GROUNDBREAKING SCIENCE FOR A HEALTHIER FUTURE

15 stories from EU-LIFE institutes

June 2023

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To cite this work please use the following sentence:

EU-LIFE (2023). *Groundbreaking science for a healthier future - 15 stories from EU-LIFE institutes*. https://eu-life.eu/groundbreaking-science

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Preface

I am very pleased to present this collection of scientific stories from EU-LIFE institutes highlighting the beauty and impact of fundamental research.

These stories showcase how curiosity-driven research, sometimes conducted decades ago, is helping us better understand ourselves and respond to current medical challenges, leading to unexpected and life-changing outcomes. In this booklet you will also find examples of how citizens can contribute to a healthier future, how scientific breakthroughs make their way from the lab to the patient, and the inspirational careers of researchers who are leaders in their fields.

The texts of this collection were produced or collected by members of the EU-LIFE Science Communications Working Group. This initiative follows up the Narratives project, aimed at developing expertise in innovative narrative methodologies for communicating science.

These stories demonstrate how fundamental research can have far-reaching consequences, beyond the initial discoveries. They serve as a reminder of the importance of investing in science, encouraging curiosity-driven studies, and nurturing a supportive research environment.

I hope you enjoy reading these narratives and appreciate the impact of fundamental research as much as we do at EU-LIFE!

Mónica Bettencourt-Dias
Chair of EU-LIFE
Director of Instituto Gulbenkian Ciência

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J.G. Mendel: The story of an unappreciated genius and what we can learn from it

By Ester Jarour

Johann Gregor Mendel is considered to be the father of modern genetics. Mendel's contributions to the field of genetics are still recognised and celebrated today, and he is remembered as one of the most influential scientists of his time. However, this was not the case during his lifetime. J.G. Mendel made his groundbreaking discovery in the mid-19 century in Brno. Today, Brno is an important science and technology centre in the Czech Republic. EU-LIFE member institute CEITEC Masaryk University is proud to build on Mendel's legacy and continues to advance modern genetics research in the birthplace of this important discovery.

Although Mendel's laws laid down the foundation for the field of genetics, and his work is now considered one of the most important contributions to modern biology, his work went largely unnoticed by the scientific community during his lifetime. It was not until the early 20th century that the scientific community rediscovered and fully appreciated his work. Why was this genius scientist unappreciated during his lifetime, and what can we learn from his story?

Mendel was a monk who conducted a series of experiments with pea plants in the 19th century and discovered the basic principles of heredity, which are still widely used in genetics today.

Mendel's experiments involved the selective breeding of pea plants and tracking the inheritance of specific traits, such as flower colour, seed shape, and pod colour, across several generations. He observed that traits were passed down from parents to offspring in a predictable way and that some traits were dominant while others were recessive. Historical records say that Mendel was known for his persistence and exceptionally elaborate methodology. He consistently recorded his research data and was patient enough to wait until he discovered an obvious pattern. To be absolutely sure, he repeated each of his experiments to ensure reproducibility. One could say that Mendel possessed the ideal characteristics of a successful scientist.

Interestingly, Mendel did not have a formal education in biology and was not a scientist. As a monk, he received an education in theology, philosophy, and natural history, which included a rather limited study of plants. Mendel's interest in biology was sparked by his work as a gardener at the monastery, where he conducted experiments with pea plants in his free time. In modern terminology, we would say that Mendel practised citizen science. Some scientists are still a bit sceptical about the value of citizen science. However, Mendel´s story teaches us that citizen science can indeed be a valuable tool for advancing scientific research, which is only one of many other benefits of citizen science.

One of the main reasons that Mendel´s work was not appreciated during his lifetime was that it was ahead of its time. The scientific community of his day was not yet equipped to fully understand and appreciate his discoveries. This would probably not happen today in the globalised world of science with the internet, open access and international mobility.

Another factor that contributed to the lack of recognition for Mendel's work was the fact that he did not actively promote his findings or seek to publish them in scientific journals. Instead, he presented his work to a small group of scientists in his own country, and his results were not widely circulated or discussed outside of that circle. This fact teaches us valuable lessons about the importance of international mobility, scientific networking, knowledge-sharing and science communication.

Furthermore, Mendel's findings challenged the prevailing scientific beliefs of his time, particularly the idea that traits were blended together in offspring. Mendel's work showed that traits were inherited in a more complex and predictable way. His ideas were met with scepticism and resistance from some scientists who were reluctant to accept new ideas that challenged the established theories.

New ideas often represent risk and uncertainty, and people may hesitate to embrace them for fear of failure or negative outcomes. Or people may be afraid of new ideas simply because they do not have enough information or knowledge to understand them fully. When people lack the information or expertise needed to evaluate new ideas, they may be hesitant to embrace them for fear of making a mistake or being seen as ignorant or uninformed.

New ideas often represent change, and change can be scary for people who are comfortable with the status quo. People are influenced by the opinions and attitudes of the people around them. When a new idea is introduced, it may be met with resistance from peers or other members of one's social group. This can create social pressure to conform to the prevailing attitudes and beliefs, even if they are not aligned with one's own beliefs or values.

Overall, people may be afraid of new ideas for a variety of reasons, but overcoming these fears is essential for the growth and progress of the entire society. Embracing new ideas and perspectives can lead to innovation, discovery, and positive change in all areas of life. And to make people ready for new ideas, we must communicate science and especially emerging technologies and frontier research. Mendel didn´t have the luxury of science communication experts at the Augustinian Abbey in Brno in the mid-19th century, but modern research institutes do. And they should make sure that frontier discoveries will not be unnoticed and that society is ready to appreciate their value.

Finally, it is important to note that Mendel's work was conducted in relative isolation. He did not have access to the sophisticated tools and technologies that scientists have today to help them understand genetics. This made it more difficult for him to grasp the implications of his own findings fully and to explain them to others in a way that was easy to understand. This fact highlights the need for scientific networking and sharing innovative and seemingly crazy ideas during conferences, internal seminar series or talks within your own research institute or during informal gatherings with science-savvy colleagues and friends in bars or pubs.

The full potential of genetics research has not yet been fully exploited. Genetics research, such as that done in CEITEC's laboratories, already leads to a much better understanding of genetic diseases. It helps us to understand the genetic basis of many diseases, including cancer, diabetes, Alzheimer's disease, and heart disease. This knowledge will grow into the development of more effective treatments and preventative measures. Genetic advances have already led to the development of personalised medicine, which involves tailoring medical treatment to an individual's unique genetic makeup. This approach improves the effectiveness of treatments and reduces the risk of side effects. Modern genetics allows us to manipulate and engineer genetic material. This has the potential to lead to the development of novel treatments or to the creation of genetically modified organisms that can be used to solve problems such as hunger and disease.

Gene editing technologies like CRISPR-Cas9 have the potential to cure genetic diseases by editing or replacing faulty genes. This could have a massive impact on the future of medicine. Modern genetics can also provide insights into human evolution and migration patterns by studying genetic variation within and between populations. This knowledge can help us understand our origins and better predict how we may evolve in the future. Overall, modern genetics has the potential to improve our health, increase our understanding of ourselves and the world around us. Genetics can help us solve some of the most pressing problems facing humanity. However, it is essential to approach these advances with caution and consideration of ethical implications.

Despite all the described challenges, Mendel's work eventually became recognised as one of the most important discoveries in the field of genetics, and his contributions to the study of heredity are still celebrated today. Mendel planted a little seed of new knowledge 150 years ago in Brno. Today the scientists at CEITEC and worldwide are building upon this knowledge and have grown it into a tree full of precious fruits that have the power to improve and even save human lives. This story highlights the importance of fundamental science and discoveries that are so groundbreaking that they are hard to comprehend.

Overall, basic science is progressing much faster today than in the time of Mendel, thanks to a combination of factors, including technological advancements, global collaboration, increased funding, interdisciplinary research, science communication, and open access to infrastructure and scientific information, that were lacking during Mendel´s lifetime. These trends will likely continue driving scientific progress in the years to come so that no more geniuses will have to be unrecognised, and no more important discoveries will be unnoticed. Still, we must together continue to support fundamental research – we must keep planting new seeds of knowledge.

Since its establishment in 2011, CEITEC has quickly developed into a cutting-edge infrastructure for research which performs highly alongside the best institutes in Europe. Among the main priorities of CEITEC are the promotion of a motivating and dynamic international scientific environment, the provision of state-of-the-art research infrastructure, and the policy of open communication and equal opportunities.

IEO
European Institute of Oncology

It's never too late to change

By Greta Caprara

Since I was a child I've always loved science.

In the beginning I was passionate about animals and nature, leading later in life to a curiosity to uncover all the mechanisms behind any biological process. This is why I became a research scientist, but that was not the unique reason: I also sought to help people to fight their battle against tumors and eventually win it.

However, after a while, I realized that what I really wanted to do was to use the extensive experience I have accumulated working in the lab, and everything I have learnt about the scientific method, to solve more practically the 'real-world problems'. So, I decided to make a career change, but, of course, without ditching science! While still working at the bench, I enrolled in a Master Degree Program in human nutrition and dietetics, thinking that helping people to improve nutrition could be a great opportunity to effectively and rapidly ameliorate their health and prevent cancers, rather than understand and treat them.

Despite the difficulties encountered while working and studying, I did not give up and, after a couple of years, I left the lab and began working as a researcher, nutritionist and science communicator in a research program aimed at promoting healthy diet and lifestyle to prevent cancer and other chronic diseases (such as cardiovascular diseases, type 2 diabetes and obesity).

Nowadays, chronic diseases account for more than 70% of all death worldwide and their burden is even expected to rise. As documented by several studies, unhealthy diets, physical inactivity, tobacco use and excessive alcohol consumption are the main risk factors causing the escalation of these pathologies.

The good news is that all these detrimental behaviours can be modified; as a result, up to 80% of cardiovascular disease and type 2 diabetes cases, and 40% of cancers can be prevented by changing our lifestyle.

Despite the common disbelief, we can achieve this very easily: let's decrease the consumption of higher energy-dense foods (such as processed food, refined grains, food rich in sugars and saturated fats, red and processed meat and alcohol), while emphasizing the intake of plant-based foods (like legumes, unrefined cereals, vegetables, fresh fruits, nuts, and seeds) and incorporating some fish, dairy products, eggs, and poultry. At the same time, we need to be more active: 30-60 minutes a day of moderate aerobic physical activity (a quick walk, moving around by bicycle, climbing stairs instead of using the elevator, etc.) are a great start to counteracting sedentary behaviors.

The Covid-19 pandemic and the current climate emergency further made the prevention and control of these pathologies moral and economic imperatives! Changing our lifestyle, being more active and adopting a healthy diet can eventually improve the planet's wellbeing, decreasing for instance the greenhouse gas emissions due to car usage and specific food production and consumption (such as red meat and ultra-processed foods).

Five years have passed since I've left the lab, and I've never regretted my choice! I'm really happy and satisfied with my current job, which also helps me to understand even more clearly than before, that healthy diet and lifestyle are crucial for both ourselves and the planet.

We are facing a pandemic and a climate emergency: we need to act now if we want to achieve a better future! Personally, I will do my best to effectively communicate the benefits of healthy and sustainable diets/lifestyles, in order to influence individual and political choices and ultimately improve people, animal and planet wellbeing.

The Department of Experimental Oncology (DEO) was founded in 1995 as a research wing of the European Institute of Oncology (IEO), one of the world's most prestigious hospitals and the fastest growing comprehensive cancer centre in Europe. The DEO focused on the deep understanding of the molecular mechanisms involved in cancer development, as a tool to integrate and complete the knowledge among fundamental, translational and clinical science, hence accelerating knowledge into clinical practice.

VIB
science meets life

How camel blood leftovers led to five VIB spin-offs and a multitude of applications

By Katrina Wright

A scorching hot livestock market in Rabat, Morocco, in the early 1990s. A Belgian scientist named Serge Muyldermans is dealing with a local trader. Although Serge is clearly not in his natural habitat, he looks excited. The camel he just bought for 40,000 Belgian francs – now around 1,000 euros – could be the start of a promising new research avenue for him and the late Vrije Universiteit Brussel (VUB) professor Raymond Hamers. Little do they know that they're about to write one of the most successful international biotech stories ever told.

Fast forward to 2021. More than three decades of research on camel and llama blood has resulted in multiple waves of impact.

Over the years, five Flanders Institute For Biotechnology (VIB) spin-offs have been founded, dozens of potential medicines have been developed, and the biggest biotech acquisition in Belgian history took place in 2018, when French pharma player Sanofi acquired Ablynx for 3.9 billion euros.

And the research is anything but finished. Since 1996, the VIB-VUB Center for Structural Biology, co-led by Professor Jan Steyaert, has served as a hotbed for progress in this promising domain. And as we speak, new innovations in the fields of medicine, animal medicine and crop protection are being developed. All of them go back to a seemingly ordinary day in 1989.

Serendipity meets curiosity

Another day at university in 1989. VUB biology students are everything but looking forward to their immunochemistry lab, where they must detect and sort antibodies – substances that attack invading diseases – from animals such as mice, dogs, rabbits and birds. It's an experiment with predictable outcomes: all antibodies are more or less similar. That is, until Professor Raymond Hamers suggests also testing dromedary blood, because he happens to have some leftover blood samples in the freezer from an earlier research project on sleeping sickness.

When Hamers reviews his students' work, some of the results seem to be off. Perhaps the students simply misinterpreted the data? However, Hamers decides to look beyond the obvious explanation. When postdoc student Serge Muyldermans comes to the exact same conclusions, both men are stunned. Dromedary antibodies, and all camelid antibodies in fact, seem to share a unique and simple structure – one that could offer huge potential for a wide variety of applications.

But in 1989, there was no VIB, no biotech ecosystem, no substantial financing and no professional tech transfer system to protect and further develop the invention. In other words, Hamers and Muyldermans were pretty much on their own.

And that is how, a couple of years later, Serge Muyldermans found himself in a Moroccan market buying a camel to continue researching these particular antibodies, which were soon to be called 'nanobodies'.

Antibodies 2.0

Science can be a bumpy road, especially when you're pioneering. The first years came and went with ups and downs. But despite some setbacks in the lab and the mysterious disappearance of the Moroccan camel (probably stolen), the duo was able to further develop their findings. They managed to isolate one part of the camel antibodies, creating 'single-domain antibodies', or 'nanobodies'.

In the meantime, Raymond Hamers took steps to protect the invention. "The whole patent story was no walk in the park," he said in previous interviews. "We even paid for it ourselves at an intellectual property office in Paris. Even more, we weren't careful enough in terms of confidentiality and ownership of our invention. We ran into some issues, but many things changed after our first publication in Nature in 1993. Everybody gradually started to take us seriously."

Not only pharmaceutical companies reached out, but governments also started to show interest in what was going on in the labs. VIB was founded in 1996, and not a day too soon for this burgeoning new enterprise. Its dedicated Innovation & Business team is concerned exclusively with technology transfer and supports VIB scientists with valorization. Biologist Jan Steyaert came on board to further develop the technology and the business plan. "Finding investors was the trickiest part," says Professor Steyaert. "Investors tended to follow scientific hypes, which mainly featured synthetic antibodies at the time. We were those weird guys that suggested to immunize camels (laughs)."

Only five years later, VIB brought forth its first nanobody-based spin-off: Ablynx.

In Ablynx's wake

The launch of Ablynx was only the start of the nanobody success story. The long, rocky road from origin to impact also served as a foundation to jumpstart new ventures. Under CEO Mark Vaeck, Ablynx started out with ten employees and increased to 27 two years later. In 2006, the new CEO Edwin Moses took charge to guide crucial steps in the further evolution of the company. The pipeline was extended to 16 new substances with the potential to serve as foundations for new medicines. Ablynx continued to grow to approximately 500 people and expanded its patent portfolio, pharma collaborations and projects, which had domestic and international press regularly singing its praises as a company that put Flanders on the worldwide biotech map.

In 2018, Ablynx launched the first nanobody-based drug, caplacizumab, which treats aTTP, a rare blood clotting disorder. The successes of Ablynx convinced French pharmaceutical player Sanofi to acquire the company in 2018 for 3.9 billion euros.

Edwin Moses: "Three years after leaving Ablynx, I'm very proud to see that Sanofi continues to invest in the nanobody platform both in Gent and around the world, with the aim to generate more new medicines based on this fantastic technology, and in addition, there are now about ten former Ablynx employees who have become CEOs. It is fantastic to see this remarkable contribution of Ablynx to the local and international biotech scene."

On top of Ablynx's rise, VIB propelled new developments in nanobody research, resulting in the birth of four more spin-offs. Biotalys (2013, formerly AgroSavfe) is using Agrobodies® to fight plant disease in agriculture. Confo Therapeutics (2015) is developing a new class of drugs and partnered up with Roche in 2017. ExeVir Bio (2020) is harnessing the technology to treat Covid-19. And for Animab (2020), the focus is to ensure the intestinal health of livestock.

From nano to mega

Parallel to the creation of new ventures, Jan Steyaert and his team at the VIB-VUB Center for Structural Biology are continuously taking the technology to the next level. In Flanders, the VIB Nanobody Core makes nanobody technology available to academic and industrial partners for a variety of applications.

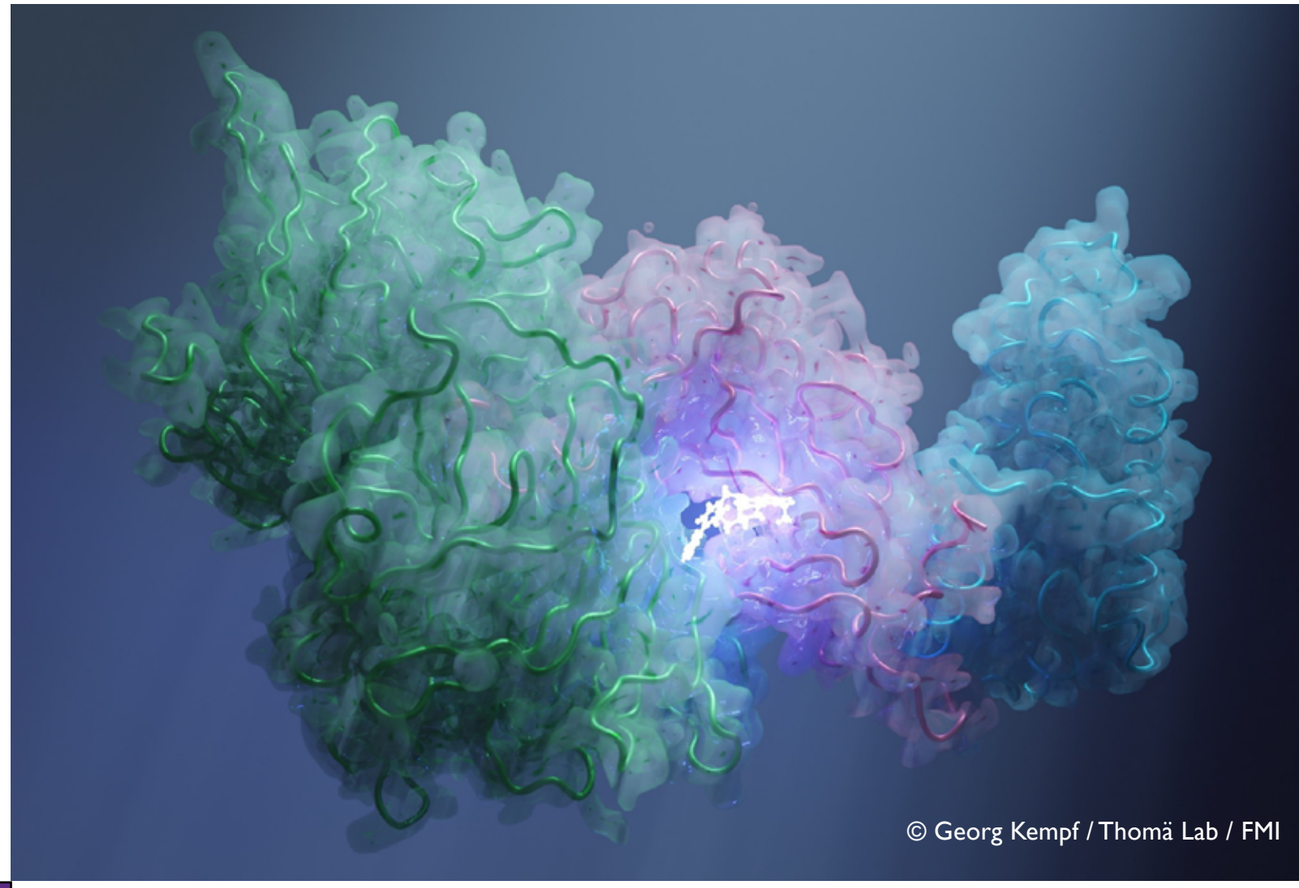
Today, VIB has contributed to more than 400 nanobody-related peer-reviewed publications in high-ranking journals, the establishment of several biotech companies, and of course new breakthroughs. For example, the last couple of years have seen new 'Megabodies', a novel kind of engineered nanobodies, being applied in cryo-electron microscopy to zoom in on the smallest proteins. Or 'AcTakines', that combine mutant cytokines with nanobodies, could be used in new treatment approaches for cancer and immune- or inflammation-related disorders.

And the founding fathers? They can be proud of what they achieved. The Nobel Prize in Chemistry received by Brian Kobilka and Robert Lefkowitz received in 2012 for the discovery of G protein-coupled receptors, based on the groundbreaking structural biology research at VIB, can be seen as the ultimate reward. Looking back on the development of his brainchild, Jan Steyaert likes to quote Louis Pasteur: "Change only favors minds that are diligently looking and preparing for discovery".

Strategic research in life sciences and biotechnology.

VIB researchers explore the basic molecular mechanisms of life, from microorganisms to plants and human beings. Our entrepreneurial technology transfer approach ensures that scientific discoveries are turned into tangible innovations that benefit society.

FMI
Friedrich Miescher Institute
for Biomedical Research



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Small molecules to treat big diseases

By Giorgia Guglielmi

In 1961, Australian doctor William McBride wrote a letter to *The Lancet* voicing concern about "severe abnormalities" — including shortened limbs, malformed hands and damaged internal organs — in babies born from women who had taken a drug called thalidomide during pregnancy.

McBride's concerns about thalidomide, which was being used in dozens of countries for treating morning sickness in pregnant women, were soon confirmed by other doctors in Europe. The drug was banned in winter 1961, but by that point it had affected thousands of babies.

Despite the tragic legacy, thalidomide and its derivatives have later resurfaced as effective treatments for some cancers. How these drugs work to slow cancer's progression remained a mystery until the early 2010s, when scientists discovered that thalidomide can trigger the destruction of specific proteins that are overactive in cancer cells.

In the past ten years, researchers led by structural biologist Nicolas Thomä at the Friedrich Miescher Institute for Biomedical Research (FMI) in Basel, Switzerland, have deciphered the molecular and atomic mechanism through which thalidomide binds to and destroys these proteins.

Their findings have opened the door to a new, potentially revolutionary strategy in the development of treatments for tough diseases such as cancer.

"Our results suggest that novel drugs can be developed for applications that were previously unthinkable," Thomä says.

Molecular glues

For a long time, scientists thought that two proteins would bind if they had complementary shapes that fit exactly into one another — like a key into its lock.

Thomä's work has contributed to upending this idea, showing that some keys alone can't open specific locks unless a 'molecular glue' is present. Molecular glues are molecules that stick together two proteins that normally wouldn't interact. They achieve this by changing the surface properties of their target proteins.

Thalidomide acts as a molecular glue: it binds to specific target proteins, including some that turn genes on and off, and makes them come together with an enzyme that causes the target to be broken down by the cell's protein degradation machinery.

Essentially, thalidomide can promote the degradation of disease-causing proteins, leading cancer cells to die. But thalidomide can also degrade proteins that are important during embryonic development, which explains why the drug caused congenital conditions when taken during the first trimester of pregnancy.

Next-gen therapeutics

Using a powerful technique for imaging structures at the individual atom level, Thomä and his team have been able to observe thalidomide and its derivatives in action, linking target proteins to the enzyme that marks them as waste.

In recent years, Thomä's team has provided key insights into how thalidomide and other molecular glues target harmful proteins and release them for degradation. "That opened the door to an entirely new strategy for going after these types of targets," Thomä says.

For his groundbreaking work on targeted protein degradation, Thomä received the Otto Naegeli Prize for Medical Research in 2022, one of Switzerland's most prestigious scientific awards.

The revolutionary mode of action of thalidomide is now leading the way for the next generation of therapeutics — small molecules that can trigger the breakdown of disease-causing proteins on demand. Many of these molecules have been found by chance, but now researchers are racing to discover and develop more.

By revealing how molecular glues function, Thomä's work could help reach an ambitious goal: find molecules that can target any protein, thus enabling the treatment of uncurable diseases.

The Friedrich Miescher Institute for Biomedical Research (FMI), based in Basel, Switzerland, has a twofold mission — understanding the molecular mechanisms of health and disease, and training early career scientists.

Focused on fundamental research in neurobiology, genome regulation and multicellular systems, the FMI is affiliated with the University of Basel and the Novartis Institutes for BioMedical Research.

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From fundamental immunology to novel anticancer therapeutics

By Enzo Poirier

When Dr Eliane Piaggio left Argentina and her successful diagnosis laboratory business to pursue a research career in France, little did she imagine of her future successes, as both a lab head in academia and a biotech entrepreneur. The 53-year-old scientist currently leads a team at Institut Curie, focused on unravelling the role of Tregs — a type of immune cell — in the immune response against cancer. In parallel to her fundamental research efforts, she has established a striving company, Egle Therapeutics, that is bringing the Curie team's discoveries to the clinic. Her story is one of passion, resilience and audacity, that brightly illustrates how cutting-edge basic research can translate into the development of anticancer therapeutics.

Back in the Argentinian 90's, the young Eliane Piaggio, freshly equipped with a diploma in biomedical diagnostics, decides to launch a diagnostic laboratory. The Rosario-based operation swiftly becomes a successful business, dealing with dozens of patients and thousands of samples a day. Eliane Piaggio is busy, but nonetheless bothered by a feeling that one could trivially call boredom:

"I think that I was simply missing science! At one point, it became so bad that I was giving immunology classes to the physicians sending patients to the diagnostic lab. I really wanted to come back to that."

Eventually, that is precisely what she did, undertaking a PhD while still working her day job. It is a success, and Dr Piaggio pursues a career in academia, following a soon-to-be-old flame to Paris to become a postdoc. She moonlights with a specific subtype of white blood cells, the T lymphocytes (also called T cells). This particular type of lymphocytes is pivotal for the orchestration of an efficient immune response. Typically, when a disease-causing agent, a pathogen, invades the human body, or when a tumor develops, the immune system switches to defense mode. It culminates with adaptive immunity being kicked into action, a highly accurate mechanism that recognizes and memorises pathogens and other threats.

This kind of acquired immunity is performed by B and T lymphocytes, which are immune cells circulating in the blood and sitting in organs. If B cells are responsible for producing antibodies that can specifically recognize a pathogen and trigger its demise, T cells play more varied roles. A subtype of T cells called CD8 T cells, for example, detects and kills cancer cells, as well as cells infected with viruses. Another subtype of T cells, termed regulatory T cells (Tregs), is present to curb the immune response and prevent it from going into overdrive. This is not a role to be underestimated, as activation of the immune system comes with a variety of measures toxic to cells, which, if left unchecked, can target and destroy the body. Failing to pull the breaks on immune activation can result in autoimmune diseases, in which patients' organs are wrongly recognized as dangerous and attacked by the immune system. Tregs are central to this process of immunity control, and maybe because their biology is exquisitely complicated, they become the central focus of Eliane Piaggio's research work:

"I was looking at finding immune system-based therapies for autoimmune diseases such as multiple sclerosis and Type I diabetes. We were the first ones to reposition interleukin 2, a small protein acting on Tregs, for treatment of autoimmune diseases."

This was the first of a long series of discoveries on immunotherapies, or treatments that modulate the activity of the patient's immune system.

Jump ten years on to the early 2010s and Dr Eliane Piaggio is now a permanent researcher at Institut Curie, one of the most prestigious French cancer research centers. She still explores the biology of Tregs, not in the context of autoimmune diseases, but in tumors. And the role of the immune system in fighting tumors is firmly established. CD8 T cells, for example, are documented to play an important part in killing tumors cells. Tregs also have a role, although not the expected one. If, in the context of a regular immune response, Tregs are tasked to shut down immune activation to prevent autoimmunity, they take their role a little too seriously in a cancer setting. The presence of Tregs abnormally dampens the activation of immunity against cancer cells, ultimately preventing the control of tumor growth. Targeting Tregs to block this adverse function, or simply destroy them, is thus an interesting strategy to boost anti-tumor immunity in cancer patients. The blockbuster drug Ipilimumab, which revolutionized treatment of solid tumors such as melanoma, renal or colorectal cancer, is based on this very principle. The Piaggio team explores one molecule called interleukin 2 (IL-2), a small, blood-circulating protein that acts as a survival signal for Tregs. With IL-2, Tregs thrive; without it, they stop multiplying and disappear. The team's approach was to elaborate ways of inhibiting this survival signal:

"In collaboration with Felix Rey at the Pasteur Institute, we started a line of work on the engineering of a specific molecule that drives IL-2 away from Tregs. We serendipitously ended up with an artificial molecule that inhibits IL-2 signaling only in Tregs, and starves them to death."

The IL-2 starver, which boosts immunity against cancer, is very promising, but has only been tested in vitro, also sometimes called test tube experiments, and in animal models. Attempting to bring it to the clinic is another game entirely, one that is usually quite foreign to academic researchers. "I just had to do it. It was exciting. These drugs are my babies, I wanted to see their development through to the end" is the answer Dr Piaggio gives when quizzed on the reasons that led her to undertake such a daunting endeavor. Equipped with her experience of the private sector, she — to put it mildly — does it brilliantly. She founds Egle Therapeutics in 2020, hand-in-hand with CEO Luc Boblet. The team quickly manages to secure a strategic partnership with the international pharmaceutical company Takeda, bankrolling Egle to settle and grow:

> "A fascinating aspect is that Egle keeps changing at tremendous speed. At the beginning, we were doing a lot of bioinformatic analysis to optimize the targeting of Tregs. Then we turned into a drug discovery company to find the best reagents to destroy Tregs, before implementing a lot of preclinical approaches, such as in vitro experiments, to test these reagents. It is intellectually very challenging and exciting."

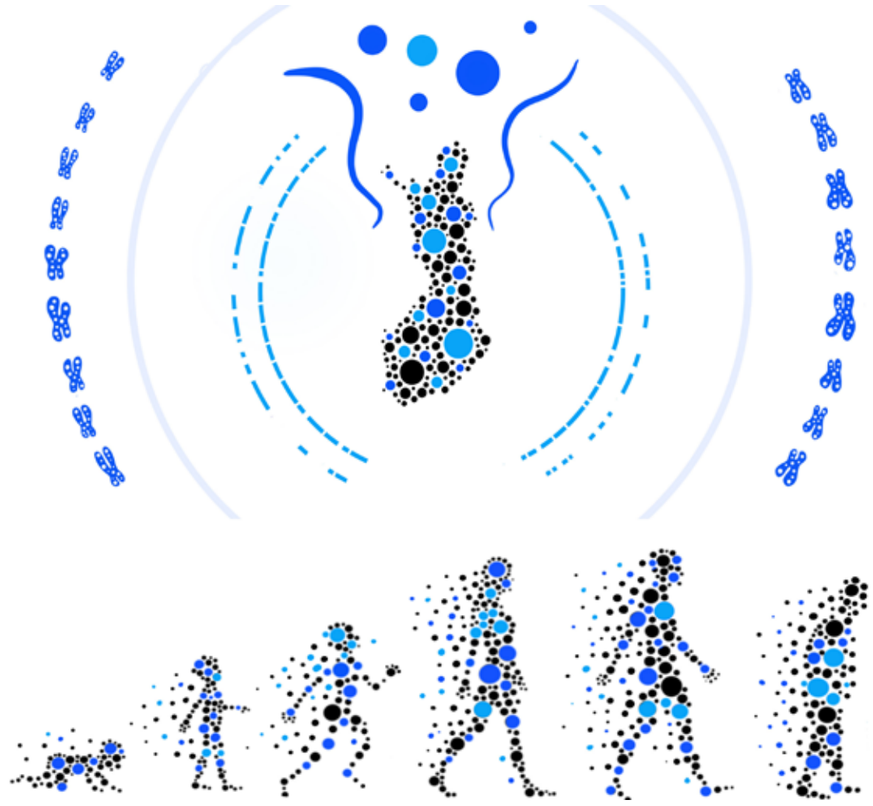
Egle Therapeutics is now warming up for clinical trials of several drug candidates, all focused on modulating the activity of Tregs in cancer and autoimmune diseases. If successful, the molecules developed by the Piaggio team will become part of the clinicians' arsenal to treat patients. When asked for a last word, Dr Piaggio obliges with the candor of the knowledgeable:

"Don't be afraid and go for it."

Institut Curie Research Center consists of 13 mixed research unites, in conjunction with the CNRS, Inserm and certain universities in the Paris region, and involves more than 1,200 employees spread across three sites in Ile-de-France: Paris, Orsay, and Saint-Cloud.

Institute for Molecular Medicine Finland
Nordic EMBL Partnership for Molecular Medicine

FINNGEN



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Unlocking the power of genetic insights: FinnGen study

By Mari Kaunisto

We humans are all unique. The individual characteristics of our genes, combined with our environment and lifestyle, should be considered when we get sick and need treatment.

Most current drugs have been developed using a 'one size fits all' approach, which means that commonly used medicines are not effective for all of us. In precision medicine, this individual variability is taken into account when selecting treatment or prevention choices. However, we are still trying to understand much of this variability — what makes us unique and why we react differently to different medicines.

Furthermore, there are many patients with diseases that can't yet be treated. Either the biological mechanisms causing the disease are not yet known or the targeting of these processes is too challenging. New drugs are needed but the pace of drug development has been dramatically slowing down and only about one in ten clinically tested new drug candidates eventually ends up being approved.

Researchers at the Institute for Molecular Medicine Finland (FIMM), University of Helsinki, are building a large-scale genomic study cohort called FinnGen. This initiative is not only providing new clues about underlying genetic disease mechanisms, but also enhancing drug development.

Genetic evidence can help drug developers to select, among the various lead molecules, the ones that are most likely to succeed. It can also help to identify the patients that will benefit from the treatment and thus demonstrate the efficacy of potential new drugs in clinical trials.

FinnGen's eventual goal is to produce and study the genome — the complete genetic makeup of an individual — of 500,000 Finns. In addition to large investments, building such cohorts requires that hundreds of thousands of people are willing to donate their health data and DNA samples for research purposes.

This is an achievable goal, since in Finland, the value of genomic data in disease prevention, diagnostics and precision medicine is acknowledged and there is more and more interest in putting such scientific knowledge into practice. Both patients and the wider population are willing to support medical research by donating their samples to biobanks, knowing that the information produced from their samples can make a difference to future generations. Thanks to their contribution and consistent with the original timeline, FinnGen will reach the target and complete this huge dataset by autumn 2023.

Even when working with coded samples and data, as we do, privacy concerns remain. Keeping such personal data safe while accessible and following all national and international regulations requires special expertise and advanced technical solutions. But, as FinnGen has shown, it can be done. A prerequisite for our success has been that policy makers, academics, biobanks, industry, patient organizations and other stakeholders cooperate with each other.

But why do we need to delve into so many study participants' genomes? When we talk about genetics, big is beautiful. Larger studies provide stronger and more reliable results. When a new genetic variant is identified for the first time, in one single person, its health impact can't be interpreted. But if we see it in tens or even better, in hundreds of individuals, we start to understand whether it predisposes to some diseases or offers protection from others. Furthermore, in some cases even one sample can make a huge difference.

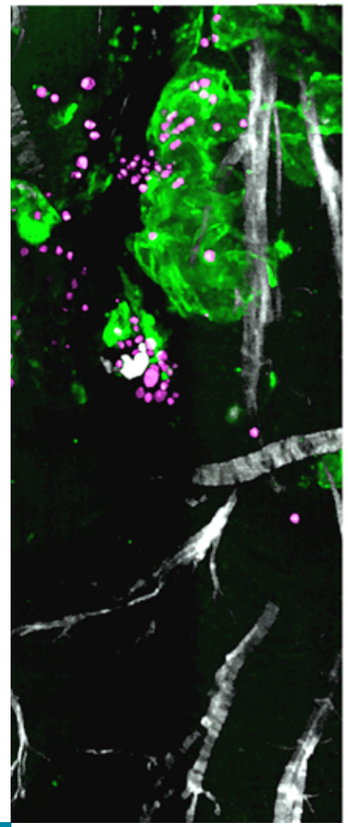
It is impossible to know who of us carries scientifically valuable, intriguing clues in our genes — clues that can change what we know about medicine.

Due to the Finnish people descending from a rather small group of ancestors, our genetic pool is limited and we have much less genetic variation than most other Europeans do. Some variants that are extremely rare elsewhere in the world have, just by chance, become more frequent here. What makes things even more interesting is the fact that many such variants happen to cause the complete disruption of the gene in question, thus providing hints about potential drug targets. If a person can live healthily and happily without any working copies of a particular gene, it also is very likely that a drug targeting that same biological pathway is well-tolerated.

Since the human genome is so variable, making all of us unique, identifying these medically important variants from the mass is like finding a needle in a haystack. What makes Finland a great place for genetic research is that the haystack is so much smaller.

FiMM is a translational research institute focusing on human genomics and precision medicine, with a driving mission to perform innovative research on patients and populations targeted towards understanding drivers of health and disease. It aims at delivering improvements to the safety, efficacy, and efficiency of healthcare in Finland and beyond.

FORTH
INSTITUTE OF MOLECULAR BIOLOGY & BIOTECHNOLOGY



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An iron armor against fungal pathogens

By Eva Zacharioudaki

Patients with a weakened immune system are at constant risk of life-threatening infections by opportunistic organisms, including airborne saprophytic fungi (fungi feeding on dead organic matter). Nowadays, fungal diseases are occurring more frequently because of the increasing number of patients with acquired immune defects, including patients on targeted therapies for malignant and autoimmune diseases and those recovering from sepsis syndromes (e.g., influenza, COVID-19).

Fungal diseases are associated with high mortality rates, especially among patients with deregulated iron metabolism, due to the lack of efficient treatments.

The group of George Chamilos at FORTH-IMBB, a EU-LIFE partner institute, is studying how the immune system fights off these infectious fungal diseases.

George Chamilos was raised in a village of South Crete, Greece, where helping people in need has been a core value of this small society, so he decided to become a doctor. Over the years, his daily interaction with patients who suffered from terminal stage diseases made him realize that medical doctors are often powerless to fight against them and efficiently help those people. After finishing his residency in Greece, he visited the US to perform research and a clinical fellowship in infectious diseases at a major cancer Institute, where he discovered that traditional antimicrobial therapies offered very little to immunocompromised patients who suffered from fungal diseases. Over half of these patients died from disseminated fungal infection while in complete remission from cancer, despite the fact that they had received appropriate therapy with potent antifungal agents. This experience made him realize the major gap in knowledge on the pathogenesis of infections in the immunocompromised host and the need to invest in fundamental research for development of host-directed therapies aiming to restore immune deregulation in these patients. He was determined at that point that he should pursue this research path.

However, research was challenging during the first years of his return from the US to Greece. At the beginning of his career as a Principal Investigator, George had limited resources and time for research. A successful application for a Marie Curie Reintegration Grant was the driving force that allowed him to continue in research and develop his career as a scientist. During that time, he used a tiny fruit fly called *Drosophila melanogaster* as a research model since it is easy to grow in the lab, it has a short life cycle and an evolutionary conserved immune system. Macrophages are the 'frontline soldiers' of our immune system that patrol the human body and swiftly eat up foreign particles, microbial pathogens (bacteria and fungi) and dying cells (a process called phagocytosis) to maintain our body's health. Amazingly, they have remarkable similarities with the macrophages of fruit flies.

Chamilos' group discovered that the presence of melanin (a pigment that normally protects us from sun radiation and is responsible for the dark color of our skin) on the cell surface of fungi protects them from elimination by macrophages by inhibiting the process of phagocytosis and affecting iron metabolism. These findings were of great interest and led to securing a prestigious grant of 1.5 million euros from the European Research Council.

The group will now exploit their fungal infection model in Drosophila to perform targeted genetic screens to identify the master regulators of iron metabolism in macrophages and how they orchestrate protective immunity against fungal pathogens. This way, the group will uncover evolutionarily conserved mechanisms of protective immunity mediated by iron inside macrophages. At the next stage, they will extend their research to mammalian macrophages in mice, and finally human patients, to validate their results. Chamilos hopes that his current work will result in the development of an alternative class of drugs that can fight fungal infections by optimizing the host immune response to resolve the immunopathology of the disease rather than targeting the pathogen with the use of traditional antimicrobial therapies.

Chamilos never forgets the patients he failed to cure. Their memory has been a driving force in his career, to keep on learning and trying harder. He admits that working on a challenging quest awakens one's passion for research and fosters creative thinking to resolve complex scientific problems. He is grateful for the grants that helped him develop his research, the outstanding members of his group that carried out all the research, his long-term international collaborators, and is a strong advocate that the European Union should increase investment in discovery-driven research.

IMBB is one of the most prominent life science research institutions in Greece, with an outstanding record of scientific achievements, state-of-the-art infrastructure and a broad range of research, innovation and educational activities. IMBB's main mission is to pursue cutting-edge research and promote scientific excellence.

Game changer: from discovery-driven research to therapeutical applications

By Ana Morais

Understanding how the body functions and how we can regulate it remains a secret in many ways. A myriad for scientists. A future to shape.

When it comes to infections, they can range from being mild to severe, they affect newborns or the elderly, sometimes they are manageable, with low costs and effects, other times the organism starts to fight against itself and the disease wins the battle. In this fight, the immune system, the body's defense against infections or other harmful invaders, is our hero. It is made up of cells, tissues and organs that work together to protect us. But what secrets does this hero keep?

How can we reach a deeper understanding of the body´s response to infection and of how scientists can intervene to maximize the power of the immune system to improve quality of life?

This key question at the heart of Luís Moita´s research project, principal investigator at the IGC, emerged back in 2013 and was driven by curiosity. What triggered Luís to study the immune system was not a special event. Luís is an MD and research soon took over his career. A holistic view of the body, its development and the unknown secrets of its working systems have been the driving forces in Luís´s research for the past 20 years.

One of the uppermost causes of death, estimated to kill 11 million people every year around the world, is sepsis. This death toll is equivalent to Portugal's entire population. Sepsis arises from a deregulated response of the organism to an infection, leading to organ failure and malfunction, and is still poorly understood as a disease.

With a commitment to unveil new knowledge and understand the immune system and the response to infection, Luís began to look more closely into drugs approved for clinical use to gauge their abilities to interfere with basic functions. The aim? To find yet undiscovered mechanisms that act on the organism and describe how they affect the immune system. Let´s be clear: it was not a straight road! Scientific knowledge is an accumulation of failures, eureka moments and searches for funding, all carried out by scientists focused on finding answers for a better future.

After ten years and the funding needed to pursue this idea, in 2015 Luís was awarded a prestigious European Research Council grant. The first drugs he studied were those used to treat cancer patients (anthracyclines). Surprisingly, his team found that these drugs confer a strong protection against sepsis. The research team discovered that anthracyclines act therapeutically by promoting disease tolerance to sepsis.

The disruptive finding revealed a highly effective power of providing protection against severe sepsis in mice, even when used up to 24 hours after the onset of infection. This therapeutic window, as Luís explains,

“is likely to be sufficient to make these drugs good candidates as useful therapeutic options in the clinic to reduce the mortality from sepsis in most patients who are either in the hospital or that seek medical attention within the first few hours of symptoms onset”.

Although the research team began investigating the use of anthracyclines in sepsis by virtue of their effects on inhibiting inflammatory cytokine expression in myeloid cells in vitro, they also identified a mode of protection that was much stronger and perhaps completely independent of such effects. Instead, it manifested an effect at the level of DNA damage response and autophagy-induced protection in the lung.

New findings do not normally lead a scientist to dead ends. On the contrary, they lead them to new paths to follow clues. At this stage, Luís and his team wanted to extend the study and look for other uncovered mechanisms related to disease tolerance and the role of mitochondria in these processes. They started a new study by selecting a group of medical drugs known for their ability to interfere with basic cell functions. Spoiler alert: new discoveries were made.

After seven years of studying the effects of a specific class of antibiotics in the lab (tetracyclines, which were identified back in 1948), they discovered such antibiotics can reduce the damage caused by infection, independently of their antibacterial effects. By partially inhibiting the activity of cell mitochondria, these antibiotics induce a compensatory response in the organism that decreases tissue damage caused during infection. A new door in the field of disease tolerance positions this group of antibiotics as potential adjuvant treatment for sepsis due to their effects that go beyond the control of bacterial burden.

For decades, certain families of antibiotics have been known to provide benefits that go beyond their important antibacterial properties, but so far, the mechanisms remain unexplained. The results obtained in this study highlight that the beneficial effect of doxycycline reaches the lungs, reducing cell damage, and promotes activation of tissue repair mechanisms. Additionally, in the liver, the stress response is activated together with metabolic changes that promote tissue repair.

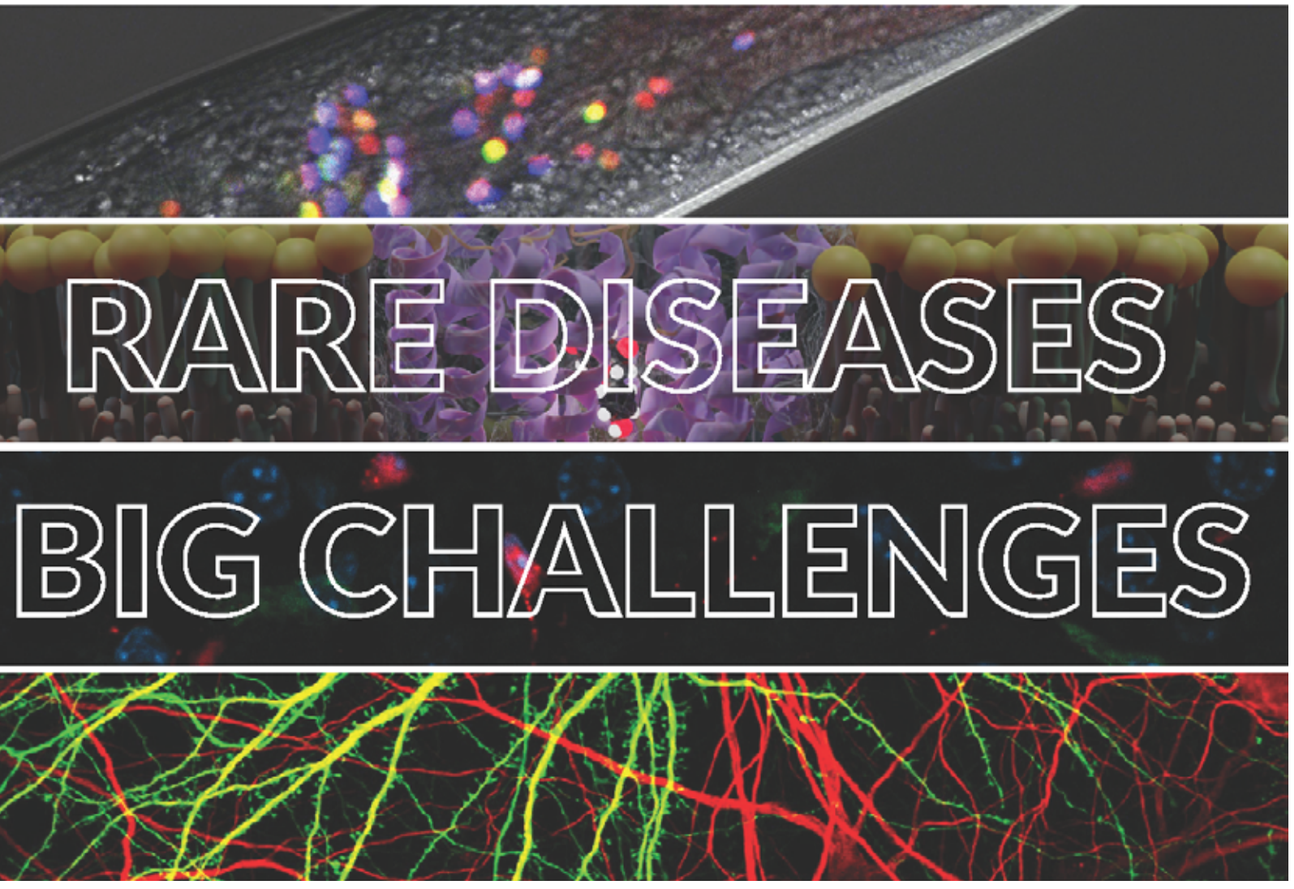
It is an incredible opportunity to upcycle an old antibiotic that revealed a very well-kept secret: a beneficial impact on disease tolerance (meaning that the drug will protect the organism from failure caused by sepsis and, ultimately, death) — a priority for research with impact in human life and sustainability.

Searching for new therapies against diseases like sepsis will definitely decrease death, the burden of disease and the social and economic impact of it (hospital admission, intensive care treatment, and recovery).

A commitment to making a difference, curiosity-driven research led by Gulbenkian and enriched and supported by different international researchers creates hope and protects life. The research is continuing to advance in the clinic: a new clinical trial with several patients treated with cancer drugs is starting in Germany. Science and discovery, curiosity and innovation: all working together to change the game and shape the future.

IGC is an institute dedicated to biological and biomedical research and innovative postgraduate training, placing science at the heart of society.

Four hundred scientists, from 44 different nationalities, aim to understand the fundamental principles of biology, in particular how the organism is formed and interacts with its environment, leading to novel approaches towards disease treatment and world sustainability.



Rare diseases — big challenges

By Małgorzata Staszkowska

Imagine a young patient: A nine-year-old boy with neurodevelopmental disorders, a lack of speech, impaired coordination of movement and issues with balance. Genetic testing reveals the presence of an undescribed and ultra-rare mutation in the FEM1C gene. However, doctors do not know whether the indicated mutation has any connection to the boy's disease, nor which therapy should be taken. And here lies the key message: where available knowledge ends, scientists step in.

Rare diseases are conditions affecting no more than five in 10,000 people, most often genetically determined, and tend to manifest themselves in childhood. We call them 'rare', but it does not mean they are rare indeed. It is estimated that 6-8% of the world's population suffers from them.

Currently, more than 7,000 rare diseases are known to medicine, but the list expands regularly as doctors recognize and describe new conditions.

It is a long and difficult process to search for the causes of rare diseases, as it is difficult to grasp all the molecular aspects that allow for a clear answer to the question: does a detected mutation really cause a particular disease? How can we know the exact reason for its occurrence? What is the best way to understand the mechanism behind the disease? What is the right therapy and how should it be applied?

Science and model organisms such as nematodes, fish and mice can be helpful here. This is because it turns out that most of the genes that influence the development of many organisms, including human development and the formation of diseases, are common to both humans and animals.

For example, the heart of a popular aquarium fish — the zebrafish, which is also an invaluable model organism in biological research — shows remarkable similarity to humans in terms of resting heart rate, electrophysiological properties, as well as the shape and duration of their action potential. Also, many genes of the nematode *C. elegans* have functional counterparts in humans, making it an extremely useful model for many diseases, such as neurological and metabolic diseases. *C. elegans* is equipped with nervous, digestive, muscular and reproductive systems and shows age-dependent physiological changes similar to humans.

In simple terms, research using model organisms consists of mapping a human disease in another species and then conducting a series of experiments on it. All this is done to support patients and doctors in making the right diagnosis, monitoring changes, and in following the course of the disease itself. A major challenge for scientists is to fully understand the multidimensionality of the changes to various tissues or organs that rare diseases bring. Their in-depth analysis provides insight into the molecular mechanisms that are the actual cause of the disease, which is crucial for developing new therapies or implementing available treatments.

The use of model organisms has been a breakthrough in biological research and has contributed to the understanding of hundreds of human diseases, as well as enabling the discovery of many modern drugs.

Research on rare diseases using model organisms has been successfully carried out by the scientists at the International Institute of Molecular and Cell Biology in Warsaw. They have made the understanding of the causes of many rare diseases more complete. Continued progress in research conducted in this area allows us to hope for the development of further modern experimental therapies and the improvement of patients' quality of life.

The main research directions at the IIMCB are RNA biology and cell biology, both aimed at understanding the fundamentals of human diseases, which are the basis for creating innovative therapeutic and diagnostic methods.

MAX DELBRÜCK CENTER

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Discovery for tomorrow's medicine: The tissue engineer

By Mirco Lomoth

Dr Mina Gouti cradles the petri dish in her hand so that the tiny white spheres move around in the pink liquid. She casts a protective glance at them. Her colleague brought the organoids to life a month ago, and since then they have grown to just over a millimeter. "In the beginning they are given nutrients every day to ensure they grow and thrive, and later on every two to three days," Gouti says, carefully placing the dish with organoids back into the incubator, which keeps the temperature at a comfortable 37 degrees Celsius, just like in the human body. "If we take good care of them, they can grow to six millimeters in size and live up to two years."

The organoids Gouti creates in the lab are organ-like tissue structures made of spinal cord nerve cells and associated muscle cells. It's easy to tell the difference between the two — the dark core of muscle and the lighter rim of surrounding nerve tissue — when looking at them under a microscope. The tiny bundles of muscle twitch rhythmically. "They contract like muscles in the human body," says Gouti, who heads the Stem Cell Modeling of Development and Disease Lab at the Max Delbrück Center. Her enthusiasm is infectious. "This is fascinating because it shows that we have generated functional tissue."

She is developing the organoids from reprogrammed stem cells from patients suffering from neuromuscular diseases like spinal muscular atrophy. The fatal disease causes the motor neurons responsible for bodily movements to eventually die. "The children experience paralysis in the first months of life, and in the end they can't even breathe," Gouti says. "With the help of these organoids, we want to understand why exactly the motor neurons die and find ways to stop this process." Gouti is also looking to organoids to shed light on other currently incurable neuromuscular diseases such as amyotrophic lateral sclerosis, which affects adults.

"I fell in love with stem cells"

Mina Gouti is a developmental biologist. She left her hometown of Athens to study molecular biology in London. In the lab she saw postdocs conduct research on cell cultures derived from mouse embryonic stem cells. "The stem cells were off limits for me at the beginning," Gouti recalls. "But when I finally got to work with them, I was totally excited and instantly fell in love with them because of their unlimited potential. If you want something from stem cells, you have to learn to control them."

She mastered all the necessary techniques and studied what signaling pathways cause stem cells to differentiate into central nervous system cell types as part of her doctoral thesis. Just two years earlier Shinya Yamanaka of Japan had produced the first induced pluripotent stem cells (iPSCs), ushering in the ability to reverse cell fates: all of a sudden it was possible to reprogram a skin cell into a stem cell, from which in turn any other cell in the body may be created.

Now Gouti was generating neurons of the brain and cervical spine from pluripotent stem cells. But she hit a roadblock with respect to neurons of the lower spinal cord. At the Francis Crick Institute in London she became aware of neuromesodermal progenitors (NMPs), a transient cell population first discovered in 1884 that can differentiate into neurons and muscle cells. Were they the crucial precursor for all other cells of the spinal cord? In May 2013 she succeeded in producing in the laboratory the first NMPs from pluripotent stem cells, which were also capable of forming neurons of the lower spinal cord and the associated skeletal muscle.

Three surprises

As a group leader at the Max Delbrück Center, Gouti bet everything on the NMP card. And rightly so, as it soon turned out. Her lab focused on pluripotent stem cell-derived NMPs that resemble those in the human body. "Shortly thereafter I had the bold idea of growing them into neuromuscular organoids and seeing if they would actually form both cell types — neurons and muscle cells in 3D — just like in the human body," Gouti says. No one had been able to do that before.

She created the perfect environment, placing the NMP cells and nutrient solution into the wells of a non-adherent microwell plate, and watched as small, intact spheres emerged. "After five days we saw through the microscope that both tissue types were indeed forming." It was the first of three surprises. The 3D cultures were so robust that they stayed alive for a month or more. On day 40 Gouti and her graduate student Jorge Martins noticed that the organoids were contracting. This meant that the motor neurons were extending their axons to the muscle cells and causing them to move through a synapse called the neuromuscular junction or endplate. The spinal cord and muscles were exchanging signals. What a sensation!

They also discovered that in the neuromuscular organoids (NMOs), Schwann cells and an advanced neural network had formed, and that these had assumed the function of central pattern generator-like circuits — i.e., they were sending out rhythmic signals such as those needed for breathing and walking. This was another sensation. Her high-profile paper appeared in *Cell Stem Cell* in 2020. "For the first time we were able to observe such a complex network in a human model," Gouti says. "Those are the moments you live for as a scientist — to see something completely unexpected, but that makes 100 percent sense."

Can organoids grow old?

The successes confirmed her hope that NMOs could help in the search for targeted and timely therapies for neuromuscular diseases. She now wants to culture position-specific organoids that correspond to particular spinal cord segments and their associated muscles. And she wants to coax these organoids to develop blood vessels, so they can grow larger and older to more closely resemble adult tissue. "We could then track exactly when and where an adult disease like amyotrophic lateral sclerosis appears in the tissue and whether other cell types are affected before motor neurons die and paralysis ensues," Gouti says. "We could try to save these cells before it's too late." NMOs are also opening up new avenues to study neurodegenerative diseases.

Gouti's long-term goal is to create all central nervous system cell types from stem cells and develop an organoid that can transmit neural signals from the brain along the entire spinal cord all the way to the muscles. She wants to observe where and how communication goes wrong when people get sick. Since 2020 she received the European Research Council Consolidator Grant and Proof of Concept Grant to pursue these new endeavors.

"Organoids also help us reduce animal research leading up to clinical trials," Gouti says.

"Unfortunately, we can't stop doing such research completely. We need more complex models that better mimic human physiology."

Stained neurons and muscle cells become true works of art

Her team is setting up a high-throughput imaging system one floor above the organoid lab. A robotic arm pipettes hundreds of different drugs and tests them on patient-specific organoids to see if they are effective for treating spinal muscular atrophy. The first images suddenly appear on the screen. These stained muscle cells and neurons with long axons — microstructures exploding in greens, yellows, reds and blues — are veritable works of art.

For all her enthusiasm for the workings of motor neurons, stem cells, and organoids, Gouti is also enamored by their beauty. She has published in Greece a book of images of her lab work and displayed them in two exhibitions. She wants to bring stem cell research closer to the public. For each picture she interviewed writers and children with cancer. "In the red-stained astrocytes that were generated from stem cells, the writer saw dancing cells and the girl a tunnel leading to an unknown destination," Gouti says. "I very much hope that we can use organoids to find ways to better help people with fatal neuromuscular diseases."

The Max Delbrück Center is one of the world's leading biomedical research institutions. Max Delbrück, a Berlin native, was a Nobel laureate and one of the founders of molecular biology.

Their researchers analyze the human system — investigating the biological foundations of life from its most elementary building blocks to systems-wide mechanisms. Basic research discoveries aim to benefit patients in health and disease.

CeMM
SCIENCE IS OUR MEDICINE

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Science is our medicine: How fundamental research shapes the future's health

By Anna Schwendinger & Prudence Donovan

Personalized, individualized medicine holds enormous potential to improve diagnoses and therapies for patients. Especially in times of an increasingly aging society, the question of how we grow older in a healthy way is becoming more and more important. One essential part of the answers could be found in our genes. But to solve this puzzle, we must improve the molecular understanding of our body, and the interrelationships between genes, cells, and tissues. With this knowledge, we can revolutionize the therapeutic approaches to be applied in clinical practice.

CeMM, the Research Center for Molecular Medicine of the Austrian Academy of Sciences, was founded 16 years ago as a highly innovative research institute that conducts interdisciplinary research into human genes and their interaction at the highest level. With high-end technologies, biologists, physicians, chemists, physicists, and bioinformaticians work together to explore the molecular relationships in the human body, CeMM creates the scientific bridge to the clinic and works towards medical needs. To do research as close as possible to clinical practice and to connect research, academia, and patients, the institute was built in the middle of the campus of Vienna General Hospital and the Medical University of Vienna.

The success of this collaboration can be seen in the high-quality publication output of CeMM followed by successful technology transfer that nowadays improves the lives of many patients.

Within a short time, CeMM turned its outstanding scientific findings and innovations into six spin-off companies and a number of licenses with biotechnology companies to develop new applications, services, and treatments for patients. With these partnerships, CeMM has developed a kit to diagnose specific blood cancers and the first functional drug screening in human tissue to find the most efficient treatment for cancer patients. In addition to this, CeMM through these partnerships will continue to improve the therapy of neurological diseases, metabolic disorders, and infectious diseases, as well as unveil the fundamental mechanisms of aging to expand our healthy lifespan. So, what becomes clear is: investments in basic life science research are direct investments in the health of us all.

CeMM is an interdisciplinary research institute of the Austrian Academy of Sciences committed to achieving maximum scientific innovation in molecular medicine to improve healthcare. Located in the campus of the Medical University of Vienna, CeMM integrates basic research and clinical expertise to develop innovative diagnostic and therapeutic approaches for precision medicine. Research focuses on cancer, inflammation, metabolic and immune disorders, rare diseases, and aging.

Babraham Institute


Portrait of Alec Bangham by Humphrey Bangham, 1985
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How fundamental research keeps on giving

By Honor Pollard & Louisa Wood

The Babraham Institute in Cambridge, UK, is a centre for expertise in cellular and molecular biology. Supported by cutting-edge scientific facilities and technical experts, the Institute's research teams delve into the intricacies of how our bodies function, right from the moment of conception, with one united aim: to sustain health throughout the life course and reduce the physical decline and disease vulnerability of our bodies seen with age. Today's discoveries will provide the foundation for health gains in the future.

A discovery made at the Babraham Institute (then known as the Institute of Animal Physiology) in the 1960s played a part in the 2020-2021 COVID-19 vaccination development efforts, and continues to enable innovation in cancer treatment.

This 50-year journey provides an example of how a strong foundation of fundamental research secures our ability to respond to urgent challenges facing humanity.

A field founded on a serendipitous observation

Of the three COVID-19 vaccines used in the UK during 2020 and 2021, two — the Moderna and Pfizer/BioNTech — are mRNA vaccines. Often described as 'plug and play' due to the potential for the mRNA template to be tweaked as required, the critical element of these vaccines is a lipid vesicle coat that is essential for the template mRNA to be safely transferred into cells. The discovery of how to create membrane vesicles goes back over 50 years when a new field of scientific discovery was founded that would eventually give rise to the lipid vesicles used in COVID-19 vaccines.

In 1961, the Babraham Institute received a gift from the Wellcome Trust of an electron microscope. Among the first in the queue to test it out was Alec Bangham, a researcher and former physician, and his colleague Robert Horne. Bangham was investigating the properties of red blood cells, in particular why they don't stick to each other. During his experiments, Bangham began to model the cell surface using lipids. Scientists had already shown that lipids formed different structures when immersed in water but, because they exist on a nanoscale, their exact shape was difficult to image directly. After the arrival of the electron microscope, Bangham and his colleague Robert 'Bob' Horne took the opportunity to put liposomes under the lens and for the first time were able to image the double layer vesicles formed by lipids using a negative stain technique developed by Bob Horne and Sydney Brenner. Bangham and Horne submitted their paper, 'Negative staining of phospholipids and their structural modification by surface-active agents as observed in the electron microscope' to the *Journal of Molecular Biology* on 11 December 1963.

Branded 'liposomes' by Bangham's collaborator Gerald Weissmann, these molecular vesicles had a surprisingly useful property: they are able to fuse with the surface of cells, releasing their contents inside. In research terms, Bangham and Weissmann were pleased to have found a good model for cells, creating a system for studying cellular membranes. In impact terms, the recognition that liposomes could be used as a drug-delivery mechanism opened the door to a huge range of therapeutic opportunities.

Developing liposomes for drug delivery

The key step forward in the journey to drug delivery came in 1970, with the work of Gregory Gregoriadis, a colleague of Bangham's, and Brenda Ryman at the Royal Free Hospital School of Medicine. Gregoriadis and his team confirmed the prospect of using liposomes as a potential immunological adjuvant for vaccines for the purpose of generating an enhanced immune response. Liposomes consequently became a key interest for pharmaceutical companies, but before drugs could be packaged into liposomes, more research was needed to show that liposomes would be safe inside the body.

Research into liposomes expanded over the subsequent decades with major developments coming in the form of modifications to the membranes surrounding the cargo for delivery. In the early 2000s, several drugs for rare diseases were produced using liposomes but they remained difficult to manufacture. Eventually, researchers refined the structure of the lipid vesicles, creating the great-grandchild of the liposome — the lipid nanoparticle.

Building a new type of vaccine

In parallel to the development of lipid nanoparticles, mRNA technology was breaking new ground by providing a way to give instructions to cells that would help treat diseases. The two worlds would unite in 2020, when Pfizer/BioNTech and Moderna received approval for their mRNA lipid nanoparticle vaccines against the SARS-CoV-2 virus.

The speed of development of the mRNA vaccines was only possible because of the foundation of work that enabled this sprint start, such as that of Alec Bangham at the Institute, and the subsequent development of his invention by academic scientists, funders and life science and pharmaceutical companies who recognised the field as having potential. Also vital was the longstanding investment in basic research that led to the two technologies coinciding. The global success of the COVID-19 vaccines has shown the power of lipid-based drug delivery and the approval of lipid nanoparticle vaccines for COVID-19 is laying the groundwork for the treatment of other diseases.

The importance of the 'knowledge arsenal'

Dr Simon Cook, Director of the Babraham Institute, commented: "The trajectory of Alec Bangham's work is certainly inspiring for researchers whose focus is to understand the fundamental workings of cells. There is a lot to learn from the story of liposomes, including the importance of close collaborations with industry to make life-changing interventions possible and accessible."

Sir Brian Heap, friend of the late Alec Bangham and former Director of the Babraham Institute added: "The Wellcome Trust's gift to the Institute of its first electron microscope and ancillary equipment in the 1960s proved a crucial step for liposome research. The Babraham Institute has developed a history of investment in cutting-edge facilities that continues to this day, encouraging scientists to pursue questions that can provide the critical foundation of future breakthroughs. The work in the '60s and the pace of the COVID-19 vaccine development in recent years point to the value of strong investment in fundamental research to create the knowledge arsenal needed to address future challenges."

Immunology expertise improving vaccine response

The predecessor to the Babraham Institute was focused on animal physiology in the 1960s whereas since 1993 the Institute has focused wholly on human health. The story comes full circle with Institute immunologist Dr Michelle Linterman and her lab playing an important role in 2020 in pre-clinical studies to assess the effect of age on the immune response to the Oxford–AstraZeneca COVID-19 vaccine.

"The pandemic highlighted how much of a health imbalance is caused by the immune system decline seen with age," explained Michelle. "I thought the most useful thing was for us to offer something that nobody else could contribute quickly — and that was our ability to use aged mice as a pre-clinical test of how this vaccine is likely to work in an ageing immune system."

The research indicated that two doses of the vaccine would give good protection against infection in all adults. Ongoing work in the Linterman lab continues to identify why immune response after vaccination declines with age and how vaccines or vaccination strategies may be altered to ensure a robust response, and thereby strong protection, in older people.

Today's discovery for healthcare innovation

Fundamental research continues to provide the launchpad for innovation. Running through the Institute's timeline is a dedication to discovery-led research, collecting pieces of the picture to create knowledge that can be used to improve lives.

Our future scientific and intellectual capital depends on this feedstock of fundamental research, generating invaluable understanding across the range of specialisms represented by the EU-LIFE institutes. Which of the discoveries made today will build our ability to meet the challenges of tomorrow?

The Babraham Institute undertakes world-class life sciences research to generate new knowledge of biological mechanisms underpinning ageing, development and the maintenance of health. Our research focuses on cellular signalling, immunology and the impact of epigenetic regulation at different stages of life. As part of the Babraham Research Campus, we play a vital role in advancing innovation in bioscience and translating research discoveries into benefit.

NETHERLANDS CANCER INSTITUTE
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How on earth does all of this work?

By Benjamin Rowland & Hilje Papma

Almost all medical breakthroughs are the result of fundamental discoveries. Just one fundamental discovery about a basic mechanism in our cells may provide a range of new possibilities. In this article, Benjamin Rowland, who leads the Chromosome Biology Lab in the Netherlands Cancer Institute, explains how a tiny molecular machine named cohesin controls some of the most important aspects of human health, ranging from embryonic development, to cancer, to the immune system. Sooner or later, discoveries into the mechanisms behind these processes are bound to impact treatment of diseases. But it all starts with the question: "How on earth does all of this work?"

Benjamin Rowland embarked on his career out of sheer curiosity. "I have always wanted to know how stuff works", he says. "As a little kid, I had one of those old-fashioned mechanical alarm clock in my bedroom which I could not resist opening up to figure out how it worked. That clock had a beautiful mechanism with cog-wheels and springs that made it tick. For a couple of years I dreamt of becoming a watch builder. In the end I became a scientist, but I have not changed that much, really. I still want to figure out how stuff works. But now I am studying the most beautiful mechanism of all: the secret of life itself."

Providing structure to DNA

DNA in essence is the code of life. It contains the genes that determine the behavior of our cells, which together form an individual. Each cell in our body contains the entire genetic code. Our DNA is meters in length, whereas a cell is merely a few micrometers in diameter. "These simple numbers sketch the momentous task of folding these long DNA threads in such a way that they fit inside tiny cells," says Benjamin Rowland. "This feat becomes even more challenging if we consider that within this confined space, the DNA must be organized in such a manner that the cell can perform its many vital roles."

Genes are carefully controlled by regulatory elements that also lie on the DNA, but often a long distance away from the gene. How can they regulate a gene from such a distance? This becomes possible because the DNA is folded into loops, so that distant parts of the DNA are brought close together. These loops are built by cohesin, which is a minuscule ring-shaped protein complex that can be opened and closed to entrap and release the DNA. 'But how does that work?', Rowland cannot stop wondering. And as soon as he has found an answer to one question, a new one tends to pop up.

His lab investigates the mechanisms by which this tiny ring-shaped protein complex is regulated and in turn regulates our DNA. His team has provided seminal insights into how these rings shape our DNA by building and enlarging DNA loops, and how these rings are controlled by molecular brakes and roadblocks that cling onto specific DNA sequences. When these mechanisms work well, this allows life to manifest itself in all its beauty, as Rowland has learned over the years. But when they are defective, this will lead to severe diseases, such as developmental disorders or cancer.

"What is also fascinating," he says, "is that cohesin, along with a few very similar ring-shaped molecular machines, has been conserved throughout evolution. These complexes therefore presumably shape the DNA of all life on earth. When they were discovered, some twenty-five years ago, we knew that they were important, but it is only over the last few years that we've come to understand just how important they are."

Broken DNA

"We have already learned a great deal about how cohesin shapes DNA," Rowland adds. "By providing structure to DNA, cohesin for example determines which genes can be switched on and off, which in turn determines the behavior of our cells. When this process goes wrong, it will lead to devastating developmental disorders. But cohesin also enables cells to repair DNA when this is broken. This repair is essential to prevent cells from becoming cancer cells, while it also plays an important role in determining whether or not cancer cells can be killed with specific anti-cancer drugs."

Cell division

People may remember the classical X-shape of a chromosome from their biology class. This image reflects two long but identical DNA threads, held together in the middle by cohesin rings. This connection is essential to cell division. The carefully timed destruction of cohesin triggers the two identical DNAs to be pulled apart towards the opposite poles of the cell. The cell then divides in two, with each of the two daughter cells getting precisely the same genetic content. Rowland: "The elegance of this system just keeps amazing me."

In 2023, his lab revealed how cohesin connects DNAs specifically in their middle part, at a region known as the centromere, hereby providing a molecular explanation for the X-shape of chromosomes. Cohesin can stably connect DNAs for a very long time, even for around 40 years in female germ cells. When cohesin no longer functions properly, the DNA is not accurately distributed during cell division, which causes loss of fertility, and leads to chromosomal anomalies such as Down syndrome.

From embryonic development to the immune system

In recent years, cohesin has proven to be a central player within the cell, controlling some of the most important aspects of human health, from embryonic development, to cancer, to the immune system. By building loops in the DNA, cohesin also enables the formation of antibodies, which is essential for protecting the body against, for example, viruses. Rowland: 'Who would have predicted that cohesin also plays an important role in our defense against, say, corona or influenza viruses?'

> "If we can reach a level of understanding for what makes life work, then we can also fix things when stuff goes wrong."

A molecular code in our proteins

Now that we know that cohesin controls all these major processes, this brings us to the next question: How does cohesin know to do what, and when? This, Rowland believes to be one of the most exciting open questions in biology today. And it is precisely the question he is currently addressing: "It turns out that there is a molecular code embedded in many of our cells' proteins that can direct cohesin to control specific chromosomal processes. We found that this code is used by the protein that protects cohesin at centromeres, but also by proteins that control DNA looping by

cohesin. It feels as if we are entering a new chapter in genome biology. Unraveling these mechanisms is going to be quite a challenge, but also tremendous fun."

Responsibility

"Scientists have the responsibility to keep asking the questions that have the potential to substantially change our understanding of ourselves, the world, or beyond," Rowland says. "And we should never be dogmatic in terms of methodologies or partnerships for how we go about to answer them. Our group collaborates with people all over the world, who specialize in all kinds of different but complementary techniques. We for example work together with a fantastic team of structural biologists in the UK. And we recently collaborated with an incredible crowd from Texas to discover how, across the tree of life, chromosomes are organized within the cell nucleus."

Intergenerational gift

Discovery research has, somewhat loftily, been described as an inter-generational gift. But Rowland subscribes to that notion: "We as a research community are pushing the boundaries of knowledge. What we discover today will form the basis for future generations to ask new questions and to develop applications that will make the world a better place. If we can reach a level of understanding of what makes life work, then we can also fix things when stuff goes wrong."

A bit like the job of a watchmaker? Rowland smiles and looks at the watch on his wrist. "Very much so, really. Did you know that the movement of my own body provides the energy for my watch to tick? Isn't that incredible? I guess I just love any truly beautiful mechanism."

About Benjamin Rowland

Benjamin Rowland leads the Chromosome Biology lab in the Netherlands Cancer Institute. His group investigates the mechanisms that provide structure to our genome, and focuses on the evolutionarily conserved protein complexes known as cohesin and condensin. He has been awarded several prestigious research grants, such as an ERC Consolidator Grant, an NWO Vici Grant, and several Dutch Cancer Society Grants.

The Netherlands Cancer Institute is among the world's foremost comprehensive cancer centers, combining innovative fundamental, translational, and clinical research with dedicated patient care. In our research institute, around 750 researchers from 45 countries work towards solving the mysteries of health and disease and improving the prospects of cancer patients. We gratefully acknowledge funding from the Dutch Ministry of Health, Welfare and Sport, the Dutch Cancer Society, and individual donors.

BRIC
Biotech Research & Innovation Centre

Patients forgotten by time

By Anne Rahbek-Damm

I was four years old when my grandmother died in 1986, at the age of 58. Lily died just two months after having first complained about pain in her lower back. The disease that killed her before she ever had a chance to fight back was bile duct cancer. Except for morphine, the doctors had nothing to offer her and her death was excruciating.

As years passed, I spent little time thinking about Lily's disease until 35 years later when I was employed as a science communicator at the Biotech Research & Innovation Centre in Copenhagen.

Here, a group of scientists are trying to unravel the mysteries of bile duct cancer and I now understood the chilling facts about the disease that killed my grandmother.

Cancer in the bile ducts is a very rare but extremely aggressive malignancy. In Denmark, approximately 250 people each year receive this diagnosis and most are dead within a year. As for most cancers, bile duct cancer is linked to modern life-style factors, but compared to other cancer types, the number of cases have more than doubled during the last 30 years. Unlike more common cancer types such as breast and colon cancer, where massive investments in research, awareness campaigns, screening programs, and drug development have greatly improved survival rates, the overall prognosis for bile duct cancer is still the same as it was when Lily died in 1986. For most people this cancer type is unknown. There is no bile duct cancer ribbon or walkathons, no large-scale awareness or information campaigns about risk factors and symptoms, and research-funding opportunities are limited. Patients are often diagnosed at a late stage and even with recent advancement in targeted therapies, most patients in Europe are offered standard chemotherapy. Besides a very few that are diagnosed early enough to receive surgery resection of the tumor site, patients can only be offered palliative chemotherapy (which has severe side effects and for many no effect at all) and in some cases experimental treatment.

Today, 40 years old, my chances of surviving bile duct cancer are no better than my grandmother's were in 1986.

New technologies can change the game

At the Biotech Research & Innovation Centre in Copenhagen, Group Leader Jesper B. Andersen has dedicated his career to study this rare disease in the hope of bettering the odds for patients. He and his group of researchers study and compare large sets of patient material to extract new knowledge about the molecular mechanisms that are involved in the disease. The researchers use advanced sequencing techniques to characterize and quantify different groups of molecules inside the patient's cells. This technology enables them to create detailed molecular profiles of individual patients and by comparing large sets of data, the researchers can locate overall disease patterns across patient groups.

The results show that a 'one-size-fits-all approach' to bile duct cancer treatment must be abandoned as patients who share a common diagnosis can have tumors that behave very differently. During recent years, the researchers have succeeded in identifying a number of patient subgroups who share common genetic mutations and respond to similar types of treatment. In the future, these results can be used to offer patients tailored treatments based on new and existing drugs. The researchers have also identified a number of molecular changes in the cells of patients that seem to correlate to e.g. treatment response, suspected survival, etc. For instance, an elevated level of a certain protein in the blood correlates to a poor response to chemotherapy. Such so-called biomarkers can become valuable tools in the clinic where they can help doctors decide which treatments to offer to which patients, to predict the likely outcome of treatment and when it is time to stop treatment. This way unnecessary harm, time lost, and cost to the individual and society can be avoided.

Let us improve the odds of future generations

The research results of the later years clearly show that there is hope for improving the prognosis of bile duct cancer patients. Researchers today possess the technological tools, the methods, and the necessary skills. But to realize this potential and create real impact, political awareness and investments in research and clinical practice are needed. Including genomic sequencing in the standard treatment protocol will enable doctors and scientists to offer tailored treatment to a much larger number of patients. Investing in the discovery of new diagnostic and prognostic biomarkers will enable doctors to diagnose more patients in early stages of the disease and will make it easier for patients to make informed decisions about their own treatment. And providing more public information about disease prevention, risk signs, and patient rights could lead to earlier detection and improved life quality of patients. By way of such investments, we now have a chance to restore hope and dignity to a group of patients who are currently deprived of both, and to make sure that future generations will have a better chance of defeating this disease than my grandmother or myself.

BRIC is a research center at University of Copenhagen. BRIC's mission is devoted to biomedical research, primarily within cancer and neurological diseases. Their goal is to contribute to a basic understanding of how and why disease occurs, to discover new disease-related genes, potential targets and biomarkers, in order to provide more efficient treatments for patients.

Unlocking the secrets of life: celebrating 20 years of pioneering genomic research

By Natàlia Dave

Two decades ago, the Centre for Genomic Regulation (CRG) was founded as the first institute of its kind in Spain, with a mission to unlock the secrets of life at the genome level. From the very beginning, the CRG was dedicated to promoting research of excellence, internationality and talent development, in order to produce cutting-edge knowledge that would shape the future of life sciences research.

At the heart of the CRG's mission is the belief that the medicine of the future depends on the breakthroughs of today.

With an interdisciplinary community of world-class scientists, the CRG is uniquely positioned to explore the complexity of life from the genome to the cell to the whole organism and its interaction with the environment. By providing an integrated view of genetic diseases, the CRG is paving the way for the development of personalised medicine and new treatments for some of the most challenging health issues of our time.

What truly sets the CRG apart is its innovative research model. By prioritizing diversity, inclusion, and talent development, the institute ensures that the scientific community is enriched by a wide range of perspectives and experiences, and that researchers are supported throughout their careers. Group leaders are recruited from around the world – more than 1,000 scientists from 60 different countries – and undergo regular evaluations by panels made up of renowned experts in their fields. The results of these evaluations have a major impact on the future of CRG scientists, ensuring a constant flow of fresh talent and a commitment to excellence that drives progress in the field. Many aspects of CRG's innovative research model have been implemented by other research institution not only in Spain but also in Europe. Over the past 20 years, the scientists at CRG have published 3,800 peer-reviewed articles in some of the most prestigious scientific journals in the world. These publications have not only contributed to our understanding of the world around us, but they have also inspired and informed the work of many other researchers and scientists. Importantly, CRG's community of research has raised over 500 million euros in competitive funds, half of which was provided by the prestigious European Research Council.

Career development and training is another main pillar of CRG. Since its birth, CRG has trained 300 PhD students who will go on to become the next generation of researchers and innovators. By investing in the development of these students, CRG is helping to build a strong research ecosystem that will drive innovation and discovery for years to come. In addition to its research, CRG has been instrumental in supporting the development of 5 start-ups in a very short period, raising $33 million in private funds to bring new technologies and innovations to the market. By fostering an entrepreneurial spirit and supporting the commercialization of scientific discoveries, the institute is helping to drive economic growth and create new opportunities for innovation and entrepreneurship.

But the CRG's impact extends far beyond the laboratory. The institute is committed to public engagement, reaching out to more than 300,000 people and sharing its research with the wider community. By promoting scientific literacy and engaging the public in scientific inquiry, the CRG

is helping to foster a culture of curiosity and discovery that will benefit us all. By connecting with the public and sharing its work, the institute is helping to build trust and understanding between the scientific community and society at large.

Moreover, the CRG believes that the way research is conducted is as important as research itself and has been instrumental in creating the best ecosystem for creativity to flourish, not only at the institutional level but beyond. The institute has spun out to major initiatives at the Spanish and European levels, such as EU-LIFE and SoMMa, to lobby for the creation of the best ecosystem for research for excellence.

Open science has become a fundamental pillar of CRG. With a commitment to openness, transparency and collaboration, the CRG is leading the charge towards a more inclusive and accessible scientific community. Thanks to its pioneering dedication to Open Access, an impressive four out of five papers published by the CRG are freely available to anyone, anywhere in the world. But open science is not just about making research accessible, it's also about fostering collaboration and sharing expertise. That's why the CRG is proud to collaborate with international partners on two out of three of its published papers.

By connecting with researchers from around the world, the CRG is building a global network of expertise and knowledge that is driving progress in the field. And this progress is not going unnoticed - the average CRG paper is cited an impressive 68 times, a testament to the quality and impact of the research being conducted at the institute. By sharing its findings openly and collaborating with others, the CRG is helping to drive scientific progress and thus, improve the lives of people around the world.

Through its focus on excellence, internationality and talent development, the CRG has established itself as a powerhouse of biomedical research, dedicated to unlocking the secrets of life at the genetic level for the betterment of society, public health and economic prosperity. As the institute celebrates its anniversary, marking over 20 years of pioneering research that has transformed the field of genomics, it continues to build a global community of researchers dedicated to advancing scientific knowledge and shaping the future of biomedical research to address the challenges of the future.

The Centre for Genomic Regulation (CRG) is an international biomedical research institute of excellence. Its mission is to discover and advance knowledge for the benefit of society. The CRG believes that the medicine of the future depends on the groundbreaking science of today. This requires an interdisciplinary scientific team focused on understanding the complexity of life from the genome to the cell to a whole organism and its interaction with the environment, offering an integrated view of genetic diseases.

10 years of eulife

About EU-LIFE

EU-LIFE is an alliance of research centres whose mission is to support and strengthen European research excellence. EU-LIFE members are leading research institutes in their countries and internationally renowned for producing excellent research, widely transferring knowledge and nurturing talent. Since its foundation in 2013, EU-LIFE is a stakeholder in European policy participating regularly in the EU policy dialogue. More at www.eu-life.eu

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