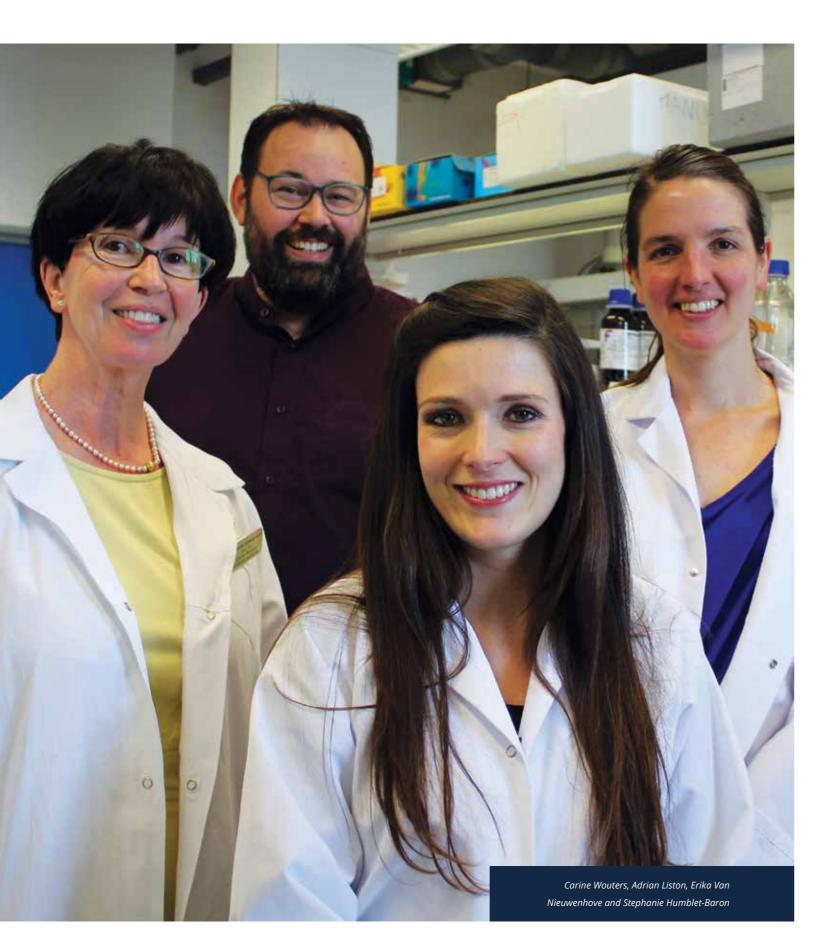
This is where cancer experts such as Jean-Christophe Marine come in. His team will exploit the single-cell methods to profile large amounts of single cells from healthy tissues and tumors. Since these individual cells can be studied over time, the researchers can track how cells evolve during the progression of a disease and in response to specific treatments.

Jean-Christophe Marine: "We have so far only performed a hand-full of single-cell experiments in our lab. Yet, it has become immediately obvious to us that the single-cell resolution is a revolution! It is creating a real shift in our understanding of biology and disease. If combined with the right models and tools this technology will simply revolutionize medicine."

Applications extend to many other diseases besides cancer and both researchers underscore the importance of teamwork in this large endeavour. Jean-Christophe Marine: "Single-cell biology is a new field that combines multiple disciplines. This is why being part of this consortium, together with experts in technology development, bioinformatics and systems biology, is so critical and exciting for us." Stein: "All of these efforts combined will generate new fundamental insights into the biology of our body, which will in turn provide a better understanding of diseases and ultimately new therapeutic avenues."

The next issue of VIBtimes will focus on Single Cell Technology at VIB





SCIENTISTS UNCOVER NEW GENETIC CAUSE OF LUPUS

A team of scientists and clinicians at VIB, KU Leuven and UZ Leuven has identified a novel mutation causing an unusual form of the autoimmune disease lupus. The genetic analysis of a Belgian family sheds new light on the disease mechanisms underlying lupus, which could possibly yield new therapeutic approaches for patients. The findings were published in the Journal of Allergy and Clinical Immunology.

Lupus is an autoimmune disorder, meaning that the body's immune system mistakenly attacks its own tissues. Lupus can affect multiple organs but its cause is often not clear. Usually a combination of genetic and environmental factors is at play.

The Leuven researchers have now discovered a novel genetic mutation in a patient that presented at the age of 12 with both lupus and problems in the ability of the immune system to fight common infections. This unusual combination of symptoms was quite puzzling.

By analyzing the patient's DNA and that of the parents, the scientists could trace the problem down to a specific mutation in the gene encoding the Ikaros protein. The protein in turn binds DNA to regulate the expression of other proteins.

Erika Van Nieuwenhove, clinician and scientist at VIB-KU Leuven, explains how the mutation caused the patient's immune system to be hyperactive: "Because of the mutation, Ikaros can no longer bind its target DNA properly. We also observed that certain immune cells of the patients were hyperactive, even in the absence of stimulation. The link between both observations turned out to be CD22, a protein that normally dampens the immune response. In normal conditions, Ikaros stimulates the expression of this inhibitor, but this was not the case in this patient."

Science meets science

About 5 million people worldwide have lupus, but a causative mutation in Ikaros is very rare. "Small changes in Ikaros are associated with susceptibility to adult-onset lupus, but because the effects are weak it is hard to work out what Ikaros is doing to the immune system," explains Adrian Liston (VIB-KU Leuven Center for Brain & Disease Research), who heads the lab for translational immunology and is lead author of the study. "In this particular family, however, a mutation created a large change in Ikaros, causing early-onset lupus. The mutation was strong enough to allow us to work out how changes in Ikaros cause lupus and immune deficiency."

Although the patient in this study has a very rare form of lupus, the discovery nevertheless helps to map the overall disease mechanisms, underscores Carine Wouters, pediatric rheumatologist at University Hospitals Leuven and co-lead of the study: "The mechanism we uncovered in this patient could also be meaningful in a different context with other patients. Now that we understand what goes wrong in this particular case, it could help us think of better targeted treatments for others as well."

Van Nieuwenhove *et al.*, 2018 Journal of Allergy and Clinical Immunology

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NUMBER NUMBER NUMBER NUMBER NUMBER NUMBER

A team of researchers led by Mike Sleutel from the VIB-VUB Center for Structural Biology in collaboration with scientists from the Institute for Complex Molecular Systems of the Eindhoven University of Technology, and the CNRS in Grenoble, have for the first time uncovered the molecular details of protein crystal nucleation, a process with great medical and scientific relevance. The team also developed a new methodology to study a broad class of systems that have remained elusive to date. Their results were published in Nature.

Mike: "It will be exciting to see this new technique being applied in the future to follow protein selfassembly processes that are implicated in a range of pathological disorders, such as liquid-liquid phase separation in eye cataract formation or the formation of amyloid fibers associated with a range of neurological disorders."

MEDICAL IMPORTANCE OF PROTEIN CRYSTALS

Mike Sleutel

Protein crystals bear great medical and scientific relevance. For decades, they have been essential for structural biologists to solve the threedimensional structures of proteins, but protein crystals are also used as bio-pharmaceutical delivery agents. Crystalline suspensions are attractive formulations to store and administer active pharmaceutical compounds because of their long-term shelf life, low solvent viscosity, and slow dissolution rate. Perhaps the best known example is insulin: insulin shots comprise the subcutaneous injection of a suspension of insulin microcrystals which dissolve slowly to yield a steady and sustained delivery over time. Despite their tremendous potential, there are two factors that limit the use of protein crystals in a broad range of applications.

CHALLENGES IN DEVELOPING PROTEIN CRYSTALS

First, growing protein crystals, as many molecular biologists will say, is more an art than a science. In fact, for many proteins, crystallization can be excruciatingly difficult. This in part follows from the fact that scientists don't understand the early stages of protein crystal formation. Any crystal originates from a nucleus, a tiny crystalline seed, which forms by the spontaneous grouping of a few molecules in solution that have to adopt a regular organization in three-dimensions. How the molecules realize this improbable feat has remained a mystery up until this point.

Secondly, a single protein can crystallize in multiple different crystal forms, this is known as polymorphism. Different crystal polymorphs have different characteristics, with the most notable ones the power to diffract X-rays (crucial for 3D structure determination), and the rate at which it dissolves (crucial for drug delivery). As of yet, it is very difficult to guide the crystallization process to the polymorph of one's liking. Scientists believe that polymorph selection takes place at the stage of nucleation, but no one knows exactly how the mechanism works.

A NEW WAY TO LOOK AT THE SELF-ASSEMBLY OF MACROMOLECULES

The group of scientists lead by Mike Sleutel have used state-of-the-art cryo-transmission electron microscopy (Cryo-TEM) to capture the birth of a protein crystal by visualizing the process of nucleation at molecular resolution. Heiner Friedrich from the Eindhoven University of Technology explains: "Because the process happens so rapidly, and at such a small length scale we needed to cryogenically arrest the sample at various stages of the process. Once frozen in time, we use a very sensitive electron microscope to visualize the proteins and how they group together to form a nucleus and finally the protein crystal."

By analyzing the Cryo-TEM images taken from a series of samples at constant time intervals, they could start to puzzle together the series of molecular collisions that need to take place to form a crystalline nucleus. Mike continues: "We were struck by the unexpected complexity of the process, which proved to be far more intricate than the working models we and other in the field had prior to these observations. For the protein that we used in our study we uncovered a hierarchical selfassembly process that involves three subsequent stages of self-assembly at ever increasing length scales." These observations are the first of their kind and provide a new way to look at the selfassembly processes of macromolecules into larger structures.

But the team went even one step further, and compared the nucleation pathways of multiple polymorphs. They showed that polymorph selection is dictated by the architecture of the smallest possible fragments formed at early timepoints. Once such structures are formed, the faith of the system is set. Alexander Van Driessche from CNRS explains: "By analyzing and understanding the differences in structure of the various nuclei, we developed strategies to guide the polymorph selection process. We achieved this by gently tweaking the different modes of interaction that exist between the molecules, steering the nucleation process in the direction of our choosing." The team believes that the new insights and methodology will significantly advance the development of protein crystals for 3D structure determination and medical applications.

Alexander E.S. Van Driessche et al., Nature 2018

QUCKSCAN



#Natural killer cells #Allergic asthma

The Bart Lambrecht and Hamida Hammad Lab (VIB-UGent Center for Inflammation Research) focused on the role of innate natural killer (NK) cells in house dust mite-allergic asthma. They used genetically engineered Ncr1-DTA or Ncr1-DTR mice, which constitutively or temporarily lack NK cells, and showed that these mice still developed a robust and intact allergic inflammatory response. Similar results were obtained by injecting NK celldepleting antibodies, and by interfering with the NK cell-activating receptor NKG2D. Thus, their findings comprehensively demonstrate that NK cells are not required for asthma development in mice. Haspeslagh *et al.*, EMBO Mol. Med. 2018



2

#GRN founder family #Clinical heterogeneity #Onset age modifiers #Neuropathology

The Christine Van Broeckhoven lab (VIB-UAntwerp Center for Molecular Neurology) performed a 10year follow-up on the Flanders-Belgian GRN founder family. The GRN founder mutation reduces levels of GRN protein by 50% and leads to a high risk of frontotemporal dementia (FTD). The updated pedigree comprises 29 branches and includes 85 patients and 40 unaffected mutation carriers. Most patients were diagnosed with FTD while others were diagnosed with Alzheimer's dementia or Parkinson's disease. At autopsy, the brains of 11 patients showed the typical FTLD-TDP type A pathology. Patients had onset ages ranging from 45 to 80 years, with some surviving till advanced ages without symptoms. Reported modifiers could not explain the onset age variability. The availability of this well-documented GRN founder pedigree will be key in the search for the main onset age modifiers using different omics technologies. Finding such a modifier might contribute to the development of a disease-delaying therapy.

Wauters, Van Mossevelde *et al.*, Neurobiology of Aging 2018 Sieben *et al.*, Alzheimers Res. Ther. 2018

3

#Plant growth-promoting hormones #Ubiquitination #Endocytosis

Brassinosteroids, plant growth-promoting hormones, are perceived by a cell surface-localized receptor kinase, BRI1. The BRI1 signaling intensity is mainly determined by receptor abundance in the plasma membrane. A collaborative study performed by the labs of Jenny Russinova (VIB-UGent Center for Plant Systems Biology) and Libo Shan (Texas A&M University, USA) discovered that plant U-box E3 ubiquitin ligases PUB12 and PUB13 control endocytosis of BRI1 by ubiquitination, which is driven by hormone perception. This work provides a molecular link between BRI1 ubiquitination, endocytosis, signaling regulation and plant growth control.

Zhou, Liu et al. Proc. Natl. Acad. Sci. USA 2018

4

#N-terminal proteoforms #Initiator methionine excision

Protein biogenesis is a fundamental and complex biological process with important implications for human health and disease. In the case of eukaryotic cytosolic protein synthesis, typically for more than half of all nascent protein chains, the initiator methionine (iMet) is cotranslationally removed by the action of methionine aminopeptidases (MetAPs). Petra Van Damme (VIB-UGent Center for Medical Biotechnology) and her team studied the omics-wide effects of human MetAP1 deletion, thereby revealing that MetAP1 is a potential target for the discovery of new anti-obesity and anticancer therapeutic strategies.

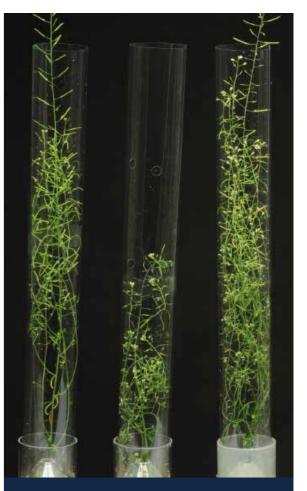
Jonckheere et al., Mol. Cell. Proteomics 2018



#Lignin engineering #Dwarfism #Bio-based economy

To ease the industrial processing of plant biomass into fermentable sugars, plants are engineered to contain less lignin. Unfortunately, this intervention typically leads to reduced yield. The Wout Boerjan Lab (VIB-UGent Center for Plant Systems Biology) has now found a way to overcome this problem. Unexpectedly, the strategy used increased the yield beyond that of wild-type plants. These findings are an important step in the development of feedstock for biofuels and other bio-based materials.

De Meester et al. Plant Physiol. 2018



Picture showing wild type Arabidopsis thaliana (left), dwarfed low-lignin mutant plant (middle) and engineered low-lignin plant with increased yield (right).



6

#Libraries #NGS #Toolbox

The paramount role of accurate nucleic acid library construction for deep sequencing is often underappreciated. Recent years have seen an explosion of new tools and enzymatic tricks to counter biases associated with library generation, but these are often scattered across literature or hidden in methods or supplementary sections. Armed with their own experience in customizing library construction for high-throughput experiments, the Nico Callewaert Lab (VIB-UGent Center for Medical Biotechnology) reviewed the vast expanse of tools and recent developments in the field to guide researchers in building their own high-quality libraries.

Boone et al, Nucleic Acids Res. 2018

#Proteinaggregation #Antibiotics

Aggregation is a sequence-specific process, nucleated by short aggregation-prone regions (APRs) that can be exploited to induce aggregation of proteins. Researchers from the VIB Switch Laboratory, led by Joost Schymkowitz and Frederic Rousseau (VIB-KU Leuven Center for Brain & Disease Research), found that while most of these regions are unique within a proteome, a small minority exist in many proteins. When they nucleate aggregation in bacteria, massive and lethal inclusion bodies are formed, indicating that targeting these redundant APRs may be an attractive antibacterial strategy. Khodaparast *et al.*, Nature Communications 2018 #Respiration #Thermography

Measurements of respiratory rate are essential in biomedical research and in clinical practice, but most techniques require the attachment or implantation of sensors. Infrared thermography, on the other hand, is noninvasive, but analysis can be complex. Researchers from the Sebastian Haesler Lab (NERF) developed a novel algorithm that extracts respiration signals based on pixel time series, eliminating the need for nose tracking and image segmentation. The algorithm allows the reliable detection of inhalation onset with high temporal precision, both in mice and humans.

Mutlu et al. Journal of Neuroscience Methods 2018

9

#Atlastin-3 neuropathy mutations #ER tethering

The ER is a complex network of sheets and tubules that is continuously being remodeled. The relevance of this membrane dynamic is underscored by the fact that mutations in atlastins (ATL), ER fusion proteins in mammals, cause neurodegeneration. Joint efforts from the Janssens Lab and Savvides Lab at VIB-UGent Center for Inflammation Research, the Timmerman Lab at VIB-UAntwerp Center for Molecular Neurology and the Bioimaging Core in Ghent have unraveled how defects in atlastin-3 disrupt neuronal homeostasis. By using volume EM in patient fibroblasts, neuronal cells and transfected cell lines, they revealed that HSAN-causing ATL3 mutants promote aberrant ER tethering hallmarked by bundles of parallel-running ER tubules. This was caused by a defect in an intermediate step in the functional cycle of the ATL3 GTPase, leading to excessive tethering of membranes. These data reveal that the effects of ATL3 mutations on ER network organization stretch beyond a loss of fusion, shedding new light on atlastin neuropathies. Krols et al., Cell Reports 2018

0

#Frontotemporal dementia #Genetic association **#Sortilin**

An international group of scientists led by researchers from the Christine Van Broeckhoven Lab (VIB-UAntwerp Center for Molecular Neurology) used genetic screening of the coding region of the sortilin 1 gene (SORT1) to identify missense mutations that are associated with an increased risk for frontotemporal dementia (FTD). SORT1 is a neuronal receptor for granulin (GRN) and mutations in the latter gene are the most frequent genetic defects in Flemish FTD patients. The risk association of SORT1 missense mutations was confirmed in three FTD patient groups in Spain, Italy and Portugal, within the frame of the European Early-Onset-Dementia (EU EOD) consortium. Several mutations were located in the SORT1 binding domain of GRN. The study's data established SORT1 as a risk factor for FTD.

Philtjens et al., Neurobiology of Aging 2018



#Hybrid sterility #Hybrid vigor

Claude Libert and Tino Hochepied from the VIB-UGent Center for Inflammation Research have collaborated with a group of geneticists in Tubingen, Germany to study genetic problems. Crossing animals of different species leads to the extreme genetics of hybrid vigor (robust resistances and fitness), but also hybrid male sterility. Tino and Claude generated embryonic stem cells from crosses of the house mouse (Mus musculus) and the Algerian mouse (*Mus spretus*). By modulating the Bloom gene, it has become possible to force mitotic recombination in male hybrid cells and generate mice from these cells. In this way, recombination in these infertile male hybrids became possible via a detour, allowing genetic studies to address hybrid vigor and sterility. Lazzarano et al., PNAS 2018



EVALUATION OF THE FOX WHITE I.O BIOMOLECULAR MEASUREMENT TECHNOLOGY PLATFORM

Biomolecular interactions can easily be assessed on the Fox White 1.0 instrument developed by Fox Biosystems, which relies on gold-coated fiber optic surface plasmon resonance probes. This benchtop instrument combines the strengths of current standards to measure biomolecular interactions in one instrument, with the accuracy of Surface Plasmon Resonance and the ease-of-use and higher throughput of biolayer interferometry. As such, binding affinity, kinetics and target concentration can be determined within minutes.

Bioreceptor molecules can be easily immobilized onto the probes, after customizing them with one of the available PEGylated functionalized monolayers, which range from carboxyl, his-tag and specific proteins, to small molecules, DNA and cells. Biomolecular interactions can be measured by dipping the probes into any type of liquid, avoiding the need for sample purification. Another advantage of Fox White 1.0 is its high sensitivity, with detection limits ranging from microto femtomolar. This technology will be evaluated in the labs of Anna Sablina (VIB-KU Leuven Center for Cancer Biology), and in the VIB-KU Leuven Center for Brain & Disease Research by the groups of Lucía Chavez-Gutierrez and Frederic Rousseau & Joost Schymkowitz.

WHOLE HUMAN DNA SEQUENCING AT VIB ON THE PROMETHION FROM OXFORD NANOPORE TECHNOLOGIES

The Tech Watch team and the VIB-UAntwerp Center for Molecular Neurology are proud to report a sequencing output of 98 GB on a single PromethION flow cell in 64 hours on a human DNA sample. This is a major leap forward for VIB scientists, as the achievement opens the door to the use of PromethION, which is still in its earlyaccess stage, for affordable full-human genome sequencing. The long reads obtained on this ONT platform provide a unique opportunity to study structural variants, including duplications and translocations, which are difficult to detect using massively parallel sequencing platforms. This approach is particularly important, since structural variants (differing in variant size and sequence) that have been implicated in multiple diseases including cancer, neurological and autoimmune pathologies. A plethora of new nanopore sequencing applications will soon be released, ranging from epitranscriptome and epigenome analysis to single-cell sequencing methods. These are very exciting times for the sequencing field, and VIB is in the center of the action!

VIB SINGLE CELL ACCELERATOR

Single-cell technologies have rapidly enhanced the molecular understanding of functional cell states underlying diseases such as cancer, inflammatory and neurodegenerative illnesses. As one of the earliest adopters of disruptive single-cell technologies (e.g. 10X Genomics Chromium), VIB is working at the cutting edge of this field. As a result, single-cell analysis is now increasingly being

TECHWATCH HIGHLIGHTS

considered an essential tool used to understand and address fundamental research questions.

A new initiative, the 'VIB Single Cell Accelerator', was launched at the VIB seminar 2018. Through this initiative, VIB scientists will have access to extra funding to evaluate, develop and integrate emerging breakthrough single-cell technologies at VIB. This initiative will run for a 2-year trial period, and VIB groups can apply for Single Cell Accelerator funding through the Tech Watch application process. Technology platforms will be placed in the Technology Innovation Lab (physically embedded in a host lab space, a PI's lab or a core facility), and these projects will be evaluated by two dedicated single-cell technology specialists. By combining disruptive single-cell platforms, specialized data analysis and modeling tools to process omics data, and coupling this expertise with respective research themes, this program enables VIB to excel rapidly in the single-cell field.

More info on www.vib.be/SCA

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REPORTER ON THE ROAD: SPARK - HOW IT ALL STARTED IN SILICON VALLEY

While Silicon Valley is widely recognized for its tech and internet industry, its historical role in life sciences is maybe less well-known. In the '70s, Stanley Cohen of Stanford and Herbert Boyer of UCSF started tinkering with bacterial plasmids in their labs. They discovered that plasmids could be enzymatically cut and pasted back together in the test tube. This enabled bacterial production of human proteins for the first time, a technological breakthrough that *led Boyer to found Genentech for the production of recombinant insulin.*

A TECH TRANSFER VICTORY

While the implications of this technology for science have been far-reaching, this also proved to be an incredible success story in tech transfer. Genentech grew to become a very prolific biotech company, launching numerous drugs for a range of human diseases. In 2009, this culminated in a takeover by Roche, a staggering \$46.8 billion deal. On the other hand, Stanford and UCSF reaped the benefits of holding these successful patents, raising awareness among other universities and institutes of the benefits of tech transfer for the success of the alma mater.

THE BAY AREA IS RIDDLED WITH INNOVATORS -IN MEDICINE AND BEYOND

Genentech is not a lone story out here. There are uncountable spin-offs and young start-ups scattered between the campuses of universities and biotech giants. Companies such as 23andMe have transformed genetics, and although their efforts were initially met with skepticism, they have now accumulated the largest database of linked genetic and clinical data in the world, used by companies and scientists across the globe.

Moreover, established internet companies are growing interested in medicine as well. Both Google and Facebook are now putting their online revenues to use in overcoming daunting new challenges, which aim to transform human medicine and health care as we know it. The Valley hasn't gotten less exciting, and the horizon is looking bright for Bay Area biotech.

A UNIQUE ECOSYSTEM DRIVING **BIOTECH INNOVATION**

But what makes this place so special? What drives young companies to move their headquarters here? "The Bay Area is a very special ecosystem," says Dr. Kevin Grimes, professor at Stanford and a tech transfer champion. "Biotech in Silicon Valley has flourished because of that ecosystem and the infrastructure that was initially laid down by the tech industry," he continues. "There are five critical players that make this area the ideal place for startups. Foremost, we have world-renowned universities that are engaged in exciting, cutting-edge research. Besides this, we have the venture capital firms, corporate attorneys, and the financial institutions. We also have the experienced workforce in the area

to guide an idea from the bench to industry at every step of the way. We have reached the critical mass needed to make biotech thrive."

CHANNELING TRANSLATIONAL KNOWLEDGE

Despite benefiting from such a supportive environment, tech transfer in the Bay Area does not miraculously happen by itself. Dr. Daria Mochly-Rosen, also from Stanford, discovered this firsthand and already shared her learnings with us during last year's VIB seminar. More than a decade ago, her research in protein kinase C isoforms resulted in the discovery of a potent peptide inhibitor, which turned out to be highly successful at reducing the size of heart attacks in a variety of non-human models. Yet despite these promising results, getting industry excited turned out to be a bit more difficult. Eventually, they decided to start a spin-off. But it turned out that there was little institutional memory of how to make this happen.

"Daria pretty much had to start from scratch," Grimes says. "The learning curve she had gone through and the realization that getting a promising drug to patients isn't something that scientists know much about, gave her an idea. She realized we needed to make use of all this translational knowledge around us. We both had connections in the biotech industry, and we started going through our contacts. A few friends offered to be advisors of our tech transfer projects, bringing industry experience from medicinal chemistry to intellectual property. We got some funding from the dean of the medical school, and SPARK was born."

INDUSTRY AND ACADEMIA TEAM UP

Think of a think tank/funding agency fusion. Researchers at Stanford with potential medical

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.



@BoeynaemsSteven

applications can apply for a SPARK seed grant. They will then have to present data and progress reports regularly. "What started 12 years ago as a small group of advisors has now turned into a full seminar room with dozens of industry specialists giving feedback and guiding these projects through every step of the process," describes Grimes. SPARKees, as project team members are called, are lured partly by the somewhat modest funding, but the main benefit is the advice and mentorship from the advisors. Attendees must sign non-disclosure agreements protecting the confidentiality of the data presented. "It turns out that our advisors are largely driven by altruism. They are dedicated mentors that really enjoy the process and sharing their expertise. We could not have wished for anything else."

50% OF SPARK INNOVATIONS ARE TRANSFERRED TO INDUSTRY

SPARK has an impressive track record. In the last six years, SPARK programs have been initiated in a dozen new academic sites on all six continents, giving rise to new collaborations to join forces in the fight against orphan diseases and conditions mostly affecting the undeveloped world. The result: a dazzling success rate of 50% of SPARK projects transferred to industry partners. An additional 10% are advanced directly into the clinic without a partner. This latter group is comprised of projects that will benefit patients, but lack the financial return to generate interest from the biopharmaceutical industry (for example, projects repurposing generic drugs, or addressing global health problems or very rare orphan diseases). In a globalized world, the success of programs like SPARK provides a clear message to all of us: when industry and academia around the globe join forces, anything is possible.



AWARDS

Our scientists put their hearts and souls into their research. Their efforts are often rewarded with awards and grants from renowned organizations around the world. These are the most recent wins of VIB's frontrunners in biotechnology. Congratulations!

Rita Cacace (VIB-UAntwerp Center for Molecular Neurology) won the Junior Faculty Award at the Advances in Alzheimer's and Parkinson's therapies AAT-AD/PD[™] meeting in Torino, Italy, which took place from March 15 to 18. The prize recognizes the top junior and trainee scientists at the meeting and offers them a stage on which to present their findings.





Research) received the Lundbeck Foundation's 2018 Brain Prize. He shares his award with German and British colleagues John Hardy, Christian Haass and Michel Goedert. The award is the world's most valuable prize for brain research, worth one million euros. The four won the prize for their groundbreaking research on the genetic and molecular basis of Alzheimer's disease.

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

Peter Carmeliet (VIB-KU Leuven Center for Cancer Biology) was honored with the 46th annual ARC Foundation Leopold Griffuel Award, a prize of EUR 150,000. The award is presented to a scientist or research team from anywhere in the world whose work has resulted in a major cancer research breakthrough.





Tim Van Acker (Business Development Manager at VIB) received the very first Biomedical Scientist of the Year Award. As a business development manager, Tim aims for improved communication of scientific information to the public and helps translate academic research into marketable projects. With the prize, the Biomedical Alumni Ghent honors him for his remarkable professional achievements.

GET READY FOR THE NEXT EDITION OF VIBES

In 2019, VIBes will once again connect PhD students across disciplines with peers from all over the world. This unique international symposium, launched by VIB in 2008, has a proven track record of five successful editions. The event is organized by PhD students for PhD students, catering specifically to the needs of young ambitious scientists.

VIBes combines scientific talks in all areas of life sciences with workshops aimed at career development. The conference offers plenty of opportunities to communicate with fellow participants and speakers alike in between talks and at planned social activities, including a conference dinner and a fun wrap-up party.

NEW YEAR, NEW TEAM

This year, a brand-new team of enthusiastic VIB PhD students takes on the organization of the symposium: Lia Martina, Silvia Radenkovic, Jhana Hendrickx, Giulia Doglio, Chiara Lonigro, Marta Wojno, Tim Van Den Bossche, Cemile Kocoglu, Ilias El Houari, Brajabandhu Pradhan, Deepanksha Arora, Ana Catarina Cascalho, Dennis Pedri, Lorenzo Canti, Rahel Park, Hanna den Bakker, Anna Chrzanowska and Anna Zimmermann. Marleen Vanstraelen and Elisabeth Stes (VIB HQ) will guide the students in this challenge.

Ludger Goeminne (VIB-UGent Center for Medical Biotechnology), who was part of the previous edition's organizing committee, speaks very highly of his experience: "Being part of a fun and committed team, I got invaluable hands-on organizational experience and opportunities to interact with world-class scientists." Jaana van Gastel (VIB-UAntwerp Center for Molecular Neurology), feels the same way: "Organizing VIBes

Do you want to know more? Keep an eye out for future announcements about the preliminary program and registrations or contact us at vibes@vib.be. We are all looking forward to another memorable VIBes!

n d A (\ h a o c e V Iff a r o n d e

was one of the most fulfilling things I have done. It was amazing how we were able to achieve so much. Even more, I met a lot of new people, from different backgrounds and with different interests." Along with her fellow students, Iryna Voytyuk (VIB-KULeuven Center for Brain Disease), can't hide her enthusiasm: "Organizing VIBes 2017 was a thrilling experience. It was so rewarding to see our team succeed with each small accomplishment, culminating in a streamlined conference experience enjoyed by our participants and speakers."

NOTHING BUT PRAISE

If you'd ask the participants of the last edition, there's no doubt that the symposium is worth a visit: 93% of them said they would highly recommend the conference. "The great diversity of the talks gave me an opportunity to broaden my knowledge and look for a potential new direction for my research," one student said. We even overheard some participants compare the presentations to the famous TEDx Talks.

Additionally, the interactive workshops seem to prove their value: "I understood that I am not alone in my problems and could exchange my knowledge and experience with others," one participant claimed. "These kinds of events are invaluable to the PhD community. Keep it up!"



STRONGER TOGETHER AT DYSTONIA EUROPE'S D-DAYS

Celebrating its 25-year existence, Dystonia Europe organized D-Days in Brussels on April 12 - 14. The three-day event united patients living with dystonia - a rare neurological disease affecting about 10,000 Belgians - with doctors, researchers and policymakers.

The brains of people with dystonia send the wrong instructions to their muscles. Those muscles then contract, leading to abnormal movements. The disease's manifestations are diverse, ranging from writer's cramp, in which patients are unable to hold a pen, to uncontrolled full-body contractions. This makes it a difficult disease for doctors to recognize. Dystonia usually stabilizes after five years, but rarely ever improves or goes away completely.

PATIENTS, CLINICIANS AND SCIENTISTS EXPLAINED THEIR NEEDS AT THE EUROPEAN PARLIAMENT

At a lunch in the European Parliament preceding the conference, prof. Maja Relja (Zagreb University) presented the first results from a survey assessing the challenges dystonia patients face in Europe. This showed that many still face barriers to access healthcare, including long delays to diagnosis.

Several members of the European Parliament heard Professor Relja emphasize "that this was still occurring in Europe, not a third world country". The politicians were also confronted with the compelling testimony of Adam Kalinowski (Poland) explaining his personal struggles being diagnosed and not receiving care at the frequency needed to retain employment.

Rose Goodchild (VIB- KU Leuven Center for Brain & Disease Research) explained the case for more basic research on the disease, as this is the only way to develop new cures. Heather Clarke, an EU policy advisor, immediately reacted to these messages and expressed her hope that they bring about change in the future: "I would like to see an EU in which national and European policymakers, patient organizations, scientists and healthcare professionals collaborate to deliver health to each and every citizen."

D-DAYS: WHERE PATIENTS, DOCTORS AND SCIENTISTS MEET

Monika Benson, executive director of Dystonia Europe also emphasized the importance of uniting the perspectives of doctors, patients and scientists: "It's only by bringing together the different people involved that we can exchange ideas and experiences to eliminate treatment gaps and promote research. "Rose Goodchild confirmed this and even added that molecular research on dystonia should look outside to other diseases. Rose: "It makes little conceptual sense for molecular brain researchers to subdivide ourselves into whether we work on infant-onset disease, mid-life diseases (like most dystonia) or late-life neurological disease; we are all ultimately asking how neurons function and become dysfunctional."

Dr. Bruno Bergmans (UZ St Jan, Brugge and former VIB scientist in the VIB-KU Leuven Center for Brain & Disease Research), a neurologist specialized in movement disorders, shed light on the causes of the disease. "What strikes me most are the rapidly



advancing insights in genetics, which help us better to understand dystonia. The research conducted in the Rose Goodchild lab is top class and we should be proud to have such great scientists in our country. We can only hope that their work will eventually lead to improved treatments."

AN ENERGY BOOST FOR PATIENTS AND SCIENTISTS

Martine De Wilde, a patient and one of the 100 attendees, called the event 'unforgettable'. "I've learned so much about the illness and its treatments. We really need these kinds of events to spread knowledge about dystonia. Highly recommended!" Another patient, Goele Peters, couldn't hide her enthusiasm either: "It was impressive to see all those patients in one room. Very interesting conference, worth every penny." The VIB team attending the event also found it inspiring: "Events like D-days are of great importance, as they create opportunities for us to connect with patients and hear first-hand what our day-to-day work really means to people."



MARK YOUR CALENDAR

Core Technologies For Life Sciences July 1-4, 2018 – Ghent

Plant Protease and PCD Symposium September 11-13, 2018 – Ghent

Agrobacterium 2018 September 12-13, 2018 – Ghent

Structural Dynamics in Cellular Communication September 20-21, 2018 – Ghent

Supernova September 26-30, 2018 - Antwerp

Cell-Nerf symposium: Neurotechnologies September 30 – October 2, 2018 – Ghent

Biotech Day October 21, 2018 – Antwerp

International Meeting on Optical Biosensors November 15-17, 2018 – Ghent

Dag van de Wetenschap November 25, 2018 - Flanders

Metabolism in Cancer and Stromal Cells November 26-27, 2018 - Leuven



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