University of Basel

BIOZENTRUM

The Center for Molecular Life Sciences

50 years Biozentrum Life Sciences

Dear readers

"Pioniergeist" – pioneering spirit – was the word that defined the launch of the Biozentrum 50 years ago. The groundbreaking idea was to bring together outstanding biologists, chemists and physicists under one roof and trust that they would determine how molecules generate life. Looking back, we can say that the Biozentrum has fulfilled and even exceeded these expectations: The institute has made transformative discoveries, spawned several Nobel Laureates, and trained thousands of students and scientists to become leaders in academia, biotech, business and society.

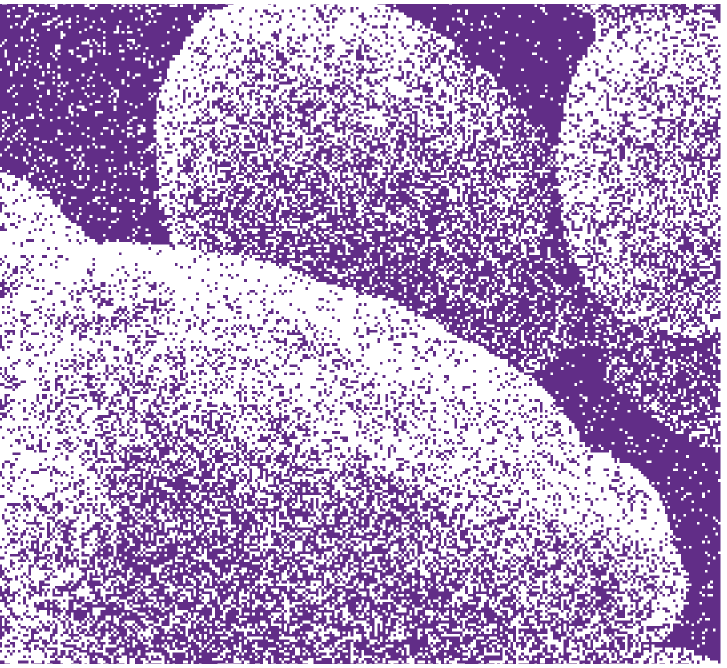
Many ingredients have contributed to the Biozentrum's success: A visionary mission and the freedom to address fundamental questions in biology; the generous support by university, government, industry and the public; and Basel's cosmopolitan culture and belief in the common good. But as you will read in this brochure, the main ingredient has been the people who have studied, researched and worked here. The Biozentrum became a magical place through creative and ambitious colleagues who brought their curiosity and passion from all over the world to Basel. So while we celebrate the 50th anniversary of the Biozentrum vision or the 50th birthday of the Biozentrum building, we are truly celebrating 50 years of world-class Biozentrists – researchers, students and staff.

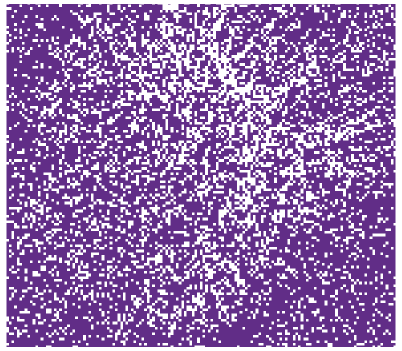
I was seven years old and lived in Birsfelden when the Biozentrum was opened, and I still remember the excitement that surrounded the new institute in our region. Now 50 years later I again feel the same enthusiasm and "Pioniergeist", because the Biozentrum has reinvented and rejuvenated itself. The 1971 founders have been followed by a new generation that is as passionate and driven as their predecessors. And the move into our brand-new building will support cutting-edge research for years to come. In another 50 years the Biozentrum will be renewed once again. In the words of Bob Dylan, the Biozentrum will stay "Forever Young".

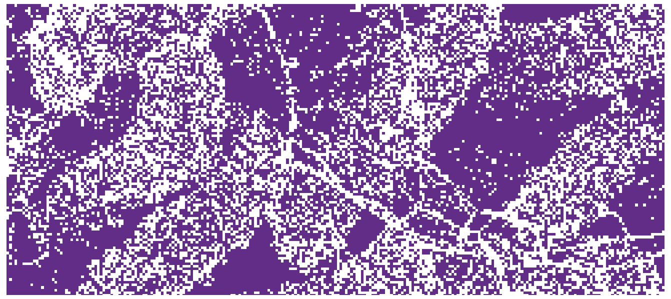
May your hands always be busy
May your feet always be swift
May you have a strong foundation
When the winds of changes shift
May you build a ladder to the stars
And climb on every rung
May you stay forever young

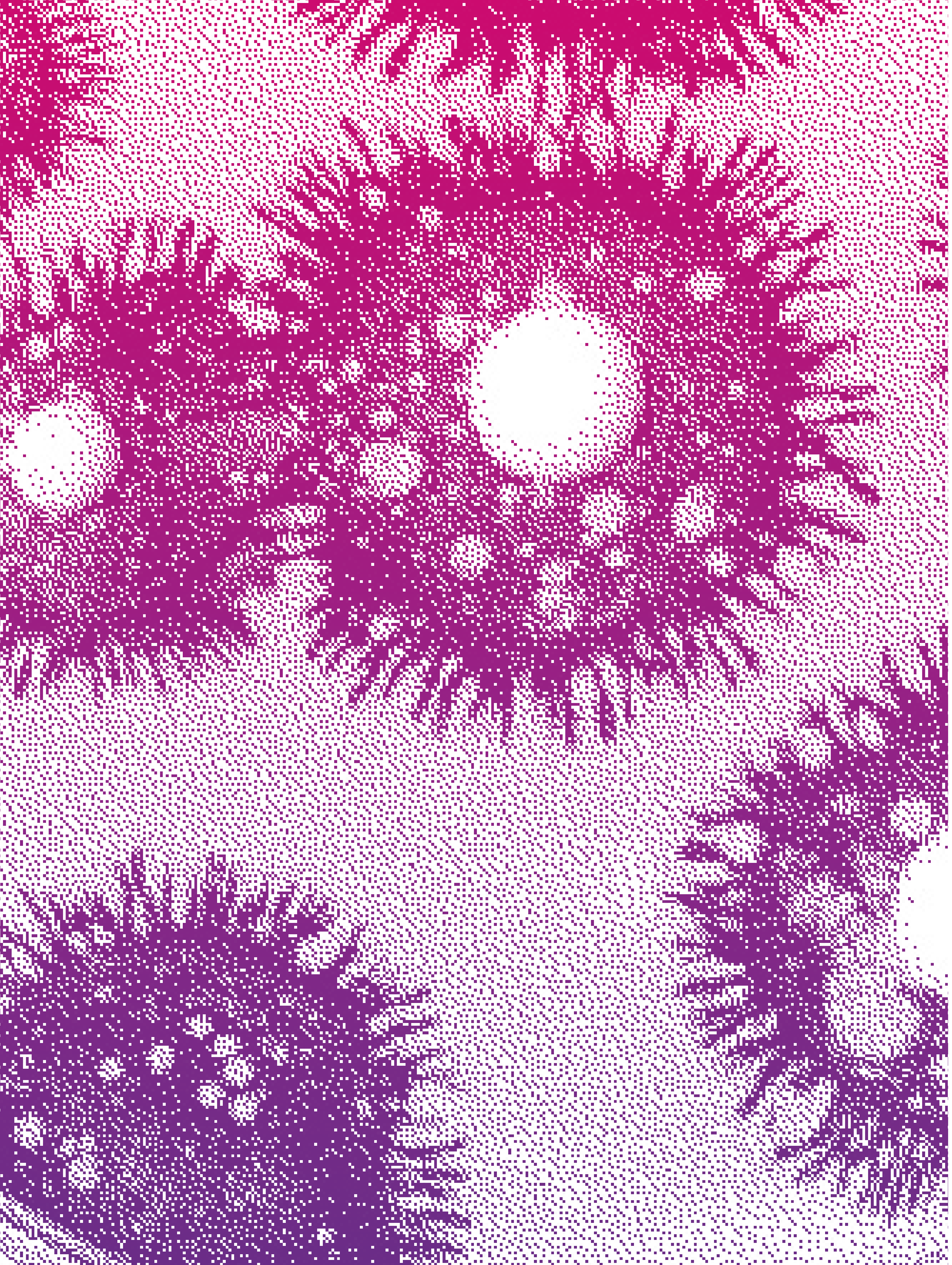
Professor Alex Schier
Director of the Biozentum, University of Basel

Contents









"For 50 years, we have been studying the mystery of how molecules and cells create life."

Biozentrum's golden jubilee

Greeting: Andrea Schenker-Wicki, President of the University of Basel

Was it the driving force of a handful of Basel personalities? Was it the excellence of the University's researchers? Or was it the exceptionally healthy public finances that made the opening of the Biozentrum possible 50 years ago? A look at the history of the Biozentrum's origins offers an answer, which can be expressed very simply: It was, without question, a huge stroke of fortune – for science, for business, and for the region's inhabitants.

The late 1960s were a time of great upheaval in biology and medicine. New findings allowed researchers to fathom the molecular mechanisms behind life processes. While the US and the UK played a leading role, Basel too was quick to realize that this was an area with great potential – and one in which it had some catching up to do.

The founding of the Biozentrum can be attributed to a number of courageous, visionary personalities from research, politics and industry who recognized a combination of favorable circumstances: a prevailing spirit of optimism in the region, the population's confidence in progress and the future, an industrial sector with money to spend on non-profit initiatives, and a generous Basel parliament with a government receptive to new projects.

Between the laboratories of the Faculty of Natural Sciences and the University Hospital, a seven-story building was erected and tailored to the needs of cutting-edge biological research: interdisciplinary collaboration, flat hierarchies rather than empires, and research groups rather than teaching chairs. And as the Biozentrum attracted some of the world's finest researchers, English was adopted as a lingua franca – an unprecedented move in the Swiss academic world at the time.

We are immensely grateful to be moving into new premises this year, half a century on from the Biozentrum's foundation. The University of Basel is proud of its sponsors – the cantons of Basel-Landschaft and Basel-Stadt, which believe in the University and its importance to the region's prosperity. Year on year, our sponsoring cantons invest many hundreds of millions of Swiss francs in our University, enabling us to provide higher education of the highest quality and compete among the top hundred research universities in the world.

The achievements of the Biozentrum over the last half century have played a key role in cementing our reputation as one of Europe's top locations for the life sciences, and broadcasting this reputation to the world. With the new Biozentrum building – as controversial as its genesis may have been – our sponsors demonstrate the same courage and belief in the future that distinguished its founders 50 years ago. In the name of the University of Basel, I am grateful for the trust placed in our institution, and hope on behalf of us all that this success story will continue for many chapters yet.

The new Biozentrum building represents a key milestone on the path to the University of Basel's Life Sciences Campus. Further new buildings are planned in the immediate vicinity of the University Hospital and the University Children's Hospital on the Schällemätteli Campus. These will provide premises for the Department of Biomedicine, the Natural Sciences and for ETH Zurich's Department of Biosystems Science and Engineering (D-BSSE). Almost 800 million Swiss francs are being invested in cutting-edge infrastructure for the Life Sciences Campus in order to provide the optimal conditions for research and teaching.

Dr. Jörg Reinhardt, Chairman of Novartis, Basel

"Since its inception half a century ago, the Biozentrum has evolved into a vital part of Switzerland's pharmaceutical and medical ecosystem, both as a research hub as well as a center of educational excellence. As part of our efforts to boost interdisciplinary research and strengthen collaboration with academia, Novartis is proud to have established strong ties with the institute in areas such as structural and molecular biology as well as fundamental research into diseases such as cancer, among others. I am convinced that this spirit of innovation will form the basis of successful collaborations in the future."

Dr. Severin Schwan, CEO of Roche, Basel

"Many great minds have led to the outstanding success of the Biozentrum since its founding 50 years ago. We're proud to note that one of the original initiators of the now world-renowned Biozentrum was Alfred Pletscher, Roche's head of research at that time. Research-driven companies today enjoy the fruits of basic research done decades ago. The Biozentrum and other leading institutes will remain key to medical breakthroughs in applied research."

Dr. Vas Narasimhan, CEO of Novartis, Basel

"Basel and the Rhine Valley have a rich history in life sciences and biomedical innovation, and the Biozentrum has helped carry that legacy forward, taking the visionary step 50 years ago to develop an interdisciplinary research facility. Your work to mold the scientific minds of tomorrow embodies the spirit of innovation and commitment to science-based progress that have helped improve our world for generations – and that will keep humanity on a path of progress for generations to come."

Professor Pascale Cossart, Institut Pasteur, Paris, France

"Participating in the Scientific Advisory Board has been a fantastic experience. Science at the Biozentrum is superb and so wide open to novelty and new horizons. The SAB composition was terrific! Interactions with young and older scientists was great. Coming to Basel was a pure pleasure. I miss it!"

Professor Paul Nurse, Nobel Prize Laureate, Director of the Francis Crick Institute, London, UK

"The Biozentrum is a jewel in the crown of Swiss science. It was a powerhouse at the birth of molecular biology and continues to be an outstanding institution of excellent science. Happy 50th birthday Biozentrum!"

Professor Catherine Dulac, Howard Hughes Medical Institute, Harvard University, Cambridge, USA

"The scientific creativity and productivity at the Biozentrum over the last 50 years have been nothing short of extraordinary. The remarkable scholarship and motivation of Biozentrum scientists and the outstanding diversity and quality of their scientific endeavors make the Biozentrum a towering institution in Europe and in the entire world. I wish the Biozentrum another 50 years of stellar accomplishments!"

Professor Randy Schekman, Nobel Prize Laureate, University of California, Berkeley, USA

"In 1982 and 1983, my family and I were hosted by Professor Gottfried Schatz for a abbatical year William Wickner and I spent in his lab. The year was enriching in so many ways, including the birth of my daughter in Basel that fall. My best to all the members of the Biozentrum on this jubilee celebration."

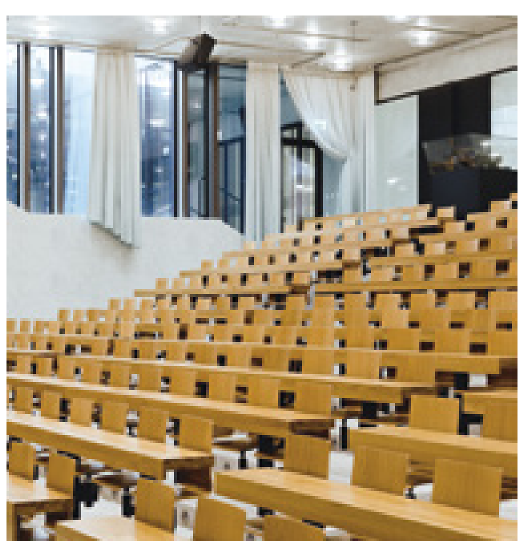
A beacon of science

Text:
Evi Sonderegger

A new highlight has been added to the Basel skyline: the recently completed 73-meter Biozentrum tower by the architects Ilg Santer. When the sun shines on its chrome steel and glass facade, the building is transformed into a beacon in the visual as well as the figurative sense. Stepping into the three-storey entrance hall with its design structure inspired by water lilies invariably elicits a reverential "wow." The foyer offers an exciting contrast to the functional layout of the laboratory tower, providing an attractive social space with its freely accessible outside area complete with seating and water features. This is where the paths of researchers, visitors and up to 900 students on their way to and from the adjacent lecture halls and seminar rooms cross in lively interaction.
On the research levels and in the sensitive scientific facilities in the basement levels, it is not so much the architecture as the infrastructure that stops you in your tracks. "Molecular biology research places the highest demands on energy, cooling, temperature stability, vibration-free and pressure conditions, biosafety and much more. Since we have a broad spectrum of research, the needs of our various groups and technology platforms vary considerably," explains Roger Jenni, Head of Technology and Logistics, who has been closely involved in the project from the beginning. "The new building is a truly remarkable feat of advance planning in terms of all the technical conditions it will have to meet in future," he concludes with unconcealed pride. Biozentrum director Professor Alex Schier also considers the new building to be a beacon, externally as well as internally: "The move to our new cutting-edge home is a significant milestone for us. Thanks to the state-of-the-art infrastructure, we remain competitive on the global academic stage and can attract the world's best scientists to Basel."

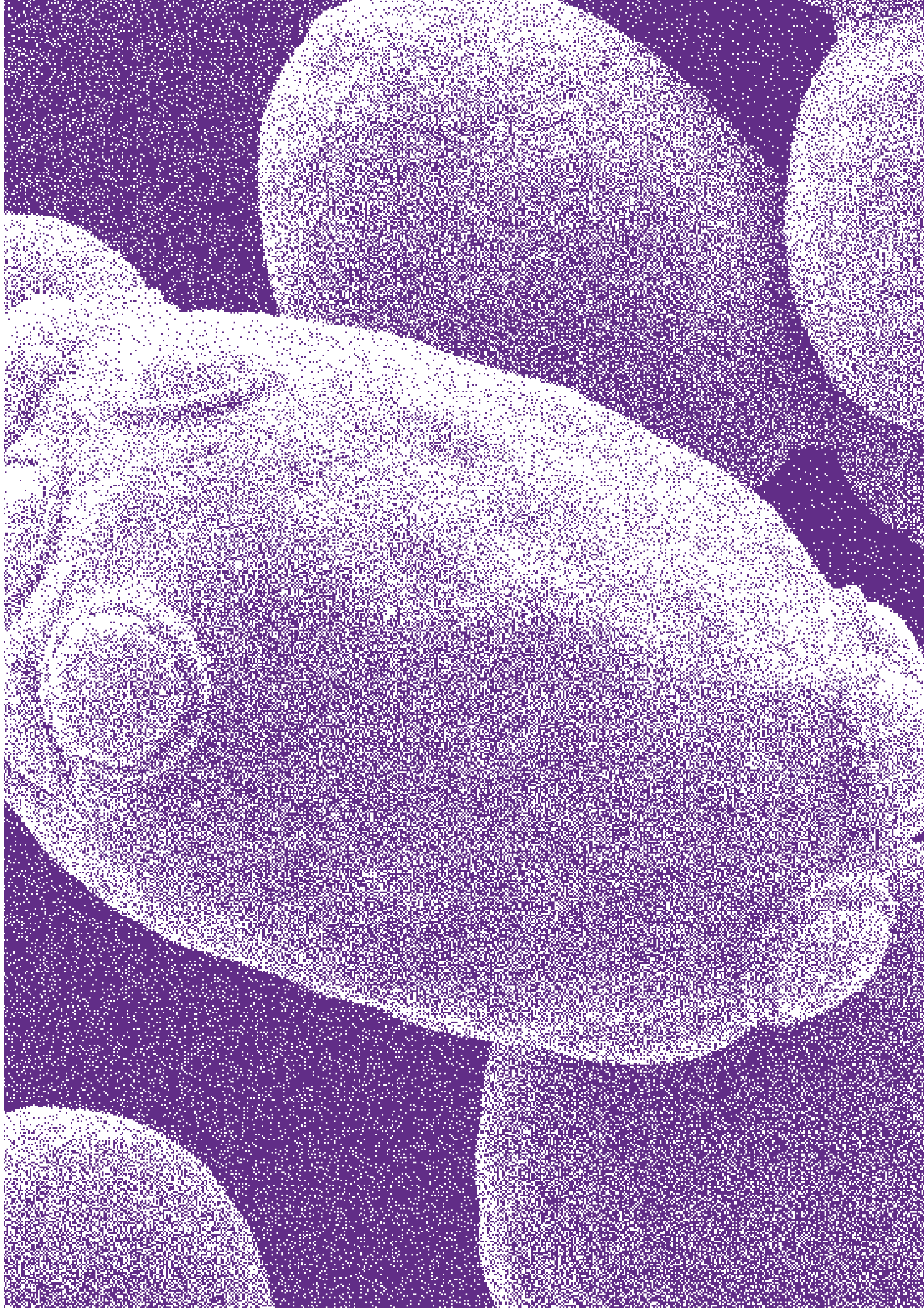
Of the building's 19 levels – 16 above ground and three below – ten will be devoted to research projects comprising around 400 employees, along with the research facilities in the basement levels. Adjacent floors are joined through an open staircase and a meeting zone benefitting scientific exchange because especially in interdisciplinary research – the bedrock of the Biozentrum – innovative ideas often arise from random discussions. This idea is also behind the decision to distribute shared technology platforms throughout the different levels, as well as the transparency that permeates the architectural design of the research levels: even the few dividing walls are made of glass, giving desk workers unimpeded views of work unfolding in the lab.

The top levels offer breathtaking views of the Basel region and the Life Sciences Cluster. Over the next few years, many of the University of Basel's Life Sciences sites dotted around the city will be brought together in the Life Sciences Campus. This physical proximity will further boost synergies among different projects.



A fascination for research

Since its foundation, the Biozentrum has been passionately devoted to studying molecules, cells and organisms to achieve a deeper understanding of the fundamental principles of life. This pursuit transcends the boundaries between research fields or countries, as the overlap between completely different disciplines is often where innovative ideas and research approaches are most likely to emerge.



A quantum of knowledge

For the uninitiated, basic research can sometimes be hard to comprehend. It asks questions that have little to do with everyday life, and although it ultimately leads to new knowledge, this knowledge is generally of no immediate use to humanity. Nevertheless, one thing is clear: Without basic research, we would still be stuck in the Stone Age.

Text:
Atlant Bieri

In the year 1905, a 26-year-old theoretical physicist sat in his room in Bern, deep in thought. The problem he was mulling over concerned the nature of light. For several decades, it had been known that shining light on two metal electrodes would result in a voltage that could become strong enough for a spark to jump across the gap. The light somehow had the effect of electrically charging the metal – the renowned photoelectric effect. Paradoxically, the charge was not affected by the intensity of the light, but only by its frequency. At the time, no explanation could be found for this observation. Light was thought to consist of a series of waves, so it was assumed that the more light there was, the greater the number of waves hitting the metal, and therefore the stronger the effect. This was not the case, however.

Concluding that the wave model was inadequate, the young physicist mentally divided the waves into tiny pieces and named them "quanta." He imagined these quanta as small packets of energy, the intensity of which depended solely on the light's wavelength, rather than how many of them there were. Under this model, if a sufficiently charged light quantum encountered a metal, it could dislodge an electron. If the light quantum was too weak, however, the electron would stay put. This theory, which was repeatedly confirmed by experiments, earned the physicist the Nobel Prize in 1921. His name was Albert Einstein.

Driven by curiosity

At the time, neither the Nobel Committee nor Einstein himself imagined how society might benefit from quantum theory or the photoelectric effect. This wasn't felt to be a major concern: The important thing was that the theory explained a natural phenomenon, as well as offering an extensive toolkit that could be applied to numerous other physical observations and fields of research.

This kind of research, driven solely by curiosity, is known as basic research. Unlike applied research, its aim is not to produce an immediate benefit for society; it is solely concerned with expanding human knowledge. That said, sooner or later most basic research inevitably yields some kind of practical benefit. "There will always be a need for basic research. Not to support it would be a fatal mistake," says Professor Michael Hall, a cellular biologist at the Biozentrum.

His career is a prime example of how ostensibly "useless" basic research can suddenly open up a broad array of potential applications. Working at the Biozentrum in the 1980s, he studied substances that suppress the immune system. These substances are deployed to great effect in transplant medicine, preventing the immune system from rejecting the foreign organ. One of them was rapamycin. "It prevented the division of immune cells, thereby diminishing their effectiveness. There was just one catch: no one understood exactly how the substance acted on cells. Our goal was to find out," says Michael Hall.

A universal switch for cell growth

After testing rapamycin on yeast cells, Hall and his team discovered a kind of universal on/off switch for cell division. It was a protein they dubbed "TOR" (short for "target of rapamycin"). Rapamycin essentially acted as the finger that flips the switch. Further tests revealed something even more astonishing: TOR did not actually control cell division, as they had assumed, but cell growth.

"The accepted wisdom at the time was that cells simply grew whenever sufficient nutrients were available," Hall explains. "That moment was a dream come true for us. We had discovered an entirely new field of research." Nevertheless, outside of Hall's research group the discovery was met with very little enthusiasm. When they tried to publish their results in 1994, the study was rejected seven times by various scientific journals. A year passed before the results were finally printed.

From knowledge to application

Since then, TOR has shot to fame as a control switch for cell growth, with far-reaching implications for applied research. "We now know that TOR plays a key role in numerous diseases like cancer or diabetes, as well as biological processes such as aging. The pharmaceutical industry has jumped on the bandwagon, and is using the discovery to search for new treatment strategies and life-prolonging drugs."

And what became of Einstein's photoelectric effect? Over the next hundred years, his groundbreaking theory laid the foundations for the development of the solar panels that power pocket calculators, houses, satellites and space shuttles. The same principle also paved the way for the light sensors used in alarm systems or garage and elevator doors. So if you still doubt the importance of basic research, next time you're in a high-rise building feel free to take the stairs!

Fighting cancer with bacteria

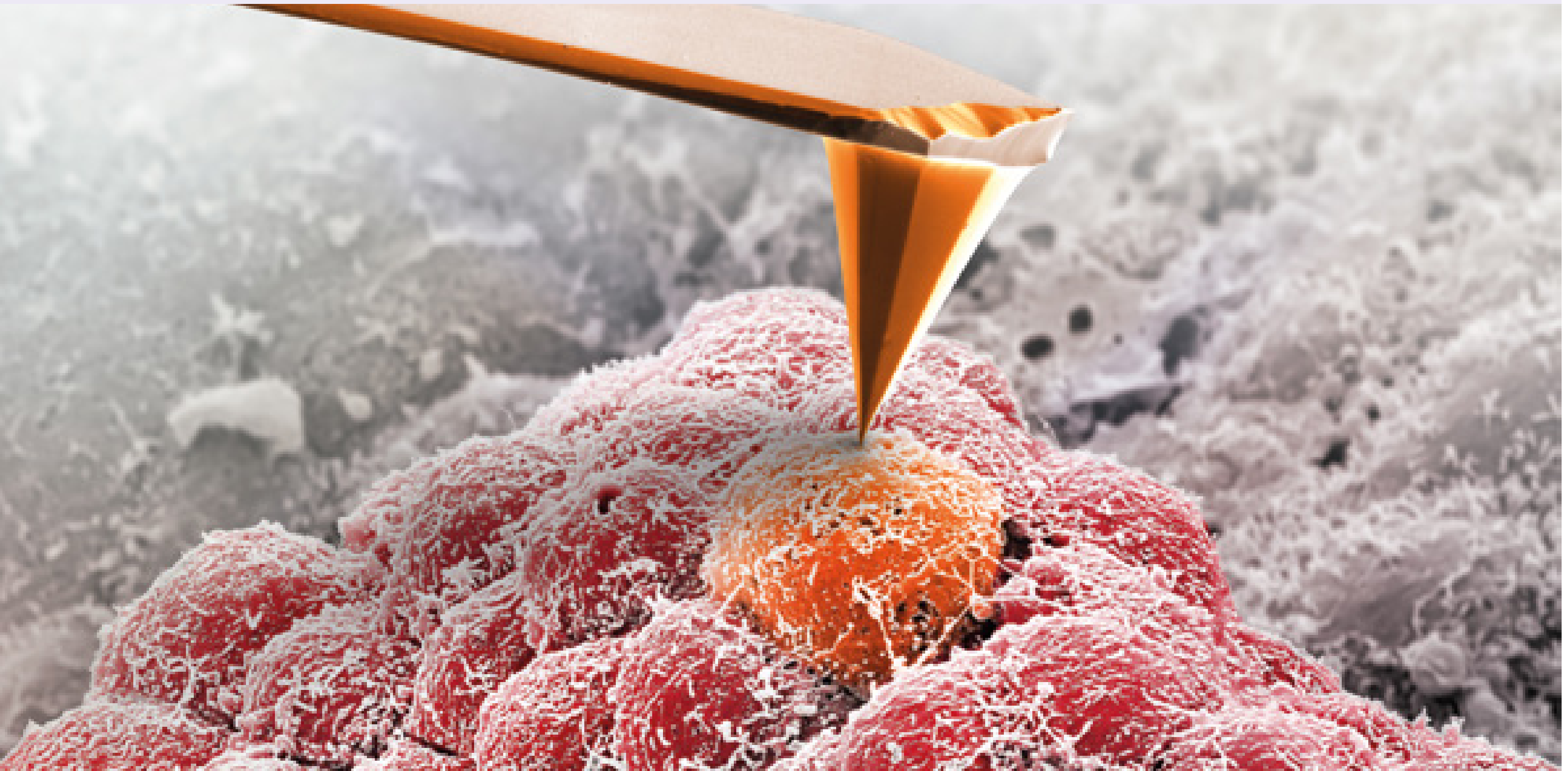
The idea for an application or the creation of a start-up often has roots in findings from basic research. This was also the case for the Biozentrum spin-off T3 Pharmaceuticals. Founders Simon Ittig, Christoph Kasper and Marlise Amstutz did research on bacterial nano-syringes at the Biozentrum, initially as doctoral researchers and later as postdocs. These structures, known as type III secretion systems, are used by bacteria to import foreign proteins into cells.

The team made use of this feature to develop a new generation of cancer treatments, reprogramming the bacteria to selectively inject therapeutic proteins into cancer cells, either killing them or activating the immune system in a particular way. It is the first cancer treatment to directly suppress tumor growth by using live bacteria and their nano-syringes. The first clinical trials are due to start soon. The start-up's innovative approach has been enthusiastically received by investors and foundations as well as researchers and clinicians. At the Falling-Walls Conference in Berlin in 2018, T3 Pharmaceuticals was proclaimed "Science Start-Up of the Year."

Nanotech for cancer diagnosis

Meanwhile, the spin-off ARTIDIS is devoted to refining atomic force technology for cancer diagnostics. The company was formed by Biozentrum researchers in 2014. ARTIDIS stands for Automated Reliable Tissue Diagnostics. The centerpiece of their solution is an atomic force microscope that can be used to inspect surface features.

The founders of ARTIDIS, led by Marija Plodinec and Marko Loparic, found an entirely new application for this nanotechnology: they use it to "probe" cancer cells, which exhibit a lower degree of stiffness than healthy cells. This enables them to create nanomechanical profiles of biopsies that shed light on whether they are cancerous, whether they are malignant, or how aggressive a particular tumor is. The new diagnostic tool could enable oncologists to find the optimum treatment for their patients faster in the future. The practical feasibility of ARTIDIS is currently being tested in collaboration with several hospitals.



Unlocking the mystery of life

Text:
Katrin Bühler

Contemplating everything that is happening at this very moment in each cell of our body is guaranteed to inspire a sense of awe. Cellular copying machines faithfully transcribing genetic material, countless ribosomes tirelessly producing proteins, mitochondria providing the energy to power it all, cells import and export molecules and they communicate with their neighbors – the body is like a bustling city that never sleeps.

This dazzling array of vital processes is reflected in the diverse range of questions posed by researchers working at the Biozentrum. What exactly happens inside a cell? How do genes regulate the intricate biochemical machinery? How do neurons communicate with each other and how does the brain control our movements? Why do we sleep? How do viruses spread? How do bacteria stay under the radar of our immune system? How does a stem cell know what it is supposed to become? And how does a healthy cell turn into a cancer cell?

United under the umbrella of the Biozentrum, researchers tackle disciplines as diverse as neurobiology, cell biology, developmental biology, infection biology, structural biology, biophysics or computational and systems biology. With over 30 research groups and staff from around 50 nations, it brings together a variety of expertise, perceptions, experience, approaches and forms of creativity. This has been its strength for the last 50 years. What all these researchers have in common is their fascination for the single overarching question: "How do molecules and cells create life?" With tireless curiosity and limitless ingenuity, they are committed to solving this puzzle one piece at a time. Together.

What motivates and drives them is the prospect of creating new knowledge with their research and contributing to a greater whole with their discoveries.

In the following pages, eight Biozentrum researchers share what fascinates them about their work. Their conquest of uncharted territories is facilitated by the Biozentrum Technology Platforms and Services teams.

“It’s not just about minor details, but rather about fundamental questions”

Interview:
Yvonne Vahlensieck

Structural biology operates at the very smallest scale, investigating how molecules interact inside cells. Researchers at the Biozentrum pursue this goal with the help of cutting-edge technology. Just as important, however, is lively collaboration between research groups – as Professor Maria Hondele and Professor Timm Maier explain.

– Prof. Timm Maier and Prof. Maria Hondele

Professor Maier, Professor Hondele, perhaps not everyone has a very clear picture of what is meant by structural biology. Can you explain briefly what this field is all about?

Maier — Of course! We examine the structure of all the constituent parts of living organisms at an incredibly high resolution, which allows us to distinguish the individual building blocks and structural principles. We do this not just to find out what something looks like, but also to understand how it works. We investigate mechanistic principles that apply in the fields of neurobiology, infection biology – everywhere, in fact.

Hondele — Structural biology requires highly developed technical knowledge. Not many groups have this knowledge, so collaborations are frequent. For instance, someone approaches Timm with a biological question and wants to know what the structure of a particular protein looks like so as to better understand its function in the cell.

What methods do you use?

Maier — Fortunately, we are no longer solely dependent on X-ray crystallography, which requires proteins to be crystallized before they can be studied. Increasingly, our primary tool is electron microscopy, which we can use to observe larger complexes. We can also combine individual still images to produce animations that show us how molecules twist and turn. Molecules engage in some really remarkable feats of yoga.

Which structures are you currently researching, Professor Hondele?
Hondele — We have known for some time that membranes play a key role in the organization of cells. Over the last ten years, however, it has become apparent that proteins and nucleic acids are also capable of self-organization without the help of membranes. We replicate membraneless organelles of this sort under the microscope, and try to understand the biophysics behind them. There is no set of Ikea-style assembly instructions to follow; these are highly dynamic processes. The big question is then, of course, what function these structures perform for the cell, and how they are regulated.

You are working in an area the importance of which has only become clear in the last few years. Do you see yourself as a pioneer?
Hondele — It is rather special to be working in such a new field. Sometimes one shines new light on established truths, which can ruffle some feathers on occasion. There is definitely a certain sense of heading into the unknown. It's not just about minor details, but fundamental questions with likely implications for cells at many different levels.

Professor Maier, what are you working on?
Maier — We want to understand how metabolic processes are controlled in human cells. The conversion of nutrients into energy or different cellular components is an essential process. For example, we study lipid metabolism in higher organisms, which is involved in the onset of numerous diseases such as cancer or diabetes. The proteins that we study work much like tiny computers. They receive various signals, process them, and regulate the production of new cellular components.

It must be thrilling to make these normally invisible processes visible…
Maier — Yes, there is something very special about the moment when you see a protein structure for the first time, and perhaps even hold it in your hands as a 3D-printed model.

Do you have any plans for joint projects?
Hondele — (laughs and gestures at the board on her door, which is covered with sketches for experiments)
Maier — I expect that we'll work together a great deal. For one thing, there is some overlap in terms of the techniques we use, which could be helpful for Maria's research questions. On the other hand, Maria's experience will certainly be of help in understanding highly mobile proteins.

Professor Hondele, you only came to the Biozentrum around a year ago. How have you found it so far?
Hondele — The Biozentrum is one of only a few institutes in Switzerland that brings together a variety of biological disciplines under one roof at such a high level. This is naturally very conducive to forming collaborations and tackling research questions beyond one's own area of expertise. It's also just a lot of fun to be around so much fantastic research. The facilities, with their outstanding equipment and expertise, are an extremely helpful resource that opens up new technological possibilities for us. They allow us to become much more creative in our research.

What else have you been particularly impressed by?
Hondele — The open-door policy, and how it has become second nature to the students and postdocs! I have often had someone from a different group come into my office looking for advice on a research question. I think that's great.

What should researchers looking to join your groups bring to the table?
Maier — The most important thing really is a passion for problem-solving. Also, the creativity to find the right approach, often against the advice of others. Forging new paths also takes courage, however. And of course the ability to think logically and analytically so as to properly interpret results.
Hondele — Definitely. I also think a certain tolerance for frustration is relatively important. In addition, you have to be able to take a large number of ideas and filter out just the most exciting or important ones. Above all, however, you should find out what you're really good at. After all, there are many different ways of doing research.
Maier — Exactly. A part of what we do is finding the right person for the right project. Some people invest three or four years of their life in a particular topic. It's very important that their hard work leads to a reward – not in the form of money, but of satisfaction.

"Putting the results of research that is ultimately paid for by the taxpayer behind a paywall is simply the wrong approach."

– Prof. Richard Neher

Tracking virus evolution

Text:
Yvonne Vahlensieck

"Nextstrain was originally a purely academic project. Our vision was to create a current family tree of influenza viruses online."

– Prof. Richard Neher

What Professor Richard Neher is really interested in is evolution. He wants to find out whether it can be predicted. His efforts to this end include sifting through the gene sequences of influenza viruses from the last two decades in search of patterns. As a result of this research project, in 2020 he unexpectedly found himself at the center of the COVID-19 pandemic as a member of the Swiss National COVID-19 Science Task Force and an expert in high demand by the media. "As we have been studying the evolution of RNA viruses for years, we were in a very good position to assess the situation from the outset," he reports.

A key role in fighting the pandemic has also been played by the online platform Nextstrain, which Richard Neher developed several years ago with a colleague. The application tracks mutations in the genetic material of the SARS-CoV-2 virus and provides a graphic visualization of its spread around the world in real time. This helps decision-makers to promptly develop suitable measures to fight the pandemic. Neher is unable to make predictions about the future evolution of the SARS-CoV-2 virus, however. We simply don't know enough about the virus and how it interacts with humans yet.

"Nextstrain was originally a purely academic project," he explains. "Our vision was to create a current family tree of influenza viruses online." Yet, the platform was soon adopted for a variety of practical applications – such as tracking outbreaks of the Zika and Ebola viruses. Furthermore, analyses by the Nextstrain team are incorporated into the yearly recommendation for the makeup of the influenza vaccine and Neher has been an advisor to the WHO Vaccine Composition Meetings since 2016. "This is a great example of how short the route from basic research to practical application can be."

Making science publicly accessible

The success of the Nextstrain platform is not just due to how it presents complex information in an easily understandable format – it also offers free access to the underlying code and data. This earned Richard Neher and his colleague the Open Science Prize, a distinction awarded to projects that help make scientific data publicly available online – something for which Richard Neher has been campaigning for a long time: "Putting the results of research that is ultimately paid for by the taxpayer behind a paywall is simply the wrong approach."

In future, Richard Neher hopes to shift the focus of his research toward bacteria. The evolution of bacteria – and therefore the emergence of dangerous antibiotic resistance – can be studied following the same principles. However, the challenge is somewhat greater for bacteria: their genome is much larger than that of viruses, and they do not only evolve by mutations, but also by exchanging genes among each other. "It's all a bit more complicated, but that's exactly what fascinates me right now."

"The greatest challenge remains the human brain"

Interview:
Yvonne Vahlensieck

Professor Silvia Arber has been conducting research at the Biozentrum for more than twenty years, while Professor Anissa Kempf is a recent arrival. The two neurobiologists explain what their research is about and discuss collaboration at the Biozentrum.

Professor Arber, Professor Kempf, neurobiology has a reputation as an incredibly complex research field in which progress is only made in tiny steps. What made you choose it despite all this?

Arber — Not despite, but precisely for these reasons. I never wanted to work in a field where all that remained to be done was fill gaps. The wonderful thing about neurobiology is the opportunity to do things that no one has ever done before. If I can contribute a small amount of knowledge about how the brain works that's very satisfying for me.

Kempf — I was originally motivated to do neuroscience for philosophical reasons. For instance, I used to wonder where consciousness was located in the brain. But I quickly realized that this approach wasn't going to get me anywhere. What fascinates me now is how neural networks have the capacity to encode so many different complex patterns of behavior. It is also precisely the fact that we understand so little that makes it interesting.

Can you briefly explain what you are trying to learn about the brain?

Kempf — I am interested in why we feel tired and want to sleep. We know that there are cells in the brain that induce sleep when activated. Yet, we understand very little about the physiological processes that lead to their activation. That is what we aim to find out. Right now, I am doing experiments in fruit flies. But my next step would be to look at whether the same principles also apply to mice.

Arber — We want to identify the networks that control the hundreds of movement patterns our body performs. Just recently, we discovered that there are groups of neurons in the brainstem of mice that are responsible for very specific movements, such as reaching for an apple. Now we want to know how this is controlled by the brain's higher order centers. Thanks to new technologies, we are currently progressing in huge leaps. However, the greatest challenge in neurobiology remains the human brain, which continues to elude current methods.

That's why you're both working with animal models. Are your findings nevertheless transferrable to humans, for example in the treatment of diseases?

Arber — Absolutely, for example for Parkinson's disease. One of the most important findings of recent years is that it is not enough to activate a particular region of the brain; you have to target precisely the right neuronal populations.

Kempf — Yes. Many psychological problems, neurological and psychiatric disorders including depression are associated with sleep distress. Certain sleep disorders can be an early sign of Parkinson's, for example. Yet, we understand very little about the reasons behind their co-existence. If I study sleep in fruit flies, some of the concepts and molecular targets are likely to be applicable to humans too, as many of the genes that play an important role in these diseases and in sleep are conserved.

– Prof. Anissa Kempf

– Prof. Silvia Arber

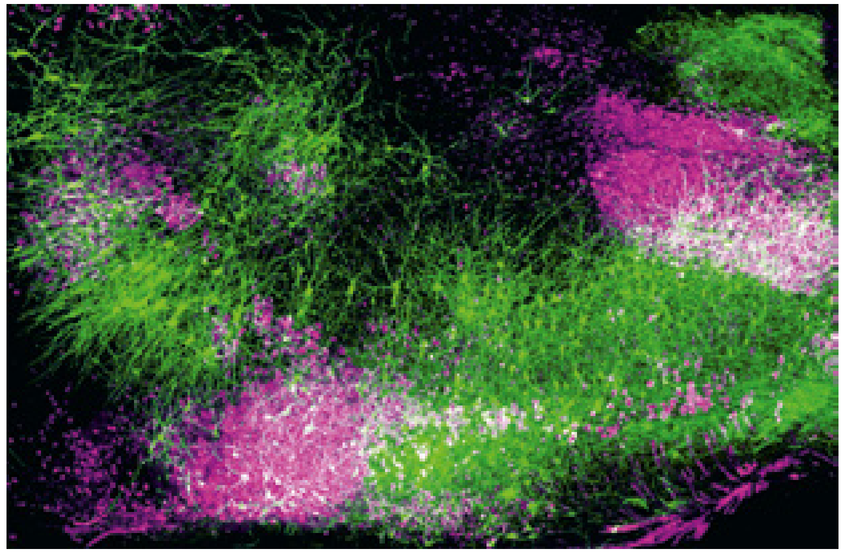
Professor Arber, can Professor Kempf count on support in Basel if she decides to perform her experiments on mice in the future?
Arber — I am sure that Anissa will have no problems at all to find help. In Basel, a synergistic environment has emerged over the years in the form of the Neuroscience Network Basel, which is stronger than the sum of its parts and has a strong international reputation, as well.
Kempf — I am delighted to be part of the Neuroscience Network Basel. On top of that, the unique combination of different disciplines at the Biozentrum provides the perfect environment for me since my work is multidisciplinary in nature.

Professor Kempf, right now you're putting your first ever research group together here at the Biozentrum. How are you going about it?
Kempf — At first, I would like to spend a lot of time in the lab to assemble many of the technical setups myself – if we can't do the experiments, we can't make progress in our projects. That's why I'm starting with a lab technician with experience in molecular biology and a doctoral researcher who has worked with fruit flies before.

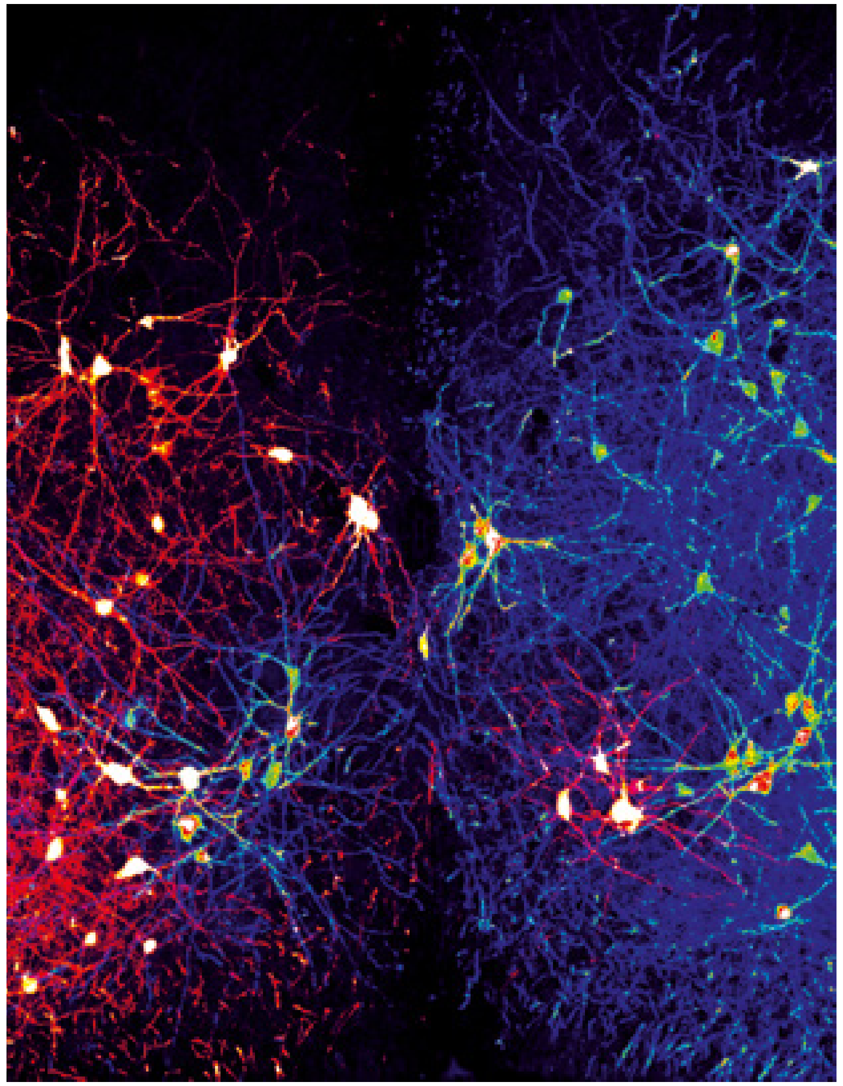
Professor Arber, do you remember the beginning of your time heading a research group?
Arber — Yes, of course. Anissa is right. The first team members are crucial, as they set the tone for the entire lab. I started out with a highly capable lab technician who still works for me today. Professor Walter Gehring was very helpful with the recruiting process at the time, as I was still in the US. It is really important to have people with experience around you who will give you their honest opinion, even if it's not always easy to hear. I have also offered Anissa my support.

Does it make any difference to you whether you mentor a woman or a man?
Arber — No, I'll support anyone as long as they are talented. That's what I have always done.
Kempf — No, I myself would like to be valued primarily for my work rather than my gender, but it is crucial that women and men receive the same opportunities. There is still a lot of work to be done along those lines and I sincerely hope that this will continue to change in the future.

Professor Kempf, you spent a number of years doing research in the UK. What did you take away from that experience?
Kempf — I learned to assert myself in a highly competitive environment. Cutting-edge research is being done in the UK under conditions that would be unimaginable in Switzerland. Working there made me realize how fantastic the research conditions are here at the Biozentrum and how spoiled we are here in Switzerland in general.
Arber — Absolutely. Many of the doctoral researchers I supervise only really learn to appreciate this when they go abroad, and tell me how great it was to work in Switzerland.



Neurons in the brain stem (green) communicate with the spinal cord to relay commands that trigger the body's movements. Viruses that jump across synaptic connections were used to reveal the distribution of these neurons between the motor neurons in the brain stem (purple).



Our brain is a network comprising some 200 billion neurons. These neurons feature numerous projections that connect them and enable them to communicate with each other.

Movements are the result of intricate interactions between the nervous system and muscles. Different areas of the brain stem control the various movements of our arms and legs, such as reaching for an object with one hand, via highly specialized connections in the spinal cord.

New approaches in the fight against bacteria

Text:
Yvonne Vahlensieck

– Prof. Christoph Dehio

Infection biology at the Biozentrum is undergoing a paradigm shift: By shedding light on the interaction between pathogenic bacteria and their human hosts under natural conditions, researchers hope to generate novel ideas for treatment.

Research on bacteria and viruses has a long tradition at the Biozentrum. From the beginning, group leaders such as Professor Eduard Kellenberger and Professor Werner Arber made use of these microorganisms to study fundamental molecular biological processes. Their groundbreaking findings can still be found in textbooks today. The last members of this "founding generation" were just about to retire when Professor Urs Jenal joined the Biozentrum a little over 25 years ago. "Microbiology at the Biozentrum had to reinvent itself," he recalls. The new groups carved out their own approach, ultimately establishing the Biozentrum at the forefront of Swiss infection biology research.

"Over time, our work has increasingly been defined by a shared interest in antibiotics research," says Professor Christoph Dehio, a group leader at the Biozentrum since the year 2000. This trend is explained by an alarming surge in bacteria that no longer respond well – if at all – to treatment with antibiotics. The WHO estimates that antibiotic-resistant pathogens are responsible for 700,000 deaths each year. These pathogens also increase the risk associated with routine operations such as appendectomies.

"We're not just interested in understanding the underlying mechanisms – we want to find ways to successfully treat these infections," explains Christoph Dehio. Efforts to this end resulted in the creation of the National Center of Competence in Research (NCCR) "AntiResist", approved last year by the Swiss National Science Foundation and led by Christoph Dehio, Urs Jenal and Professor Dirk Bumann. Aside from the Biozentrum, the NCCR includes research teams of the University Hospital Basel and the ETH Department of Biosystems Science and Engineering (D-BSSE) at its primary location Basel, while additional research groups are based in Zurich, Lausanne and Israel.

Research under real-life conditions

"Until now, all antibiotics have essentially been discovered using the same approach," says Christoph Dehio – specifically, by means of tests performed on bacteria grown in the lab under optimal conditions. Conditions inside the human body are quite different, however. "This is why we want to gain a better understanding of pathogens during the actual infection in patients." Once researchers can reproduce these processes in the laboratory, the plan is for engineers to develop test systems mimicking patient tissue to screen for new active substances.

As an example of this approach, Christoph Dehio cites his own research on *Escherichia coli*, a gut bacterium that can cause acute and chronic bladder infections – and in severe cases can trigger life-threatening blood poisoning. To understand the mechanisms behind these infections, it is necessary to consider processes in the tissue of the ureter, bladder and kidneys, as well as the immune system.

"Solving the problem as a whole requires a transdisciplinary approach," says Urs Jenal. "Such an approach depends on close collaboration between basic researchers, clinicians and engineers. With the NCCR we now have a framework that makes this possible."

Jenal himself has a long-standing collaboration with clinicians at University Hospital Basel to investigate samples from cystic fibrosis patients. These patients generally suffer from chronic infections of their lungs with the bacterium *Pseudomonas aeruginosa*. "We want to understand how, over several decades, bacteria develop the ability to survive treatment with antibiotics virtually unscathed."

– Prof. Urs Jenal

The two group leaders believe that in the medium term, the COVID-19 pandemic will result in greater awareness of the threat posed by antibiotic resistance. "The problem is not coming at us all that fast, but it is growing steadily," says Christoph Dehio. Urs Jenal agrees: "The situation is going to get worse gradually, like a clock ticking."

A stem cell researcher to the core

When Professor Fiona Doetsch talks about her work with stem cells, her enthusiasm is contagious. "My field draws on various different disciplines, such as neurobiology and developmental biology," she explains. "I believe it is precisely at these intersections that the most exciting research takes place."

Text:
Yvonne Vahlensieck

The Canadian-born researcher's thirst for knowledge runs in the family – her father is an engineer and her mother a classics teacher. She continued both traditions at McGill University in Montreal, studying biochemistry alongside philosophy and history of science. "This taught me to think about the bigger picture." She caught the stem cell bug over 20 years ago during her doctoral thesis at The Rockefeller University in New York – and never recovered. At the time, she was characterizing a group of neural stem cells in mice located in a niche in the lateral ventricle. These cells – the existence of which had long been doubted – have the remarkable ability to create new brain cells over an entire lifetime. Fiona Doetsch theorized that this phenomenon was central to the plastic nature of the brain, which has to constantly adjust to new circumstances. At the same time, it offered prospects for the treatment of brain diseases.

Fiona Doetsch therefore decided to stick with this topic: first as a junior fellow at the Harvard University Society, and then from 2003 as a professor at Columbia University in New York. Gradually, she discovered how the stem cells in her niche are controlled by complex interactions involving multiple factors, including signals from other parts of the brain and neurotransmitters such as endorphins.

In 2014, she accepted a professorship in molecular stem cell biology at the Biozentrum. What was it like to go from a bustling mega-metropolis to the relatively sedate city of Basel? Looking back, it was just right: "I love New York, but Basel is a great place to live." Fiona Doetsch rhapsodizes about the small but vibrant cultural scene and idyllic walks along the Rhine. What is more, her son's school activities helped the family to quickly form social ties.

The move paid off in professional terms too: In 2018, Fiona Doetsch was awarded an ERC Grant of almost 3 million Swiss francs, and two years later she was elected a member of the European Molecular Biology Organization (EMBO). Her work at the Biozentrum revolves around the question of how different physiological states such as hunger or exertion can selectively trigger the formation of certain neurons and supporting cells. At the moment, her group is eager to uncover the role of stem cells and their progeny in pregnancy and motherhood.

> **"I love New York, but Basel is a great place to live."**
>
> – Prof. Fiona Doetsch

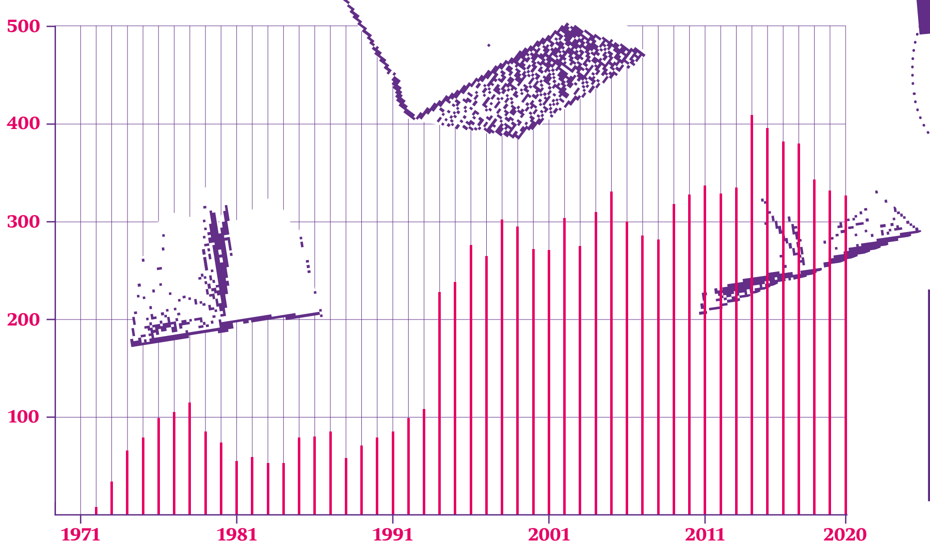
One thing is quite clear: Fiona Doetsch still finds research into "her" stem cell niche just as thrilling as on the very first day. "Only recently, we discovered several completely new types of supporting cells. We still have no idea what they do. There are so many fantastic surprises to come!"

50 years of research at the Biozentrum

Data analysis: Simone Grumbacher / Michael Podvinec

For the past 50 years, researchers from the Biozentrum have been publishing their results in a wide range of scientific journals. An analysis of the terms used in the titles and abstracts of publications over the decades reveals developments, trends and even the occasional surprise…

Number of Biozentrum publications since 1971



Discovery of TOR

Since the discovery of TOR in 1991, the term has been mentioned in a total of 453 publications from the Biozentrum.

10,111

scientific publications were published from the Biozentrum between October 1971 and February 2021.

Techniques appearing and used in the publications

1972
electron microscopy
term mentioned in 5.3% of all publications

1974
nuclear magnetic resonance spectroscopy (NMR)
term mentioned in 4.8% of all publications

gel electrophoresis
term mentioned in 1.5% of all publications

1975
circular dichroism
term mentioned in 1.9% of all publications

1990
PCR
term mentioned in 2.4% of all publications

1994
atomic force microscopy
term mentioned in 2.6% of all publications

confocal microscopy
term mentioned 4.8% of all publications

1997
isothermal titration calorimetry
term mentioned 1.1% of all publications

surface plasmon resonance
term mentioned 0.4% of all publications

green fluorescent protein
term mentioned 1.2% of all publications

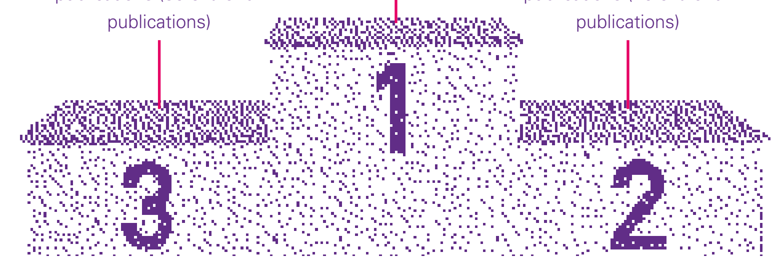
These data are based on publications linked to the Biozentrum between 1971 and February 2021. The source databases were Scopus, Web of Science and PubMed, and the term frequency was determined by searching for all combinations of one to three words in order to establish how many publications mention the terms in their title or abstract. Bibliometric data were provided by Max Hintermann from the University Library Basel.

The three long-standing themes of the last 50 years

protein
term mentioned in 5,897 publications (58.3% of all publications)

cell
term mentioned in 5,120 publications (50.6% of all publications)

structure
term mentioned in 2,687 publications (26.6% of all publications)



Research at all levels

(macro-)molecules and (multi-)molecular complexes — nanometer 0.4×10^{-9} m to 120×10^{-9} m — amino acid sequence, enzyme, binding site, nuclear pore complex, molecular dynamics simulation

single cells — micrometer 0.2×10^{-6} m to 50×10^{-6} m — organelles, cell growth and division, cell death, cell types, bacterial secretion systems

multicellular systems — micrometer to meter 12×10^{-6} m to 1 m — stem cell, development, nervous system, biofilms, skeletal muscle

fundamental biomedical research — from the individual organ to the whole organism — cancer, neurodegeneration, autism spectrum disorders, congenital and age-related muscle loss, antibiotic resistance

Characteristic terms by decade

1971 – 1981
nerve growth factor
bacteriophage
membrane bilayer
enzyme
gel electrophoresis

1982 – 1991
nuclear magnetic resonance (NMR)
gene
human liver microsomes
yeast mitochondria
membrane proteins

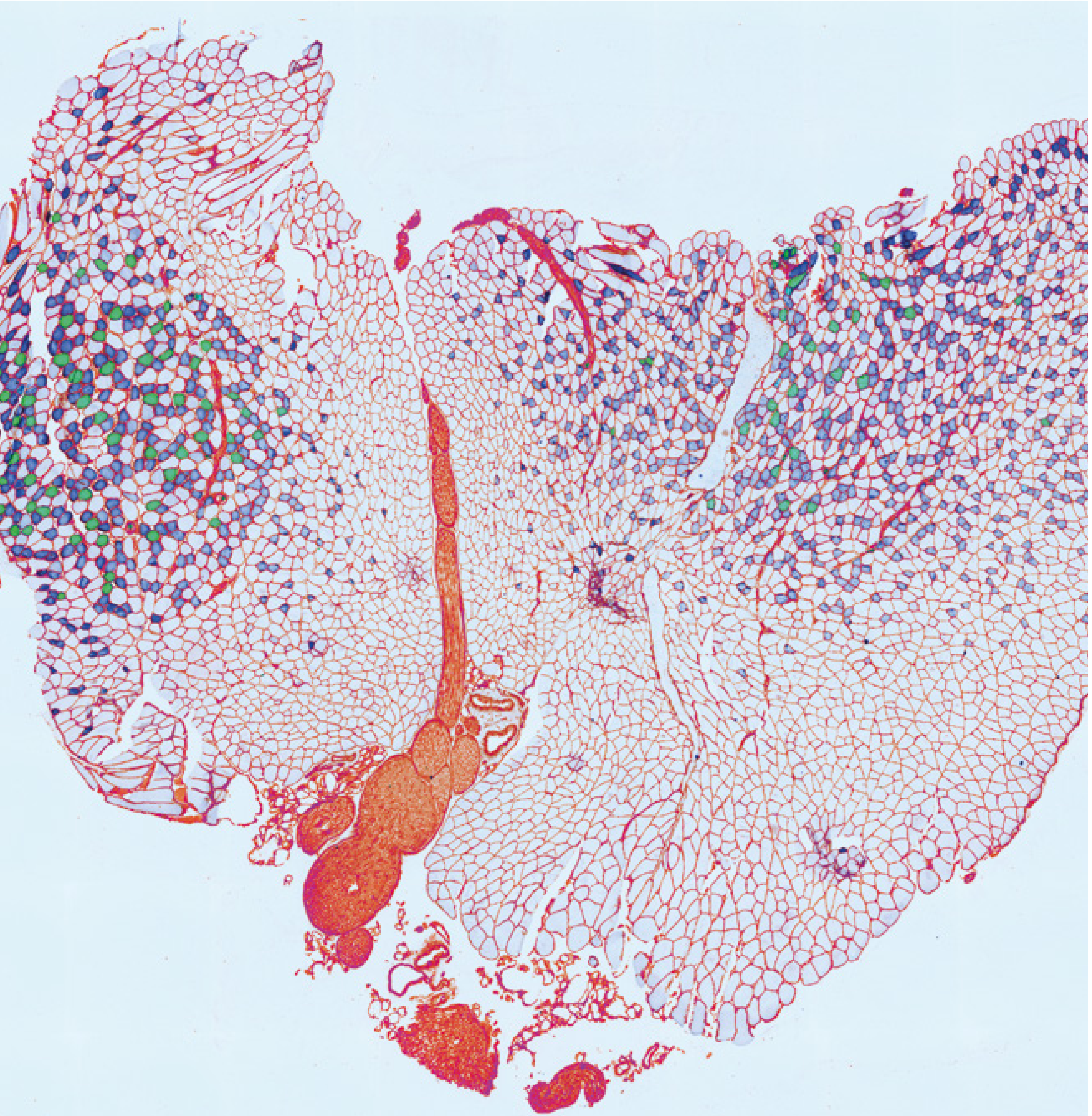
1992 – 2001
open reading frame
polymerase chain reaction (PCR)
central nervous system
nuclear pore complex
atomic force microscope (AFM)

2002 – 2011
transcription factors
binding sites
endoplasmic reticulum
development
target of rapamycin (TOR)

2012 – 2021
(neural) stem cells
skeletal muscle
type VI secretion system
Alzheimer's disease
molecular dynamics simulations

Unexpected term
"unknown mechanism"

A hallmark of science is that new findings give rise to new questions. Scientists communicate new discoveries and highlight areas where knowledge is still lacking. With this in mind, it's hardly surprising that this term has appeared in 23 publications…



State-of-the-art technology

Cutting-edge research requires the very latest technologies and specific know-how. The technology platforms at the Biozentrum give scientists access to world-class instrumentation and state-of-the-art technologies, besides supporting them with their services and expertise.

Text:
Katrin Bühler

BioEM Lab

Electron microscopy is one of the most useful techniques for studying the structure of biological molecules. The BioEM Lab offers researchers a wide range of techniques from transmission electron microscopy (TEM) and electron tomography for visualizing the fine structure of cells to cryo-electron microscopy for determining the three-dimensional structure of biomolecules such as proteins.

Biophysics Facility

The Biophysics Facility supports researchers with the use of sophisticated instrumentation to measure the interactions, reactions, stability and size of biological molecules such as proteins and nucleic acids. The equipment at the facility includes instruments for microcalorimetry, fluorescence spectroscopy, ultracentrifugation and light-scattering measurements.

BSL-3 Laboratory

The Biosafety Level 3 Laboratory offers researchers a facility for studying highly infectious bacteria and viruses that cause serious diseases under the strictest safety conditions. The BSL-3 Laboratory staff train and support researchers in their work with pathogens. The facility also has an on-site cell sorter to perform experiments with isolated cells.

FACS Core Facility

Fluorescence-activated Cell Sorting (FACS) is a very powerful technology that allows researchers to rapidly and accurately characterize single fluorescently labeled cells. Besides analysis of cell mixtures and other single particles such as bacteria and cell organelles, the FACS Core Facility also enables the research groups to purify and isolate specific cells using the flow cytometers provided.

Imaging Core Facility

Light microscopy and image analysis are important tools in modern life sciences. A wide range of highly sophisticated light microscopes enables diverse insights into the cells and tissues of organisms. The Imaging Core Facility provides researchers with technical support for imaging procedures and data analysis. The team's tasks also include establishing novel techniques and developing new applications.

NMR Facility

Nuclear magnetic resonance (NMR) spectroscopy is indispensable for the elucidation of biological structures and functions at the atomic level. Using the powerful high-resolution NMR spectrometers housed at the NMR Facility, researchers can investigate the molecular structure and dynamics of macromolecules such as proteins or nucleic acids and characterize their interactions. As part of the Swiss Ultrahighfield Solution NMR Facility consortium, the Biozentrum NMR Facility – together with the University of Zurich and ETH Zurich – operates a series of spectrometers ranging from medium field strengths to an ultrahigh field of 1.2 GHz. These NMR instruments open up entirely new research possibilities.

Proteomics Core Facility

Proteins are a major component of all living organisms. Using mass spectrometry, researchers can analyze the entire set of proteins, the proteome, expressed in an organism. For this purpose, the Proteomics Core Facility provides the latest technology and support from A to Z, including technical project design, sample preparation, optimization of analytical methods, the actual analysis of samples, and the evaluation of the data obtained.

Research Instrumentation Facility

The Research Instrumentation Facility (RIF) combines scientific consulting services with a rapid prototyping workshop. The RIF supports research groups with the selection of suitable technologies and adoption of non-commercial solutions, in addition to developing instrument prototypes. The team maintains a makerspace and assists researchers in project planning and coordination, matching their needs to the skills of the technology platforms and workshops.

Research IT

In biological research, large datasets and their analysis are increasingly prevalent, often causing difficult technical and organizational challenges for research endeavors. At the intersection between biology and information technology, the Research IT platform closely collaborates with the other platforms and central infrastructure providers. It advises and supports researchers with regard to the IT systems, tools and processes needed for smooth and effective research, data management and analysis.

Researchers at the Biozentrum can also use three other university-affiliated technology platforms: the Genomics Facility Basel, the Life Sciences Training Facility and the Center for Scientific Computing, sciCORE.

Behind the scenes

Text:
Evi Sonderegger

From custom-built laboratory equipment to pipette tips in need of cleaning or sterilizing, from radiation and laser safety training to equipping labs for practical courses – countless teams work behind the scenes to create the ideal conditions for research and teaching at the Biozentrum.

In the beginning they worked with conventional, then computer-operated, and now 3D machines. Like many other of the Central Services teams, the Mechanical Workshop has been around for as long as the Biozentrum itself. Its purpose is to allow researchers to concentrate fully on their research and teaching. This often requires considerable ingenuity. Regardless of whether the issue at hand is a technical, logistical or administrative one, the reply "I'm not sure if I can help" is unheard of at the Biozentrum, according to one new arrival. The closest one might hear is "That could be tricky, but we'll find a way." Accordingly, the Biozentrum is home to countless devices and installations that could not be sourced through standard commercial channels, from cooling microscope adapters or Faraday cages to special treadmills for mice, reflecting the multifaceted needs of a dazzling array of research topics. In most cases, researchers come to the Mechanical and Electronics Workshops with nothing more than a hand-drawn sketch. On the basis of this sketch, they create a computer model that they then implement with their teams.

Sketching and drafting are also common activities in the Communications team. After all, communicating the accomplishments of the Biozentrum in an appealing manner depends on images for media releases, brochures and websites or illustrations for scientific publications.

An administrative and technical "one-stop-shop" for researchers is available in the form of Floor Managers. Floor Managers attend to countless issues ranging from financial controlling or maintenance of cooling facilities, incubation chambers and storage rooms to supervision of seminars and courses, not to mention orders and deliveries. Fortunately, many of the items are close to hand. Store & Supply, which stocks more than 1100 different articles, has everything a researcher might ever need. Here, Biozentrum staff can order anything from office supplies to antibodies, cell cultures, enzymes, solvents, pipettes or test tubes. Speaking of pipettes and test tubes: cleaning their lab equipment is another thing that researchers don't have to worry about. Glassware is conveniently collected from the ten research levels via a circulation system and delivered to a central Media & Labware Preparation kitchen, where it is cleaned, sterilized or refilled before being returned to the appropriate level ready for use. What is more, the kitchen employees also take care of preparing nutrient media for microorganisms.

Safe working conditions in the lab are a primary concern. New staff are trained in biological and chemical safety, laser safety, storage and disposal of chemicals and handling of radioactive materials. Safety is also a top priority for the Technical Services team, which monitors thousands of alarm systems and fault detectors 24 hours a day, 365 days a year, as many research projects involve incubation chambers or cooling facilities. Also responsible for ensuring the Biozentrum's smooth operation is the IT Services team, which oversees the center's more than 1500 computers.

Research and teaching go hand in hand. The Rooms & Courses team is responsible for equipping the student labs with microscopes, pipettes and consumables for the practice-oriented block courses, besides supporting teaching staff in lecture halls and generally maintaining good order.

Last but not least, Financing & Controlling keeps tabs on the equipment, investment, utility and personnel budgets as well as more than 400 external funding and Swiss National Science Foundation accounts, while HR deals with employment contracts, further training, family-friendly working conditions and, in collaboration with the administrative assistants, residence permits for employees from around 50 different countries.

Facts and figures

The Biozentrum in figures

206
junior researchers
comprising 109 doctoral candidates, 97 postdocs

1971
foundation
of the institute for molecular biology – the first of its kind in Europe

134
laboratory and equipment
staff members

200
publications
in scientific journals each year

32
professors
in research and teaching

482
staff members
from 50 countries

65,400,000
Swiss francs
total yearly expenditure including external funding

Biozentrum new building

73
meters
is the height of the research tower, the imposing lobby is 13 meters high

23,400
square meters
of total usable area

40
percent
of the building's total volumeis underground

1,891
doors
to labs, lecture halls, offices and facilities

900
students
can use the lecture halls and seminar rooms

40
labs
were custom-designed for the various research groups

Science

200
billion
neurons make up the human brain

2,000
grams
of bacteria live inside the human body

50
million
new cells are formed each second

40
hours
is the average duration of cell division

30
trillion
cells interact in the human body

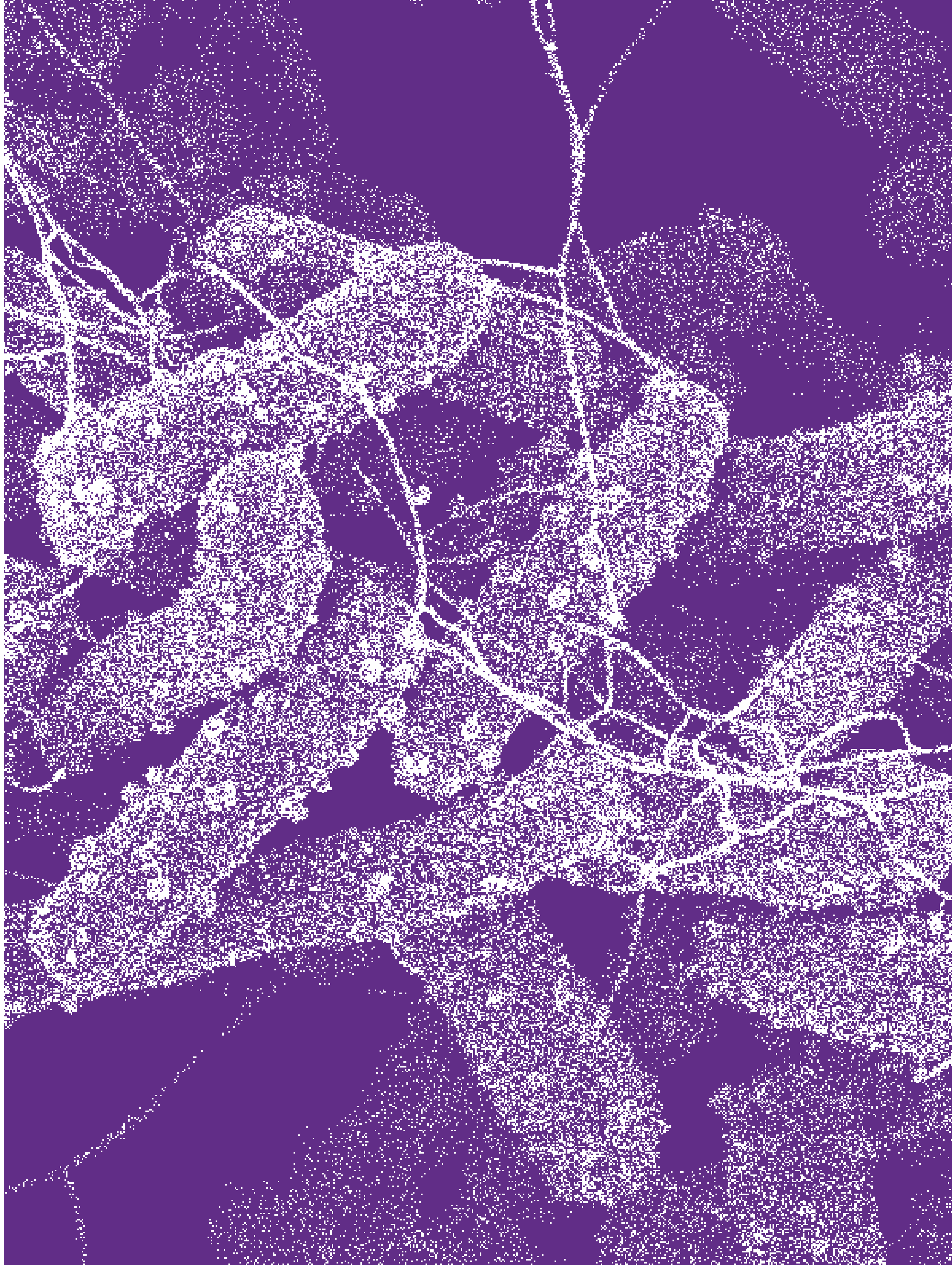
150
billion kilometers
is the length of the DNA in a single human being if the two-meter strands in each cell were laid out end to end, this is around 1,000 times the distance from the earth to the sun

100 x
larger
is the difference in size of a bacteria compared to a virus, human cells are 25 x larger than bacteria

Education

Between lecture hall and lab

A research project of their own, first-class science and supervision, and access to a team of researchers from all over the world are just a few of the reasons students have for embarking on a Bachelor's, Master's or doctoral program at the Biozentrum. With the Biozentrum Research Summer and the Basel Summer Science Academy, the Biozentrum offers even the youngest researchers an opportunity to experience the world of research firsthand.



Studying at the cutting edge of research

Text:
Evi Sonderegger

"It's a huge step from having an experiment explained to you in a lecture to finally get some hands-on experience," says Julian Dommann with delight when talking about the third year of his Bachelor's degree. The early involvement of students in the research lab has always been a tradition at the Biozentrum. It is this exposure to real-life questions, along with the outstanding guidance in the problem-solving process and modern technological infrastructure that make studying at the Biozentrum so attractive to many students.

During the first two years, students get to grips with the fundamentals of all natural sciences: mathematics, physics, chemistry and biology, at the same time having a first glimpse into biomedical disciplines: biochemistry, microbiology, immunology and neurobiology. After that, it's off to the lab. In four six-week block courses they acquaint themselves with the molecular biology toolkit – from using a pipette or a microscope to working with cell cultures. "It is during the block courses, when you are in the lab the whole day, that you really start to understand what research is all about," says Catherine Helbing, another Bachelor's student. During this time, students get to know the research groups and laboratories, which was another key aspect for Catherine, as this has helped her figure out the direction she would like to take after her Bachelor's degree.

Yet even a winning formula evolves with the times: "Four years ago, we launched the Biozentrum Research Summer to give motivated students an opportunity to experience cutting-edge research first-hand even earlier in their career," explains Professor Sebastian Hiller, Chair of the Teaching Committee at the Biozentrum and program director. Many participants describe their six-to-nine-week summer internship in one of the Biozentrum's research groups as a unique opportunity to step out of the school mentality and immerse themselves in the practical world of research as early as their second year of their Bachelor's study. And next year the Bachelor's degree program will become even more practical, a one year laboratory course for experimental molecular biology being introduced.

The Biozentrum offers a number of specializations on the Bachelor's program, tailored to the diversity of biomedical sciences. Besides the more traditional specialization in molecular biology, a major in computational biology is also offered, reflecting just how radically the availability of "big data" and the developments in computer science have transformed research in the natural sciences. Students who are interested in engineering applications in biology can also apply for the trinational biotechnology program in which the Biozentrum participates after four semesters.

"With the Biozentrum Research Summer we give motivated students an opportunity to experience cutting-edge research first-hand even earlier in their career."

– Prof. Sebastian Hiller

Research becomes the main focus for students by the time they start their Master's at the latest. At least ten months of the three-semester program is spent on lab work, which is followed by the publication of the results in a Master's thesis. Meanwhile, students further expand their horizons by attending courses of the Graduate Teaching Program, which is offered by the Biozentrum in collaboration with researchers from the Friedrich Miescher Institute for Biomedical Research, the Department of Biosystems Science and Engineering at ETH Zurich, the Department of Biomedicine and the Swiss Tropical and Public Health Institute.

The Biozentrum is committed to sparking an enthusiasm for science among very young learners. The Basel Summer Science Academy, launched in 2019, offers high-school students a taste of the research world during two week-long workshops, while the kid@science weeks by "Schweizer Jugend forscht" or the Pestalozzi School Camp give even primary-school pupils an opportunity to explore the world of molecular biology that is invisible to the naked eye.

Nurturing outstanding young researchers

Text:
Evi Sonderegger

> **"It was really interesting to be able to get a feel for the different groups before making a decision."**
>
> – Đorđe Relić, PhD Student

Karolin Berneiser's choice of the Biozentrum for her doctorate was inspired by a Biozentrum alumnus she met in a lab in Boston. "A unique aspect of doing research here is the close proximity of so many different fields. And not just spatially – people take an interdisciplinary and cooperative approach to their work. Then there are the synergies with other academic institutions such as the FMI or the D-BSSE of the ETH Zurich and cooperations with industry partners." It's not just the broad range of cutting-edge interdisciplinary research, however, that attracts prospective PhD students to the Biozentrum. "We're a colorful bunch of people from different countries, and complement each other really well," Karolin says of her research group. A total of 120 PhD students are currently working at the Biozentrum, which is home to people from around 50 countries.

Karolin is a recipient of one of the coveted Biozentrum PhD Fellowships. "The program is a unique tool that allows us to actively recruit outstanding young researchers from around the world," explains Professor Marek Basler, Head of the PhD Fellowships Program. Ten PhD fellowships are awarded per year according to a competitive selection process – excellence is the sole deciding factor. The most interesting feature of the fellowships is that they are not tied to a particular research group or project. The fellows can choose their research project after rotating through up to three different research groups at the Biozentrum. "It was really interesting to be able to get a feel for the different groups before making a decision," says Đorđe Relić, another PhD fellow. "And not just because of the research topic, but also with regard to the different working methods." This can also be a decisive factor. Enea Maffei, for instance, deliberately chose to work in a smaller team because he believes that being able to quickly exchange ideas and information is an advantage.

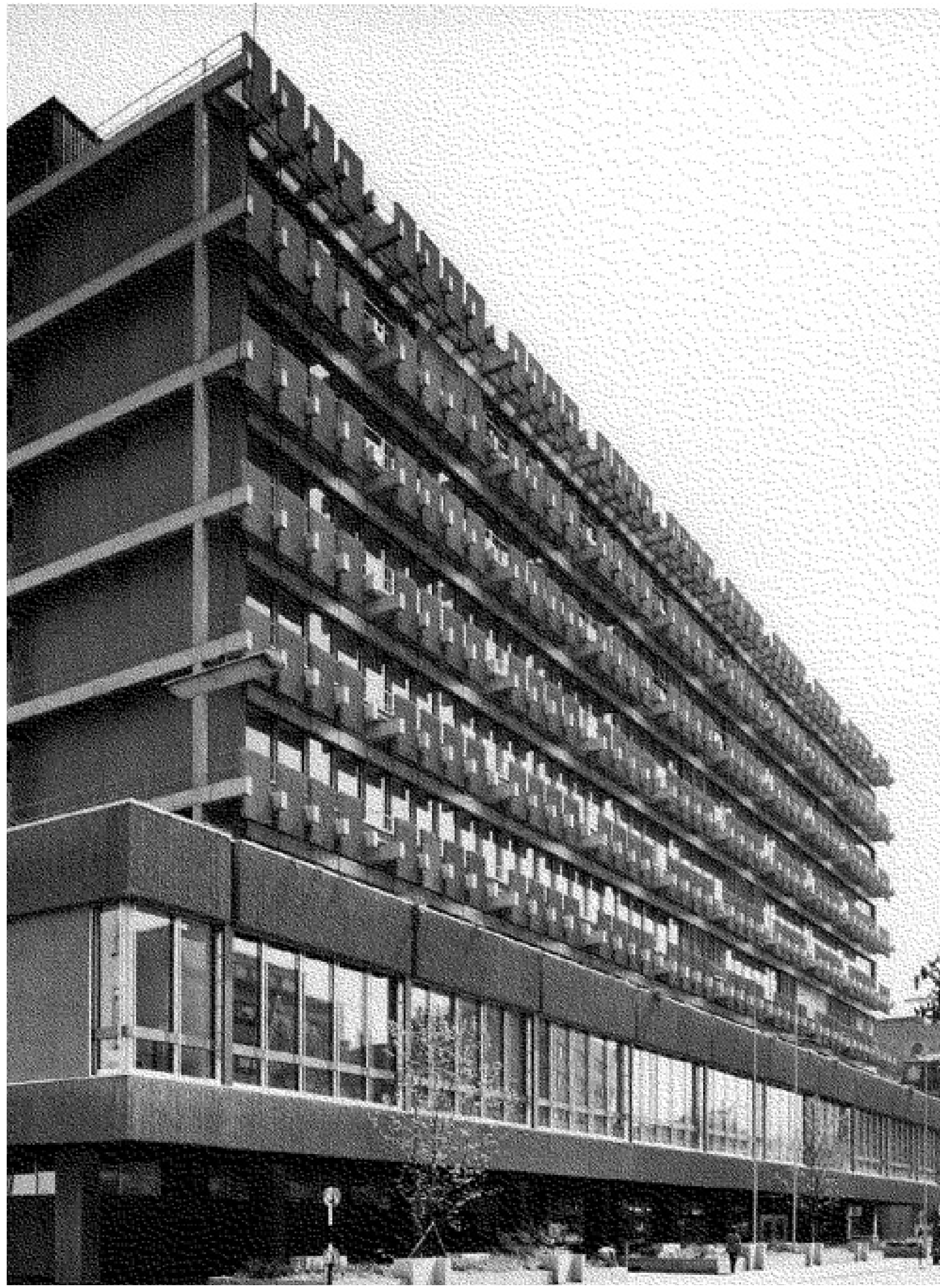
Exchange of this sort is the lifeblood of scientific research, which is why the Biozentrum also offers plenty of opportunities to engage in it outside of the research groups. "We try to combine research with social life," says Enea, a member of the PhD Student Association Committee Board. "We organize lectures, the PhD Lunch Talk where doctoral researchers present their project, apéros and much more." A particular highlight for Enea is the Life Sciences Party, organized together with other institutes and companies in Basel, while Đorđe, also a board member, singles out the two-day PhD Retreat. The internal lecture series Discovery Seminars, and the annual Biozentrum Symposium with over 300 participants are also key platforms offering junior researchers the opportunity to present their findings to a large audience and gain insights into different research fields.

Another important, international and highly qualified group of junior researchers at the Biozentrum are its 100 postdocs. After earning their PhD, many young researchers decide to go abroad for a few years, as international experience at a renowned institution and expertise in a particular research field are essential prerequisites for an academic career. The broad range of research conducted at the Biozentrum makes it an ideal place for postdocs to kick-start their career. They enjoy the support of their group leader, but also their peers: The Biozentrum Postdoc Society advises its members on career issues, as well as holding networking events to help new arrivals find their way around and extend the Biozentrum's global network. On completing their postdoc at the Biozentrum, these modern nomads head off in every conceivable direction: Today, countless Biozentrum alumni work as professors at prestigious universities or as top executives in industry and business.

More than 300 participants attend the annual Biozentrum Symposium. The aim is to promote scientific exchange and interdisciplinary teamwork between the research groups. Furthermore, it offers young scientists in particular a platform to present their research findings to a broad audience. The symposium is also a great opportunity to strengthen the Biozentrum community.

Pioneering spirit meets research

The 20th century was a time of great upheavals and discoveries for biology. It saw the emergence of molecular biology and of the Biozentrum, which over the decades was to become a globally renowned research institute in this field. It owes this success to a winning formula of pioneering spirit, foresight, courage and the willingness to try something new.



Biozentrum highlights

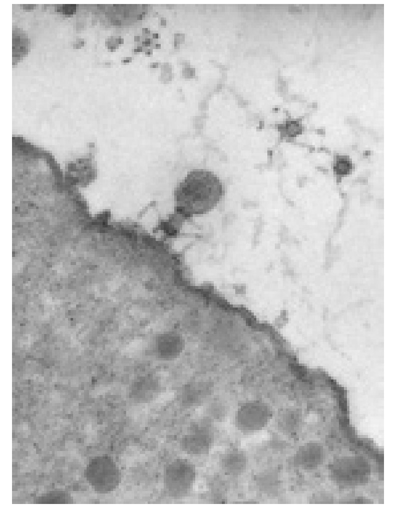
1971 to 2021

1968

Pioneering concept
The potential of molecular biology was recognized early in Switzerland – in the 1960s. Due to the visionary leadership of Arnold Schneider, a member of the Cantonal Executive Council, and generous financial support from the Canton of Basel-Stadt and the local companies Roche, Ciba, Geigy and Sandoz, construction of the Biozentrum began in 1968.

1971

Interdisciplinary research
At the time of its opening in 1971, the Biozentrum was the only interdisciplinary institute of its kind in Europe. Eduard Kellenberger was appointed Professor of Microbiology and entrusted with establishing the research institute. He brought two members of his group with him from Geneva, the future Nobel laureates Werner Arber and Jacques Dubochet.



1976

Innovative curriculum in biology
A new and innovative "Biology II" curriculum was created. It included introductory courses in mathematics, physics and chemistry, followed by more intensive hands-on "block courses." The first class, consisting of two students, graduated in 1976. Since then, the Biozentrum has conferred almost 1,000 "Diploma" or Master's degrees.

1978

Nobel Prize for Werner Arber
The Nobel Prize in Physiology or Medicine was awarded to Werner Arber, with the two American researchers Daniel Nathans and Hamilton Smith, for the discovery of restriction enzymes. These enzymes, which cut DNA molecules like scissors, are still one of the most important tools in molecular biology. All of Basel joined in the great celebration.

1983

The homeobox
Walter Gehring received worldwide recognition for his discovery of Hox genes. These genes contain a characteristic homeobox and play a key role in organismal development. Just over a decade later, Gehring and collaborators again attracted attention with the discovery of PAX6, a master control gene for eye development. Walter Gehring's research was honored with many awards, including the Gairdner Award, the Kyoto Prize and the Balzan Prize.

1985

Information technology
The Biozentrum was connected to the University Computer Center, extending its research to bioinformatics and computational modeling. Researchers at the Biozentrum and the Swiss Institute of Bioinformatics pioneered the field of automated 3D protein structure modeling. The SWISS-MODEL server was the most cited Swiss resource from 1999 to 2009 and is still one of the most widely used servers worldwide.

1986

Center for electron microscopy
Maurice E. Müller generously donated 40 million Swiss francs to establish the Maurice E. Müller Institute for High Resolution Electron Microscopy at the Biozentrum. This allowed the Biozentrum to strengthen its excellence in determining the structure of biomolecules.

1989

Distinguished mitochondrial researcher
Gottfried Schatz received the Gairdner Award for his studies on the transport of proteins into mitochondria. In addition to his outstanding research, Schatz was also renowned for his exceptional teaching skills and his training of a new generation of researchers. He was the author of more than 200 scientific publications, three volumes of essays, an autobiography and a novel.

1991

Protein kinase TOR
Michael N. Hall discovered the highly conserved, nutrient-activated protein kinase TOR. As a central controller of cell growth, TOR plays a key role in development and aging and is implicated in various disorders. For his discovery of TOR, Hall received many prizes including the Albert Lasker Award, the Breakthrough Prize in Life Sciences, and the Gairdner Award.

1995

Nobel Prize for developmental biologists
The Nobel Prize in Physiology or Medicine was awarded to Biozentrum alumni Christiane Nüsslein-Volhard and Eric F. Wieschaus for their discovery of genes crucial for embryonic development. Both were members of the Gehring laboratory in the 1970s.

1996

Neurosciences at the forefront
The University of Basel, the University Hospital, the Friedrich Miescher Institute and the local pharmaceutical industry jointly founded what is known today as the Neuroscience Network Basel. A few years later, the trinational alliance Neurex, comprising 100 research groups and about 1,000 scientists, was established. Basel has one of the highest concentrations of neuroscientists worldwide.

1999

Cutting-edge NMR spectroscopy
With support from Novartis and Roche, the Biozentrum enlarged its nuclear magnetic resonance spectroscopy platform with a new 800 MHz NMR spectrometer. The new high-end spectrometer was also used by the local medical institutes and pharmaceutical industry for diagnostic purposes.

2000

Successful start-ups
In 2000, researchers at the Biozentrum founded Santhera Pharmaceuticals, a company specialized in drugs for the treatment of rare neuromuscular and pulmonary diseases. The start-ups ARTIDIS, which uses nanotechnology to improve cancer diagnosis and prognosis, and T3 Pharmaceuticals, which develops highly specific and efficient cancer therapy using live bacteria, were founded in 2014 and 2015, respectively.

2001

A springboard for top researchers
The Biozentrum had become a springboard for countless research careers. In its first 30 years, almost 300 Biozentrum alumni had become professors at distinguished institutions. As of 2021, 1,400 PhDs and almost 1,600 postdocs have conducted research at the Biozentrum.

2005

Moving into new research areas
A new generation of professors took over the leadership of the Biozentrum. By 2005, twenty new professors had been appointed, expanding the Biozentrum faculty to 33 research groups.

2007

Fellowships for Excellence
Joachim Seelig, with a generous donation from the Werner Siemens Foundation, established the prestigious Fellowships for Excellence PhD Program. Known today as the Biozentrum PhD Fellowship Program, it offers a unique rotation-based selection of research projects to promising students from Switzerland and abroad.

2009

State-of-the-art technology platforms
Erich Nigg joined the Biozentrum as its first official director. He created cutting-edge technology facilities with highly sophisticated expertise and equipment, ensuring that Biozentrum researchers remained at the forefront of biomedical research.

2017

Nobel Prize for cryo-electron microscopy
The Nobel Prize in Chemistry was awarded to the Biozentrum alumnus Jacques Dubochet for developing cryo-electron microscopy to determine high-resolution structures of biomolecules. Dubochet worked at the Biozentrum in the group of Eduard Kellenberger from 1971 to 1978.

2018

Breakthrough of the Year 2018
Biozentrum alumnus Alex Schier was recruited from Harvard University to take over as the new director. The renowned scientific journal "Science" selected his studies on cellular development as the "Breakthrough of the year 2018".

2018

Biozentrum Research Summer
The Biozentrum Research Summer program was launched to offer Bachelor students the opportunity to perform hands-on research early in their studies. In 2019, the Biozentrum created the Basel Summer Science Academy to introduce high-school students to in-lab research.

2019

National Center of Competence in Research "AntiResist"
The Biozentrum became the leading institute of a NCCR project dedicated to antibiotics and antibiotic resistance. "AntiResist", headed by Christoph Dehio, is a collaboration of 24 research groups, 14 of which are located in Basel. Its aim is to search for new antibiotics and to develop alternative strategies to combat antibiotic-resistant pathogens.

2019

Sharing knowledge
With about 200 publications per year, the Biozentrum widely shares its research results and knowledge with the scientific community. To inform the citizens of Basel about the Biozentrum's ongoing research and to create a platform for interaction and discussion, the monthly lecture series "Einblicke Biozentrum" was established for the public.

2020

Tracing the coronavirus
Richard Neher and his colleagues were recognized as leaders in monitoring the spread and evolution of coronavirus. They used Nextstrain, an open-source web application that analyzes viral genomes and visualizes the spread of viruses over space and time, to track the COVID-19 pandemic.

2021

A beacon of life sciences
Biozentrum researchers moved into an ultra-modern building with a state-of-the-art infrastructure. They will study how living systems are designed and redesigned, and write the next chapter in the history of the Biozentrum.

It started with a spark

The Biozentrum was once the prototype for a molecular and biomedical research institution. Over the years, it became the international gold standard. It was the visionary wisdom of a new generation of researchers that led to the inception of the Biozentrum we know today.

Text:
Atlant Bieri

Professor Eduard Kellenberger took the helm of the freshly established Biozentrum in 1971.

Looking back, it is difficult to imagine the earliest days of the Biozentrum. Many of the things we now take for granted still seemed miles away at the time. At its core, the early history of the Biozentrum was built upon abundant good will, a pioneering spirit and the drive to effect fundamental change in research and education.

Nascent visions for a Biozentrum began to take shape in the early 1960s. Just one decade prior, researchers in England had discovered the structure of DNA, and scientists were now working feverishly to decode the three-dimensional structures of proteins, with their myriad loops and folds. At the same time, there was a brand-new field carving out its niche amongst the life sciences: molecular biology.

Antiquated views

Among some veteran Swiss scientists, there was a reluctance to embrace these new fields of study. According to Anna Seelig-Löffler, adjunct Professor of Biophysical Chemistry at the Biozentrum, the odd professor at the time even displayed downright distain for the new disciplines: "The professor for inorganic chemistry confronted me during my internship and asked me why I was studying chemistry. I explained to him that I wanted to pursue biochemistry later on, and he responded by telling me to 'leave off with that rubbish and study real chemistry instead."

Those kinds of attitudes might have relegated Switzerland to rapid-onset scientific obsolescence. In this new and exciting discipline, the country was at risk of sliding into obscurity. Luckily, not everyone shared those views. Research-oriented medical specialists at the University of Basel, such as the chemist and Nobel laureate Tadeus Reichstein and Christoph Tamm, Professor of Organic Chemistry, were interested in establishing an Institute for Molecular Biology. Hubert Bloch, Head of Pharmaceutical Research at Ciba and Professor of Microbiology and Immunology at the University of Basel, also took a keen interest in the project. One particularly dedicated advocate was Alfred Pletscher, Director of Corporate Research at Hoffmann-LaRoche and later Professor of Pathophysiology at the University of Basel. "Alfred Pletscher recognized that molecular biology was primed to play an enormously significant role, particularly in student education," recalls Jürgen Engel, former Professor of Biophysical Chemistry at the Biozentrum.

Grand investments for a great idea

Starting in 1965, the University of Basel gradually began to engage multiple committees in the task of fleshing out this fledgling idea. The first rough concepts were forged, and blueprints and budgets would follow in record time. In 1967, the Grand Council of Basel-Stadt approved a loan of 32 million Swiss francs for the project, a major sum at the time. "When it came to founding the Biozentrum, Basel simply bit the bullet, bucking its erstwhile reputation for frugality," wrote Gottfried Schatz, Professor emeritus for Biochemistry, in his book, Feuersucher. The companies Ciba, Geigy, Sandoz and Hoffmann-La Roche also contributed a joint sum of 50 million Swiss francs to the project, which helped to ease the Grand Council's decision. Furthermore, numerous professors and doctors sat on the Grand Council and were able to influence the political process directly. "It was a generation of generalists at work which no longer exists today," remarks Anna Seelig-Löffler. The political timbre was also decidedly progressive. Arnold Schneider, executive of the canton at that time, welcomed the novel field of research. As a result, it only took four years for the project to progress from initial concept to construction site. In 1968, the first professors assumed their posts, and students moved into the laboratories of the newly inaugurated Biozentrum in 1972.

Education was to play a key role at the Biozentrum, as advocated by its founders, and the mixture of subjects taught there was considered revolutionary at the time. In addition to mathematics, physics and chemistry, the students also learned biology and biochemistry. "It was quite an unusual biology curriculum," recollects Jürgen Engel. "We even analyzed protein structures with the students. It was really something!" That transdisciplinary approach shaped the research, too. Physicists, chemists, biologists, microbiologists and pharmacologists all worked together to study the secrets of life.

Oil prices impact research

Despite the generous start capital, the early days of the Biozentrum were rocked by financial turbulence stirred up by the two oil crises of the 1970s, each of which triggered a severe recession. The financial backing for the Biozentrum was on the line. "At the University of Basel, they were considering reducing the budget of their renowned Biozentrum," related Nobel laureate Werner Arber, Professor emeritus for Molecular Microbiology, in a text he composed for the Basel Historical Seminar.

Luckily, funding was no longer at stake once Werner Arber had secured the Nobel Prize. "Many people thought the 1978 Nobel Prize came at just the right time to reduce the imminent threat of dwindling financial support for the Biozentrum," he wrote.

And even in those trying times, the researchers were hard at work. Of the many alumni who completed their studies at the Biozentrum every year an average of ten former students went on to accept professorships at universities all over the world later on in their careers. In the 1980s, the Biozentrum was already considered one of the world's leading institutes for molecular biology. The Biozentrum model was even exported to other institutions. "Würzburg and many other cities eventually opened up their own Biozentrum. Today, the concept has taken root around the world," says Jürgen Engel.

“Feuersucher”
by Gottfried Schatz

“We were all young arrivals to Basel from abroad, full of energy and optimism,” recalls Gottfried Schatz, one of the founding professors, recruited to the Biozentrum from Cornell University in 1974, in his book Feuersucher (fire seeker). A handful of excerpts vividly capture a bygone era.

Shortly before our return [to the US], the Basel-based Austrian molecular biologist Thomas Hohn invited me to give a lecture at Basel’s recently opened Biozentrum. I had already heard about this new institute through the grapevine, and read an admiring article in an English-language journal with the title “Basel for Big Biology.” So I boarded the train to Basel with high expectations – and I was not disappointed. […] When it came to founding the Biozentrum, Basel simply bit the bullet, bucking its erstwhile reputation for frugality. […] Initially, the “exorbitant” project did not sit so well with Basel’s city fathers, but once the decision had been made the purse strings were relaxed. In an astonishingly short time, an attractive building had sprung up in the heart of the city, featuring a broad and welcoming staircase on which researchers would cross paths and chat. Even more importantly, the microbiologists Eduard Kellenberger and Werner Arber, recruited from Geneva, along with the visionary research director of Roche, Alfred Pletscher, made sure that their baby started out in life with flat hierarchies, generous employment conditions and renowned professors from all over the world. I had a feeling that a new and trailblazing chapter was beginning for European research […]. After we had returned to the US, my future colleague in Basel Max M. Burger called me late one evening in my windowless Cornell office and asked: “Mr. Schatz, would you like to join the Biozentrum?” I dispensed with the customary academic courtship rituals, and said “Yes” on the spot […].

There is nothing more wonderful than being part of the founding generation of a new research institute. We were all young arrivals to Basel from abroad, full of energy and optimism. We roamed the picturesque countryside around Basel on group excursions with our families, barbecued the traditional “Klöpfer” sausages and played football. And while we too occasionally bumped heads over organizational issues, we never knew the petty jealousies and personal intrigues that universities are so famous for. […]

The Biozentrum and its motley crew elicited their fair share of disapproving frowns all round from the city’s venerable university. Excessively casual attire, unprofessorial behavior, a lack of respect for the traditions of our faculty, inadequate knowledge of German, unnecessary trips abroad and general “American vices” were just a few of the transgressions we were accused of. Even our nocturnal work habits were met with umbrage: As an anonymous neighbor delicately put it in his letter of complaint, “the nighttime light from the Biozentrum interfered with his marriage.” As many of us spoke only broken German or none at all, we became conspicuous for our absences from faculty meetings, earning a reputation – not always undeserved – as arrogant and uncooperative. Moreover, many in Basel struggled to accept that we regarded living beings as chemical and physical units. Even the term “molecular biology” was, for many of them, a barbaric profanation of life. “A molecular biologist will never be able to explain the wondrous shape of a rose,” a prominent Basel biology professor once prophesied before we came along – and was fortunately no longer around to see our colleague Walter J. Gehring decipher the role of genes in the formation of the eye. Later, when we were among those spearheading the triumph of modern gene technology, there were even some faculty colleagues who regarded the Biozentrum as a symbol of contempt for nature and scientific megalomania. I fear that not a great deal has changed, even though gene technology has not recorded a single noteworthy accident in its almost 50-year history, and is today one of our most effective weapons against virus pandemics and countless other biological threats.

Schatz, Gottfried: Feuersucher, 1st edition, published by Neue Zürcher Zeitung, Zurich 2011.

Studying phages

Text:
Atlant Bieri

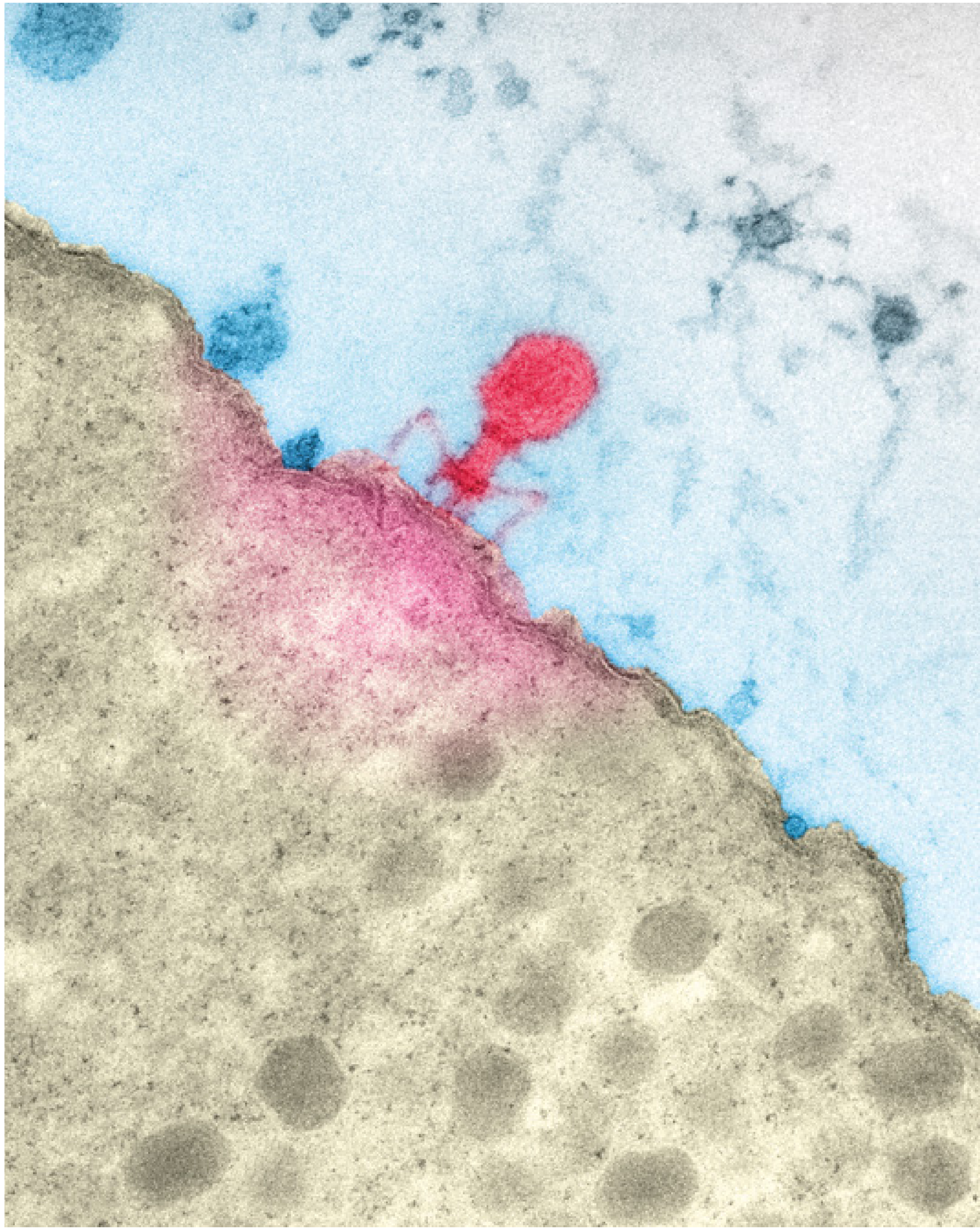
The study of bacteriophages and their effects on bacteria has played a very important role in the history of the Biozentrum. This research culminated in a Nobel Prize, awarded in 1978 to Werner Arber for his discovery and study of so-called restriction enzymes.

Phages are a type of virus that replicate solely inside bacteria, and from an evolutionary perspective, they are as old as their bacterial hosts. Their discovery came in 1920 and was followed apace by a wave of intensive research, in the hope of developing an effective means of combating devastating diseases caused by bacterial infections. Antibiotics had yet to be invented.

Phage research reached its peak between 1940 and 1960, particularly in the United States. It was this line of study that led to the postulation of the genetic code and gave rise to the field of modern molecular biology. The advantage of researching phages is that they are easy to work with, explains Alexander Harms, project leader at the Biozentrum. "You take an agar plate with a bacterial lawn and add a phage to the mix. The phages attack and destroy the bacteria, and holes start to form in the lawn. By studying the size of the holes and the speed at which they spread, we can differentiate between individual types of phages. This method can also be used to identify mutations in their genome."

Physicist Eduard Kellenberger brought phage research to the Biozentrum – and Werner Arber along with it. Arber had spearheaded sensational discoveries in the field, learning that some bacteria defend themselves against phages by detecting the foreign genetic material upon infection and proceeding to carve it into pieces. The biochemical "scissors" at work here were the now-famous restriction enzymes. These enzymes would soon become an important tool in genetic engineering, where they would be used to cleave DNA to recombine sections of it at will.

Today, there is a powerful, renewed interest in exploring phage therapy as an alternative to antibiotics, and for the first time, scientists are closely studying the function of phages within the broader ecosystem. "The whole world is full of phages. They kill billions of bacteria every second, so they play a key role in controlling our environment," says Alexander Harms.



A bacteriophage infects a bacterium, killing it.

An eye on the future

Text:
Katrin Bühler

When the Biozentrum opened its doors in 1971, it was not just its way of doing research that distinguished it from every other academic institution: Its approach to teaching was also defined by an innovative and at the time unique concept designed to equip the next generation of scientists with the necessary tools for the research of tomorrow. Predicting the needs of these young students twenty years into the future, at the peak of their research careers, was no easy task in view of the dizzying rate of progress and new discoveries in the field of molecular biology. "In the face of this dilemma, I believe it is very important not to overburden people with large amounts of technical knowledge that needs to be learned by rote," writes Professor Werner Arber in a paper published in 1978 (1). "What they will need, aside from basic scientific training with as broad a scope as possible, is the ability to work independently and the flexibility to familiarize themselves with new methods and topics. Moreover, they need to be original and creative."

These precepts were implemented by the first professors at the Biozentrum under the coordination of Professor Eduard Kellenberger and Professor Werner Arber with the innovative "Biology II" curriculum. A two-year undergraduate course equipped the students with foundational knowledge in the classical disciplines of the natural sciences. The introduction of "block courses" in the third year was a highly innovative step at the time. In these six-week practical courses in various research disciplines such as biochemistry or microbiology, students acquired the tools for scientific work in the lab, from the planning and practical execution of experiments to the interpretation of results. Theoretical knowledge was imparted at lectures and seminars integrated in the block courses. "We were forty students and worked in the lab from morning till night. It was an intense and exciting time, during which we really bonded as a group," recalls Biozentrum alumnus Björn Grünenfelder.

The block courses became a big hit, and were widely emulated. The in-depth experience of different research fields and close contact with the tutors during the block courses were immensely helpful to students when it came to finding an interesting topic or a suitable research group for their diploma thesis in the fourth year of the program. The final year was all about research: For the first time, students conducted research independently on a project of their own, supervised by the group leader.

The recipe stood the test of time. Teaching in "Biology II" began in 1972, and four years later the first two students successfully completed their final exams. Half a century later, more than 1,000 students have graduated with a Diploma or Master's degree at the Biozentrum. In spite of the academic reform and transition to the Bologna system in the early 2000s, which brought numerous changes, the spirit, practical focus and outstanding quality of the Biozentrum study program remained unchanged. It provides students with a solid foundation for the next step in their academic career – a doctorate. And because learning does not come to an end with graduation, the Biozentrum supports its PhD students with training, participation in congresses and extensive networking opportunities in preparation for their future career. To date, over 1,400 young scientists have earned their doctorate at the Biozentrum.

(1): Werner Arber: Wissenschaftliche Forschung und ihre Rolle an der Universität Basel, Basler Stadtbuch 1978, published by Christoph Merian Stiftung

"In the 1980s, the Biozentrum was the most international place in Basel and a gateway to the world. I vividly remember the block courses during which the people who taught us were walking back and forth between our baby experiments on the second floor and their pro work upstairs. Discovery was in the air, it could be felt even in the staircase".

– Marcel Weber, Professor of Philosophy of Science at the University of Geneva, Switzerland

"I remain in awe at how comprehensively the Biozentrum faculty trained me in so many disciplines of modern biology, and I credit my time as a graduate student in Andreas Engel's group for giving me such an exceptional start to my scientific career. The time my father Dieter, my brother Andreas and I all pursued our research at the Biozentrum at the same time will always be especially dear to me."

– Prof. Thomas Walz, The Rockefeller University, New York, USA

"Currently, I am the chief operating officer of a biotech company and mother to two grown-up sons. My solid scientific education at the Biozentrum, which I completed with a PhD under Prof. Walter Gehring, has been fundamental to every step of my professional career. It gave me a unique perspective and has invariably served me well as a foundation for important decisions."

– Dr. Juliane Bernholz, Chief Operating Officer at AM Pharma, Utrecht, Netherlands

"During my time as a PhD student in Walter Gehring's lab, I very much appreciated working closely together with highly qualified researchers and becoming acquainted with experimental work in one of the most fascinating fields of study – EvoDevo. It was an intense time that left a profound and lasting mark on how I think, and taught me an explorative approach that I try to pass on to my pupils."

– Dr. Sacha Glardon, secondary school biology and chemistry teacher, Gymnasium Bäumlihof, Basel, Switzerland

"I came to Basel as a Swiss expat at the age of 19. The country was foreign to me, and without the Biozentrum I would hardly have stayed in Switzerland. The international atmosphere at the Biozentrum made me feel at home. The first-class education and the research stays at Woods Hole and The Rockefeller University, made possible by the professors, proved immensely valuable to my subsequent work as a journalist."

– Dr. Theres Lüthi, science journalist, NZZ am Sonntag, Switzerland

A springboard for top researchers

Text:
Yvonne Vahlensieck

Over the last 50 years, the Biozentrum has been a springboard for countless scientists who went on to enjoy stellar careers in research. In this article, we present four alumnae who have had a lasting impact on their respective fields as professors at distinguished institutions.

Catapulted into research

Susan Gasser's search for a summer job in 1979 took her to the Biozentrum and the office of Professor Jeff Schatz, who promptly hired the young American with a bachelor's degree as a doctoral researcher. For Gasser, the lab and its dozen international postdocs was "the launch pad for my career." She looks back on a heady time when research was always at the center of everything.

After completing a doctoral thesis in record time, she was free to choose her next position. She climbed the career ladder at the Swiss Institute for Experimental Cancer Research and the University of Geneva, becoming an established group leader and a professor in 1991. She claims to have been "at least 80 percent" inspired by the example of Jeff Schatz and his informal, American-influenced leadership style. It was also during this time that she settled on her research field: Using microscopic analysis, she explored how chromosomes are packed in the cell nucleus and how this controls DNA transcription.

Then, in 2005 – on the advice of Jeff Schatz – Professor Susan Gasser seized the opportunity of a lifetime: She returned to Basel to take up a position as director of the Friedrich Miescher Institute, cementing its status as a world-leading institute for biomedical research until her retirement in 2020. Does the multiple award-winning researcher and mother of one son see herself as a role model for young scientists? "I have tried to set a good example. My own experience has enabled me to offer encouragement to many talented women at difficult moments in their career."

The last postdoc

Growing up in rural Wisconsin (USA), Professor Carla Koehler originally wanted to be a vet, before she discovered a passion for biochemical research – and in particular for mitochondria, the tiny power stations that supply our cells with energy.

"At the time, hardly anyone was working on the phenomenon of mitochondrial protein import in the US, so I had to go to Europe," she remembers. This is how she ended up at the Biozentrum in 1995 as a postdoc under Professor Jeff Schatz. The move paid off: In her time there, she discovered a previously unknown mechanism responsible for transporting proteins through mitochondrial membranes. Meanwhile, she also found time to explore Alsace, the Jura and the Black Forest with her road cycling group.

Toward the end of her stay, Jeff Schatz began making preparations for retirement. The resulting downsizing of the research group meant more resources for Carla Koehler – but also greater responsibility, for example in the form of student supervision. During this time, her path often crossed with Schatz's at the weekend, as she worked on her experiments and he cleared his office. "I thought he was bothered by my loud music, but in fact he wanted my Bob Dylan CD," she recounts, remembering one such meeting.

In 1999, she returned to the University of California, Los Angeles (UCLA), as a tenure track professor with a wealth of experience and promising projects in her bags. She has found new cycling routes in the hills of Los Angeles, but remains as devoted as ever to mitochondrial research.

A puzzle with hundreds of pieces

Berlin or Basel? This is the question Professor Angela Krämer found herself pondering in 1987. In the end, she decided against a junior professorship at the MPI in Berlin to follow her mentor, Professor Walter Keller, from Heidelberg to Switzerland. Keller had taken note of the talented biochemist during her doctorate, poaching her from a colleague shortly after she returned from a research trip to the US.

What drew Angela Krämer to the Biozentrum was the opportunity to establish her own research group and study the mechanism known as RNA splicing, whereby unnecessary parts of precursor messenger RNA are expunged and the remaining fragments joined back together in a process analogous to film editing. Angela Krämer laughs at the memory: "We were so naive back then; we thought we were looking for three or four proteins. In fact, as we realized over the years, it was a massive complex." As a fledgling group leader, she benefited greatly from the constant exchange with Keller's group, with which she shared a lab. In 1989, a junior research grant from the Swiss National Science Foundation helped Angela Krämer to finally strike out on her own.

In 1992, she accepted an invitation to the University of Geneva, where she continued to piece together the many fragments of the spliceosome: "This was the perfect task for me. I have always had enough imagination to wrap my head around the most intricate details." Angela Krämer has been retired for seven years now, and is happy that her findings have contributed to the development of gene therapy for hereditary diseases.

A chance liaison with structural biology

An adventurous spirit – and love for her future husband – were what enticed Professor Karolin Luger across the border to Switzerland after studying biochemistry in Innsbruck. It was therefore largely a matter of chance that she ended up as a doctoral researcher at the Biozentrum under Professor Kaspar Kirschner in 1986 – a happy coincidence, as the young researcher from a family of engineers in the Austrian state of Vorarlberg turned out to be a born structural biologist: "The structures inside cells are like machines that you can take apart and put back together in your head."

What she remembers most from her time at the Biozentrum is the freedom she enjoyed in her research project and the "highly creative and enthusiastic" supervision she received from Kaspar Kirschner. An equally fond memory is the relaxed social interaction among the various research groups: "We would often spend a couple of hours standing on the steps of the open staircase discussing something."

After completing her doctorate (and after a gap year spent kayaking in the United States), in 1990 Karolin Luger transferred to ETH Zurich, where she used X-ray crystallography to painstakingly figure out how DNA molecules, measuring meters in length, are packed into nucleosomes in the cell nucleus – a sensational scientific breakthrough at the time. In 1999 she continued her research on nucleosomes at Colorado State University in the US, where she established the department of structural biology from the ground up. Today, Karolin Luger is a professor at the University of Colorado Boulder, where a prestigious grant allows her to do research as freely and creatively as she did at the Biozentrum 35 years ago.

History – research

Pioneers of new knowledge

In the early years, the Biozentrum was home to an assortment of aspiring young researchers. They were full of vigor, optimism and eagerness to establish a new research culture. Characters like the future Nobel laureate Werner Arber, Walter Gehring or Gottfried Schatz all left their mark, shaping the Biozentrum's style of research and teaching to this day.

The pioneer of genetic engineering

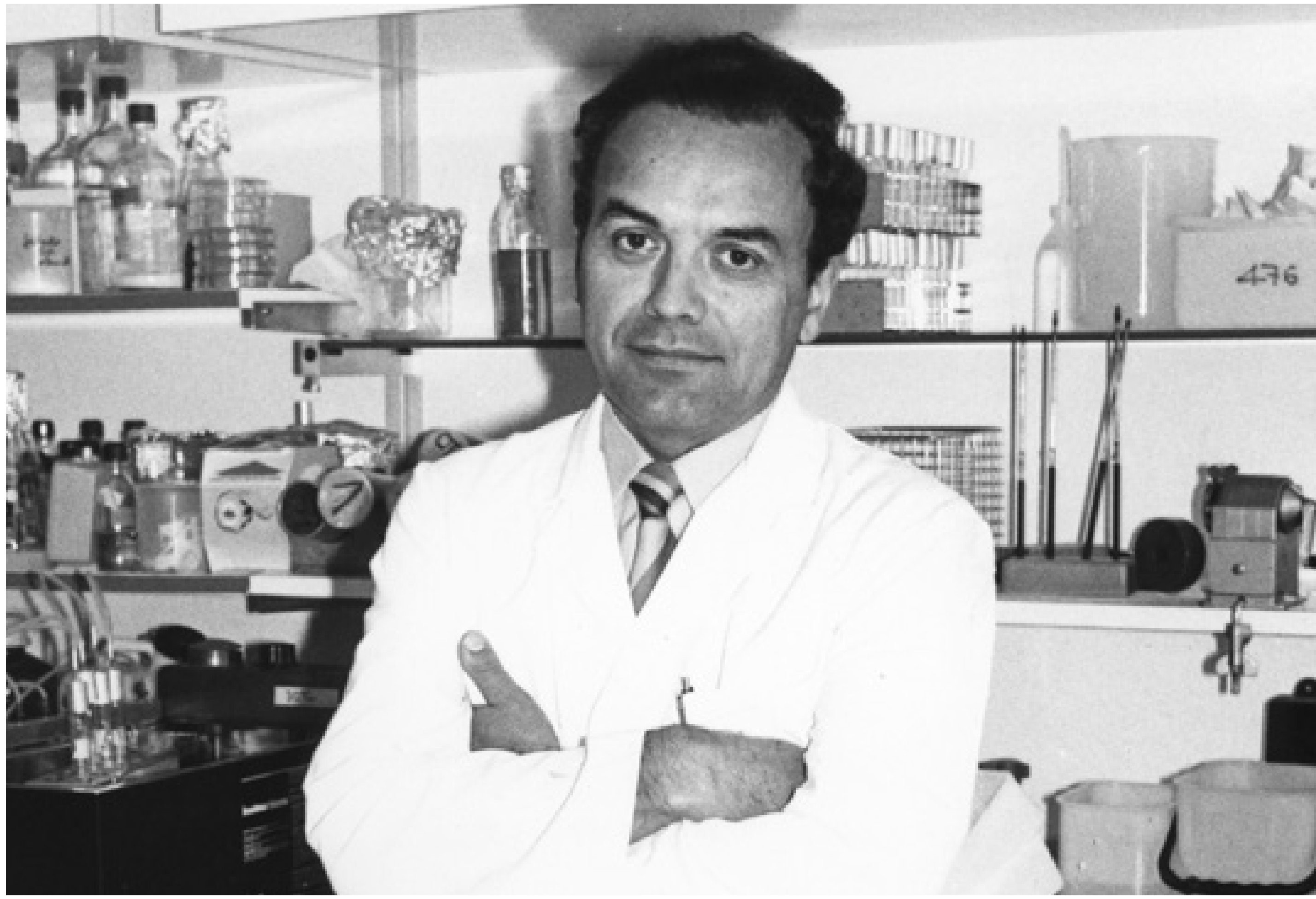
Text:
Anke Fossgreen

After commencing his doctoral dissertation at the University of Geneva in 1953, Werner Arber presented a new publication at his weekly seminar. In this article, the researchers James Watson and Francis Crick described the structure of DNA, a molecule that served to encode genetic information and that was wound into the shape of a double helix.

Raised in a farming family in Gränichen in the Canton of Aargau, Werner Arber went on to study natural sciences at ETH Zurich and developed a fascination with this mysterious molecule. Indeed, he devoted his entire research career to it. Thanks to a groundbreaking discovery, Werner Arber became one of the founding fathers of genetic engineering, for which he received the Nobel Prize in Physiology or Medicine in 1978.

The ambitious scientist had acquired the necessary skills for genetic studies during his doctoral dissertation and as part of a one-year research stay at the University of Southern California in Los Angeles. After returning to Geneva, Werner Arber devoted himself fully to bacteria and viruses. He explained the reason for this decision at a party held in his honor in 1978: "As a microbiologist, I'm convinced that many fundamental questions of biology can be explored by studying very simple systems."

Werner Arber studied the genetic makeup of intestinal bacteria (*Escherichia coli*) and their pathogens – viruses known as "phages" that infect bacteria. In the past, other scientists had observed that many strains of bacteria could defend themselves against attacking phages and released only a small number of phage progeny (or offspring). The astonishing thing was that although these progeny grew vigorously in the event of a renewed infection, they no longer grew on their previous host strain. Werner Arber, who was by then the head of a research group, wanted to know how the bacteria held out against the phages. He suspected the existence of enzymes that could act as molecular scissors to selectively identify and break down invading foreign DNA.



He and his team did in fact discover molecular scissors of this kind, which are known as restriction enzymes. The group also located the short sections on the DNA chain where restriction enzymes identified attacking DNA as foreign. In addition, the scientists answered a second question – namely, how did the bacteria protect their own DNA from being attacked by the scissors? They had noticed that the bacterial DNA featured characteristic chemical changes known as methyl groups, and it was these chemical appendages that prevented the scissors from acting at that location.

In other words, the bacteria had a sort of primitive immune system with which they protected themselves against foreign DNA. This defense system not only worked against DNA from phages produced in other host cells but also against the DNA of other bacterial strains in general. This was an astonishing finding with huge implications for basic research.

Over the next few years, it slowly became clear just how revolutionary this actually was. After all, Werner Arber and his colleagues had discovered tools that could selectively cut up the threadlike DNA molecule – even in a test tube. From then on, researchers could insert individual DNA segments into other DNA molecules. The field of genetic engineering was born.

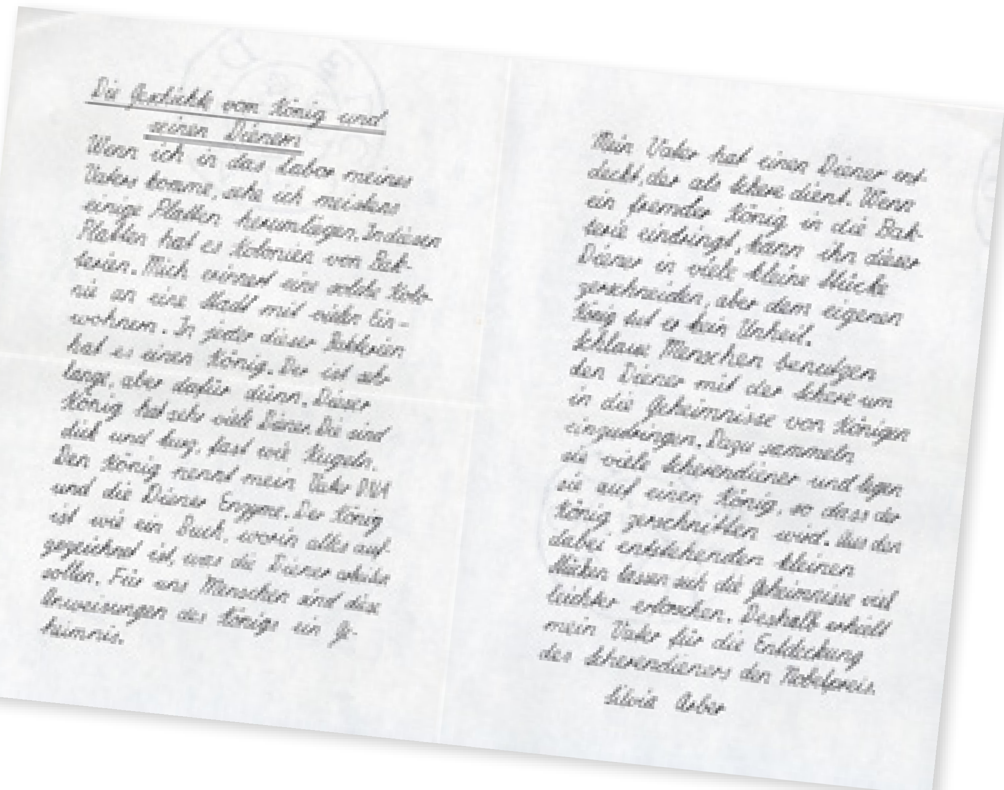
Today, researchers have access to over 1,000 restriction enzymes, which can be used at various locations in the genetic makeup. In the early years, these enzymes had to undergo a laborious cleaning process in the lab, and researchers would exchange precious droplets of them with other researchers. For some time now, however, the enzymes have been available for scientists simply to order from a catalog for use in their own laboratories. These tools allow researchers to cut genes out of one organism and insert them into another in order to genetically modify bacteria, plants or animals.

The toolbox available for genetic engineering has now acquired new types of gene scissors, the most powerful of which is known as Crispr/Cas. This enzyme was identified by the researchers Emmanuelle Charpentier and Jennifer Doudna some 40 years after Werner Arber's discovery as the pair sought to clarify another mechanism in the bacterial "immune system." Crispr/Cas has conquered the world's laboratories over the last few years and has entered practical use. In recognition of their discovery, Charpentier and Doudna received the 2020 Nobel Prize in Chemistry.

When Werner Arber received his Nobel Prize at a ceremony in Stockholm in 1978, he was accompanied by his family – specifically by his wife, Antonia, and his two daughters, Silvia and Caroline. Silvia Arber was ten years old when she gave a vivid description of her father's research, comparing the bacterial colonies to cities and the DNA to the king who ruled over them. Servants ensured that no foreign kings could enter the bacteria, and it was these servants – the scissors – that her father had discovered.

Silvia Arber is now a neurobiologist and leads a group of her own at the Biozentrum, as well as carrying out research at the Friedrich Miescher Institute for Biomedical Research in Basel. She and her sister Caroline, who is also a professor, in her case at the University of Lausanne, continue to provide a regular supply of scientific publications to feed their father's insatiable appetite for research.

The tale of the king and his servants


Die Geschichte vom König und seinen Dienern

Wenn ich in das Labor meines Vaters komme, sehe ich meistens einige Platten herumliegen. In diesen Platten hat es Kolonien von Bakterien. Mich erinnert eine solche Kolonie an eine Stadt mit vielen Einwohnern. In jeder dieser Bakterien hat es einen König. Der ist sehr lange, aber dafür dünn. Dieser König hat sehr viele Diener. Die sind dick und kurz, fast wie Kugeln. Den König nennt mein Vater DNA und die Diener Enzyme. Der König ist wie ein Buch, worin alles aufgezeichnet ist, was die Diener arbeiten sollen. Für uns Menschen sind die Anweisungen des Königs ein Geheimnis.

Mein Vater hat einen Diener entdeckt, der als Schere dient. Wenn ein fremder König in die Bakterie eindringt, kann ihn dieser Diener in viele kleine Stücke zerschneiden, aber dem eigenen König tut er kein Unheil. Schlaue Menschen benutzen den Diener mit der Schere um in die Geheimnisse von Königen einzudringen. Dazu sammeln sie viele Scherendiener und legen sie auf einen König, so dass der König zerschnitten wird. Aus den dabei entstehenden kleinen Stücken lassen sich die Geheimnisse viel leichter erforschen. Deshalb erhält mein Vater für die Entdeckung des Scherendieners den Nobelpreis.

Silvia Arber

When I come to the laboratory of my father, I usually see some plates lying on the tables. These plates contain colonies of bacteria. These colonies remind me of a city with many inhabitants. In each bacterium there is a king. He is very long, but skinny. The king has many servants. These are thick and short, almost like balls. My father calls the king DNA, and the servants enzymes. The king is like a book, in which everything is noted on the work to be done by the servants. For us human beings these instructions of the king are a mystery.

My father has discovered a servant who serves as a pair of scissors. If a foreign king invades a bacterium, this servant can cut him into small fragments, but he does not do any harm to his own king.

Clever people use the servant with the scissors to find out the secrets of the kings. To do so, they collect many servants with scissors and put them onto a king, so that the king is cut into pieces. With the resulting little pieces it is much easier to investigate the secrets. For this reason my father received the Nobel Prize for the discovery of the servant with the scissors.

Silvia Arber, 1978

"I was only ten years old when my father received the Nobel Prize in Physiology or Medicine in 1978. He explained to me at the time what it was and what his research was about, but I obviously had no idea what it all meant, and so I recorded his story in my own words. Having received piles of mail congratulating him, my father used the story in his thank-you letters – and so the tale made its way all around the world. It was printed in newspapers, and I also read it out on a Swiss radio program as a child. While I was in Stockholm with him, the Queen and King of Sweden even told me they were glad to have read the story – as otherwise they wouldn't have understood what my father's research was actually about."

– Prof. Silvia Arber

Other prestigious awards for Biozentrum professors

Albert Lasker Basic Medical Research Award
2017: Michael N. Hall

Breakthrough Prize in Life Sciences
2014: Michael N. Hall

Kyoto Prize
2000: Walter J. Gehring

Balzan Prize
2002: Walter J. Gehring

Gairdner Foundation International Award
2015: Michael N. Hall – 1998: Gottfried Schatz – 1987: Walter J. Gehring

Louis-Jeantet Prize for Medicine
2017: Silvia Arber – 2009: Michael N. Hall – 1998: Walter Keller – 1990: Gottfried Schatz – 1987: Walter J. Gehring

Marcel Benoist Prize
2012: Michael N. Hall – 1992: Gottfried Schatz – 1966: Eduard Kellenberger

Otto Naegeli Prize
2014: Silvia Arber – 1982: Walter J. Gehring – 1975: Max M. Burger

Cloëtta Prize
2003: Michael N. Hall – 1987: Joachim Seelig – 1974: Urs A. Meyer

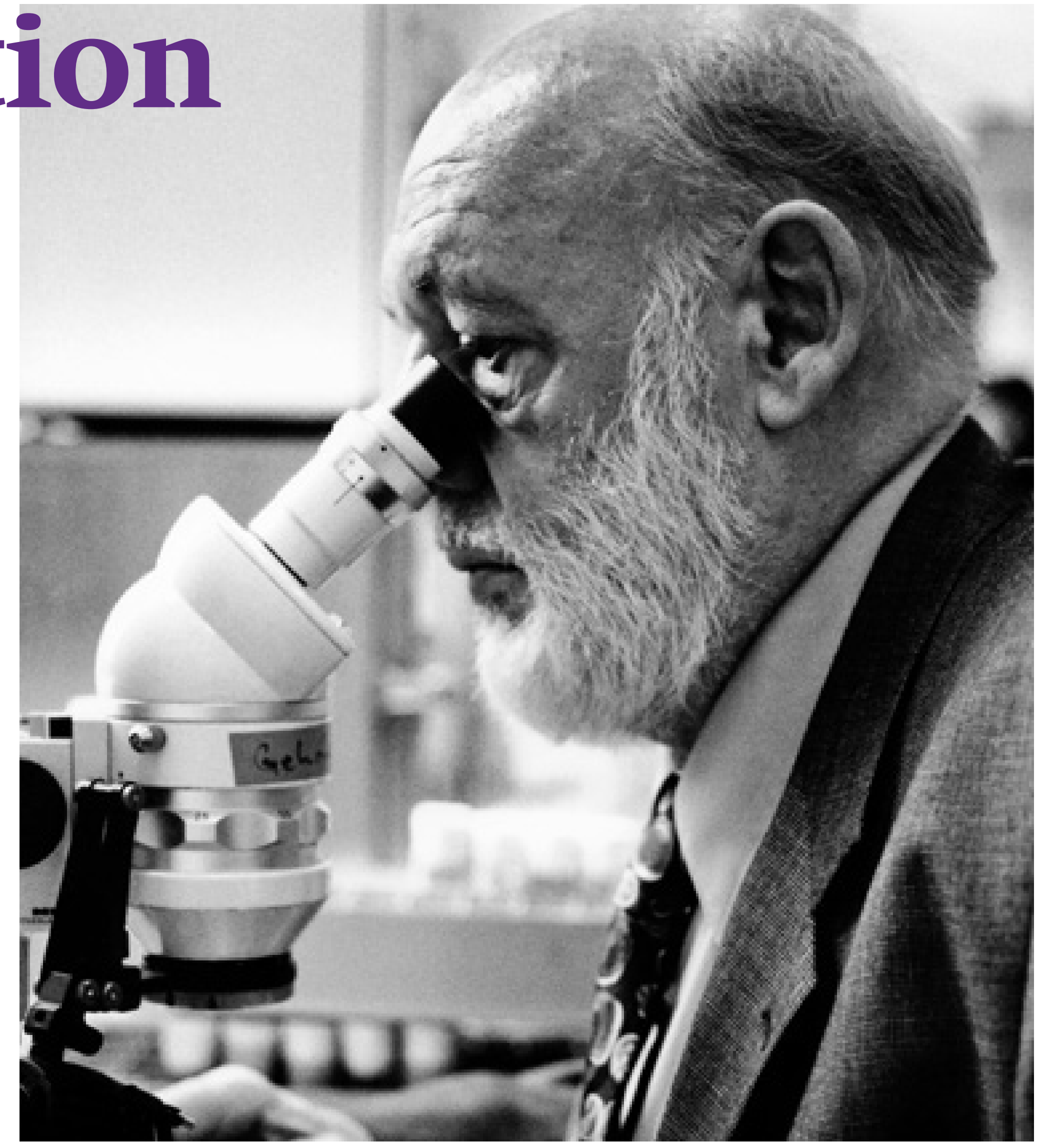
European Molecular Biology Organisation (EMBO) Members
Ueli Aebi – Markus Affolter – Silvia Arber – Werner Arber – Yves-Alain Barde – Thomas A. Bickle – Dirk Bumann – Max M. Burger – Guy Cornelis – Fiona Doetsch – Christoph Dehio – Andreas Engel – Jürgen Engel – Richard M. Franklin – Walter J. Gehring – Michael N. Hall – Johan N. Jansonius – Urs Jenal – Walter Keller – Susan Mango – John G. Nicholls – Erich Nigg – Peter Philippsen– Howard Riezman – Jürg Rosenbusch – Gottfried Schatz – Peter Scheiffele – Alex Schier – Joachim Seelig– Anne Spang – Martin Spiess – Mihaela Zavolan

National Academy of Sciences (Members and Foreign Associates)
Silvia Arber – Werner Arber – Walter J. Gehring – Michael N. Hall – Gottfried Schatz – Alex Schier

Fellows of the American Association for the Advancement of Science (AAAS)
Silvia Arber – Walter J. Gehring – Michael N. Hall – Urs Jenal – Peter Philippsen – Gottfried Schatz

Spectacular moments in evolution

Text:
Anke Fossgreen



The flies that brought Walter Gehring world fame were far from ordinary. Aside from the usual two compound eyes on their head, these fruit flies (*Drosophila melanogaster*) sported up to twelve additional eyes distributed on their wings, legs and antennae. The sensational creatures, unveiled by Walter Gehring and his team in the journal Science in 1995, astounded the scientific community – and struck fear into the hearts of the general public.

Walter Gehring designed the experiment to confirm a prediction he had made. He had postulated that a single genetic switch, a master control gene, is responsible for activating an entire cascade of genes that then work together to form a new organ. It turns out that this master control gene can trigger the formation of an eye in many different tissue types.

When it became clear that this master control gene, known as Pax6, is almost identical in a number of different animals – from worms and flies to mice and humans – the textbooks had to be rewritten. Until then, the accepted wisdom had been that eyes arose independently between 40 and 60 times in the course of evolution. In fact, Walter Gehring was guilty of perpetuating this error in his own textbook, he admitted at the time with a laugh.

Walter Gehring was originally from Zurich, where he graduated from high school before studying zoology at university. He had been fascinated by birds since his school years, but turned his attention to smaller winged creatures when he began working under Ernst Hadorn, a renowned developmental geneticist and fly researcher at the University of Zurich. Walter Gehring once said that he always sought out the best teachers as they were the ones he could learn the most from. As a doctoral researcher, he came across a remarkable mutant fly in Hadorn's lab; in place of antennae, the insect had two legs growing from its head. He named the creature "Nasobemia" – a reference to the poem "Das Nasobem" by Christian Morgenstern about an imaginary creature able to walk on its noses. He spent the subsequent years in search of the gene that had caused this mutation.

He acquired the necessary knowledge as a postdoc at Yale University in New Haven, where he also became a professor. After five years in the US, he returned to Switzerland and established a group of his own at the Biozentrum. His choice of team members could hardly have been better, as he was fond of saying – after all, two of them went on to win Nobel Prizes.

In 1984, Walter Gehring and his team finally identified the Antennapedia gene, which can cause flies to grow legs from their head instead of antennae if the gene is mutated. The discovery was a long time in the making. To begin with, Gehring created Europe's first Drosophila gene library. To this end, his group cloned all of the fruit fly's genes. The researchers then searched this gene library for genes that controlled the flies' development. When Gehring and his colleagues eventually succeeded in characterizing the Antennapedia gene, a conspicuous gene sequence helped them to discover related developmental control genes. This special gene section, known as the homeobox, opened up a broad range of possibilities for developmental biologists in one fell swoop. The special thing about this sequence is that it is conserved in numerous control genes, allowing the researchers to use it as a probe to extract these genes from the gene library in a very short time. To their surprise, they observed that these homeobox sequences are also present in analogous genes in mice, frogs or humans. Walter Gehring and his team had discovered a universal principle of nature.

The final proof consisted in modifying the Antennapedia gene in fruit flies, ultimately causing the insects to grow legs from their head. In doing so, Gehring had succeeded in deliberately reproducing in the lab the chance mutation he had observed as a doctoral researcher. In the course of these experiments, the team stumbled across another interesting Drosophila gene resembling the Pax6 gene involved in the development of eyes in mice. It was this discovery that led to the many-eyed flies that caused such a stir in 1995. Incidentally, the extra organs were in fact capable of detecting light.

His fascination with the developmental biology of Drosophila notwithstanding, Walter Gehring also remained a dedicated zoologist. Of all the Biozentrum researchers, he was probably the one with the greatest knowledge of animals, he once claimed with some satisfaction. His hobby was marine biology, acquired during a visit to Banyuls-sur-Mer in southern France as a student. Later, he would lead excursions for his own students there. During these trips they had the opportunity to experiment on marine animals at the renowned Institute for Marine Biology.

“It was an incredibly exciting time”

Interview with Professor emeritus Renato Paro, former director of the D-BSSE and a Gehring alumnus: Anke Fossgreen

Professor Paro, you studied at the Biozentrum from 1974 to 1978. What was it like?

Paro — It was an incredibly exciting time. At the Biozentrum, we could study the fledgling research field of molecular biology. This was a groundbreaking opportunity in Europe. What is more, biology had just been rocked by a revolutionary development: It had become possible to selectively cut up and replicate an organism’s genetic material – to recombine DNA, in other words.

In 1978 you took your final exams at the Biozentrum…

Paro — The final oral exam in microbiology was a special experience – one of the two examiners was Werner Arber. He had found out two days earlier that he was going to receive the Nobel Prize. He just calmly performed his duties as if nothing had happened.

After that you researched under Walter Gehring. He had a reputation for only taking on the very best graduates. What did you learn from the experience?

Paro — Walter Gehring was one of those young professors who had worked in the US – there were a few of them at the Biozentrum. This was one of the reasons for the special pioneering spirit that characterized the Biozentrum back then. During that time, I learned to sometimes work through the night if a particular experiment demanded it. That said, the group would often go out for a beer together as well.

Walter Gehring was considered a pioneer in various fields. Why?

Paro — Walter Gehring was actually a zoologist. He was a consummate early adopter of new technologies and research areas. For example, he was the first person in Europe to establish a gene library for the fruit fly *Drosophila melanogaster* using recombinant DNA.

Which you also worked with…

Paro — Yes, at the time diploma students like me had the opportunity to research where particular genes were located within the fly’s genome. This worked well in my project, so he offered to supervise my doctorate as well.

You have had an impressive career: You did research in Scotland and California, you were a group leader and professor at the Center for Molecular Biology in Heidelberg, and ended up back in Basel, where you established the Department of Biosystems Science and Engineering (D-BSSE) of the ETH Zurich. Did you stay in touch with Walter Gehring?

Paro — Yes I did, and after he retired in 2009 he used the high-throughput sequencing technology that we set up at the D-BSSE. With this technology it was possible to very quickly analyze the entirety of an organism’s genetic information.

What was Walter Gehring working on at the D-BSSE?

Paro — He was studying the genetic make-up of cyanobacteria, as they have light-sensitive receptors. Walter Gehring had previously shown that the eye did not evolve multiple times as previously thought, but just once. Now he wanted to look at whether genes similar to those that influence the development of eyes in higher life forms were also present in basic organisms like cyanobacteria. He didn’t have enough time for that, however. Sadly, he died far too soon.

How two Nobel laureates started out at the Biozentrum

Eric Wieschaus (born 1947) had already worked with Professor Walter Gehring at Yale University. When Gehring moved to the Biozentrum in Basel in 1972, Wieschaus went with him as his first doctoral student. After completing his doctoral thesis in 1974, Wieschaus took up a research position at the University of Zurich, but continued to work with members of Gehring’s research group. This is how he met **Christiane Nüsslein-Volhard** (born 1942), a postdoc who worked with Walter Gehring from 1975 to 1977. The biologist was instantly fascinated by the work with fruit flies. Specifically, she studied the flies’ eggs in search of factors that influence the insects’ development.

In Walter Gehring’s lab, Eric Wieschaus was working on imaginal discs – structures in fly larvae that develop into organs and body parts such as wings or legs after metamorphosis.

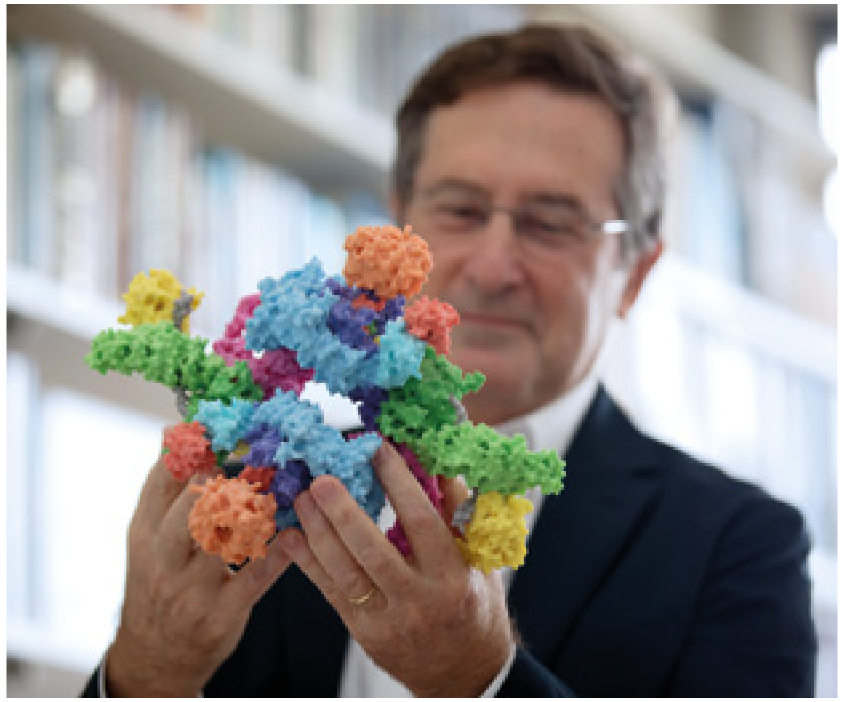
Eric Wieschaus and Christiane Nüsslein-Volhard, who always discussed their projects with each other at great length, subsequently received an invitation from the European Molecular Biology Laboratory (EMBL) in Heidelberg to create a research group together to investigate which genes are involved in the embryonic development of flies. By systematically analyzing countless mutant flies, the pair succeeded in showing how body patterns develop. In this process they found a large group of genes that specify the body axis – the fact that one end of the embryo will become the fly’s head, and the other end the tail. These genes also determine the ventral and dorsal side. They also observed that the embryo is divided into segments that assume a particular position along the head-to-tail axis.

The genetic principles in embryonic development discovered by Eric Wieschaus and Christiane Nüsslein-Volhard were later also found in other animals and in humans, suggesting that the mechanisms were conserved by evolution. In recognition of their pioneering work, Nüsslein-Volhard and Wieschaus received the Nobel Prize in Physiology or Medicine in 1995.

A hisTORic breakthrough

Text:
Irène Dietschi

Michael N. Hall was not yet 40 years old when he discovered a key protein for cell growth and communication at the Biozentrum. The protein, known as TOR, opened the door to numerous subsequent discoveries by the biochemist – some of which required him to leave the lab for the clinic.



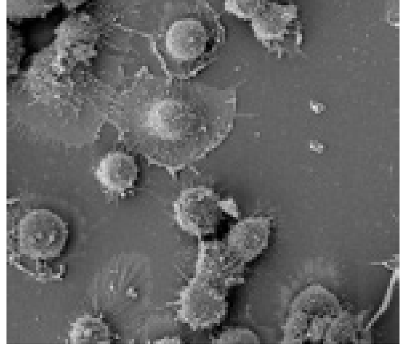
Michael Hall's first experience of clinical research left him astounded at how his colleagues in the hospital treated their samples. "It was a real eye-opener," he recalls. Hall was accustomed to thinking of cells as an unlimited resource. In basic research, cell samples are taken from mice; if an experiment goes wrong, you simply breed new mice according to a different design. "In clinical or translational research it's a different story entirely," says Hall. "There, we work with tissue from patients, with biopsies – and that's not something you can simply redesign. Each biopsy is extremely valuable, and you use whatever you can get."

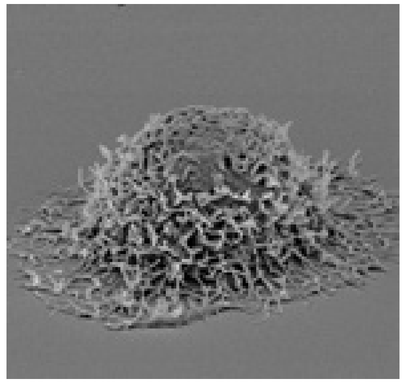
It is just one of many examples that illustrate the clash between the two research cultures. "People in clinical practice have a completely different mindset," Hall explains. "They have a different vocabulary, a different rhythm, and they're extremely results-oriented. They have to be – their main concern is saving their patients." For Michael Hall, meanwhile, as a basic researcher, the process is at least as important as the end result. At the same time, he is convinced that the foundation for all translational research is curiosity-driven basic research: "There's nothing to translate, unless you have basic research," as he puts it.

Michael Hall, who is originally from the US, is sitting at the visitors' table in his office on the 5th floor of the (old) Biozentrum building. In front of him is a glass of green tea. The multiple award-winning molecular biologist has lived in Basel with his family ever since being poached from San Francisco by Gottfried Schatz in 1987, and acquired Swiss citizenship long ago. He is one of the "dinosaurs" of the Biozentrum, and at 67, the oldest professor at the institute – possibly in the entire university. Yet Hall, an old-school pioneer for whom molecular biology was once a frontier that promised the most exciting adventures in research, has no intention of stopping.

He spent this March morning shortly before the start of spring planning his forthcoming sabbatical. Singapore, Sydney, Paris – all of these destinations are home to close colleagues with whom he hopes to discuss his latest research interest: the role of TOR (target of rapamycin, see box) in metabolism. Lean, wiry and youthful in jeans and a gray pullover over a blue striped shirt, he explains that he has already had both his COVID-19 jabs. Talking about his travel plans brings a sparkle to his eyes.

Michael Hall's flirtation with translational research – which soon blossomed into an earnest and fruitful relationship – began around ten years ago. The move spelled a departure from an old tradition among basic researchers of looking down on applied research, which many of his colleagues still regard as "superficial" and "boring". Not for Hall. First, because he realized that clinical researchers are actually doing two jobs at once: looking after patients while simultaneously pursuing projects that are anything but "superficial". The second reason concerned his own projects at the time: "With TOR, we had reached a point where we simply had to transfer our findings from the lab to actual patients."



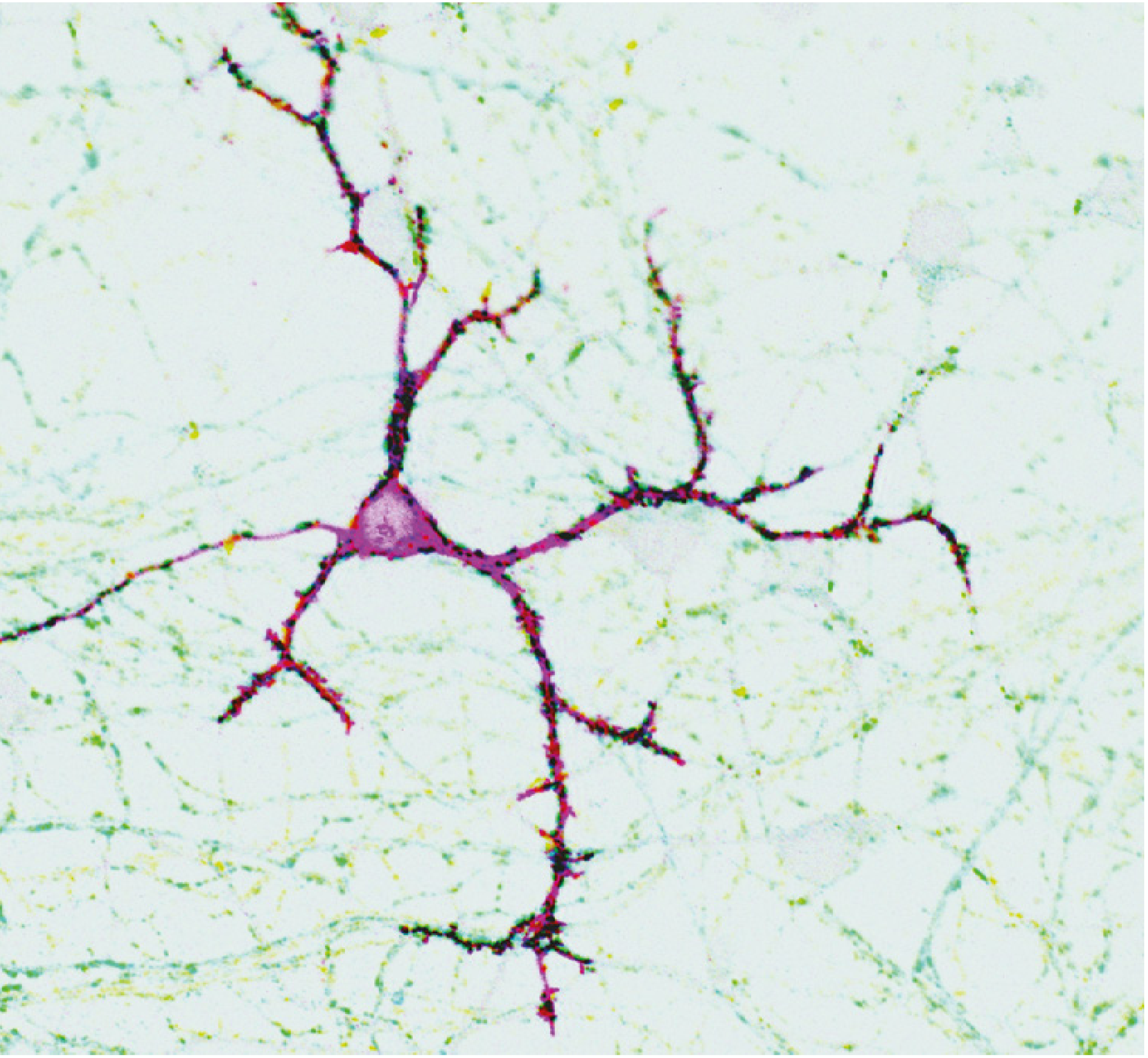


Over the years, Hall and his group had shown that TOR does not merely regulate cell growth as such, but also plays a key role in numerous diseases: diabetes, obesity – and cancer! "Cancer cells are pathologically altered cells: They grow and multiply in an uncontrolled manner." In 2014, Hall's list of accolades grew even longer when he was jointly awarded a European Research Council (ERC) Synergy Grant worth eleven million euros, along with biomedical expert Gerhard Christofori and liver specialist Markus Heim, both of the University of Basel, and mathematician Niko Beerenwinkel of ETH Zurich. Hall and his colleagues were trying to figure out one of the most pressing questions in cancer research: How do cancer cells become resistant to drugs, and which signaling pathways are involved in this process? Hall's research had already yielded ample returns for clinical practice, for instance in the form of cancer drugs, which have already been approved, known as TOR inhibitors. These drugs suppress the defective activation of TOR in tumor cells.

Hall is pleased with the past fruits of his work, but has moved on to his next research interest, metabolism: He hopes to discover how the TOR protein is involved in the onset of diabetes. "Leading a lab is like running a business," he says. "You have to keep innovating, pushing boundaries and presenting new products or ideas. And above all, you have to take risks," he adds. This seems to be harder for young researchers today than it was for my generation," he muses. Then again, he admits, they're operating in a tougher environment than that of 30 or 40 years ago. Nevertheless, his advice to the younger generation, dispensed with a twinkle in his eye, is simple: "Believe in yourself," and "stick with it!"

Aspirin for yeast cells

Michael N. Hall discovered the protein "target of rapamycin," or TOR, as a young professor at the Biozentrum in the early 1990s. At the time, the processes of cell division and cell growth were one of the most elusive mysteries in molecular biology, which countless researchers around the world were vying to solve. While most of them were experimenting with mammalian cells, Hall's group was working with simple yeast. This caused some bemusement among rival researchers – "in their eyes, it was tantamount to giving yeast cells aspirin," Hall recalls. The gambit paid off, however, leading to the discovery of TOR, which would later reveal itself to be a key protein in cellular communication: Hall and his group were soon able to show that by regulating a range of signaling pathways, TOR also played a crucial role in the cells of mammals and humans, substantially influencing their growth.



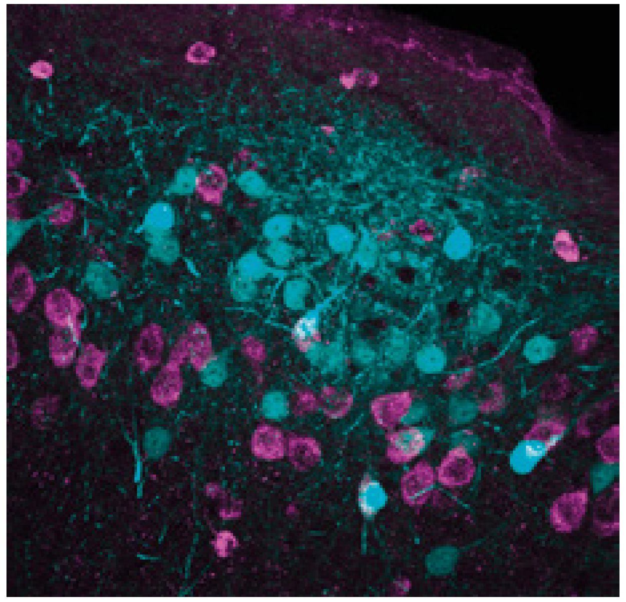
A bundle of nerves

Basel is a major neuroscience hub – in which the Biozentrum has played a key role for decades. The brain still holds countless mysteries, and researchers in Basel are coming closer to solving at least some of them.

Text:
Irène Dietschi

The neurobiologist Flavio Donato, aged 39, certainly gets around: After growing up in southern Italy and studying in Rome, he earned his doctorate at the Friedrich Miescher Institute in Basel before doing a stint as a postdoc in the far north of Europe, in the Norwegian city of Trondheim. For the last two years, Donato has been an assistant professor for neurobiology at the Biozentrum – "a fantastic place for neuroscience," as he puts it. He feels privileged to work here.

The brain, with its 100 billion neurons, each with thousands of synapses, is a source of fascination for researchers and laypeople all over the world. Recent decades have seen an international boom in brain research, with Basel establishing its position as an important hub. The university and its hospital, the Friedrich Miescher Institute co-financed by Novartis, and the city's flourishing pharmaceutical industry: The synergy among these institutions has resulted in a concentration of neuroscience expertise at the knee of the Rhine that is unparalleled anywhere in the world.



And at the heart of it all is the Biozentrum. Neurobiology is one of the institution's central pillars, comprising seven research groups – one of which is led by the young Flavio Donato. His research topic is the learning capacity of the brain in babies. "Babies are extremely good at learning," says Donato. "What they learn to do in their first years of life is truly incredible – recognizing faces, talking, walking, distinguishing their mother tongue from others, and not least: forming memories." This is the aspect that Donato finds most intriguing: Thanks to studies, we now know that the brain stores memories from early childhood, even though these memories can no longer be accessed by adults. Donato and his team study phenomena of this kind in mice models – for instance, by genetically altering neurons in order to microscopically identify the cells that are active during learning. "We then track these neurons over the course of the mouse's lifespan."

The group's research is supported by a Starting Grant of 1.5 million euros from the European Research Council. "The funding opened a lot of doors for us," Donato told us. "We are in touch with peers all over the world." Just as important to him, however, is local interdisciplinary contact at the Biozentrum. "In this respect, it is truly unique here."

This was also John Nicholls' reason for making the move to the Biozentrum in 1983. The Englishman, aged 54 at the time, held a prestigious position at Stanford University and was already known in the field for his work on the nervous system of leeches. "But I was afraid I would have to do that for the rest of my life, with no prospect of anything new," Nicholls recalls. So when his Swiss colleague Max Burger offered him a professorship in Basel, he agreed on the spot.

Nicholls is now 91, and lives and works in Trieste. He has very fond memories of his time at the Biozentrum. "Those were wonderful years, and it's all down to the people – Walter Gehring, Gottfried Schatz, Jürg Rosenbusch – all those bright minds of molecular biology, who I had so much to learn from." John Nicholls left behind an impressive legacy of his own in Basel. After his work on leeches, he turned his attention to a mammal – the opossum – and made groundbreaking discoveries on the regenerative capacity of the nervous system. He also wrote one of the standard works in neurobiology, From Neuron to Brain, and had a reputation as an inspiring and well-liked teacher. Before the COVID-19 pandemic, Nicholls used to return to Basel every year for a Biozentrum reunion.

"Those were wonderful years […] with all those bright minds of molecular biology, who I had so much to learn from."

– Prof. em. John Nicholls

Just like the other disciplines studied at the Biozentrum, neurobiology has come a long way since Nicholls' time. "Basic research and industry used to be two completely separate worlds, whereas nowadays the system has become more permeable – in both directions," explains Peter Scheiffele, another group leader who has been at the Biozentrum since 2008. Scheiffele studies cellular and molecular mechanisms that control the development of neural networks in the brain. While this may sound like quintessential basic research, Scheiffele and his team actually ended up doing applied autism research as a result of this approach. This is how it came about: Scheiffele was doing research on Neuroligin-3, a gene involved in the formation of synapses. Mutations in this gene result in defective synapses, and have been observed in people with autism.

Neuroligin-3 is just one of around 300 genes that can trigger autism, however. For some time, Scheiffele has been working with partners in clinical practice and the pharma industry to develop drugs able to suppress some of the effects of the genetic defects associated with autism spectrum disorder. "It's a great feeling when our research produces something useful," Scheiffele explains. He sees it as a way of "giving something back."

History – technology

In the service of research

New discoveries and technological progress are two sides of the same coin. Increasingly powerful microscopes allow researchers to peer into the microcosm and examine anything from cells and proteins to individual atoms. The field of bioinformatics finds hidden connections in vast troves of data.

Electron beam meets molecule of life

Text:
Benedikt Vogel

No other method has proved as valuable to the Biozentrum's efforts to understand the building blocks of life as electron microscopy. In its early years, the technology delivered groundbreaking insights into viruses. Today, it is used to examine biomacromolecules at atomic resolution.

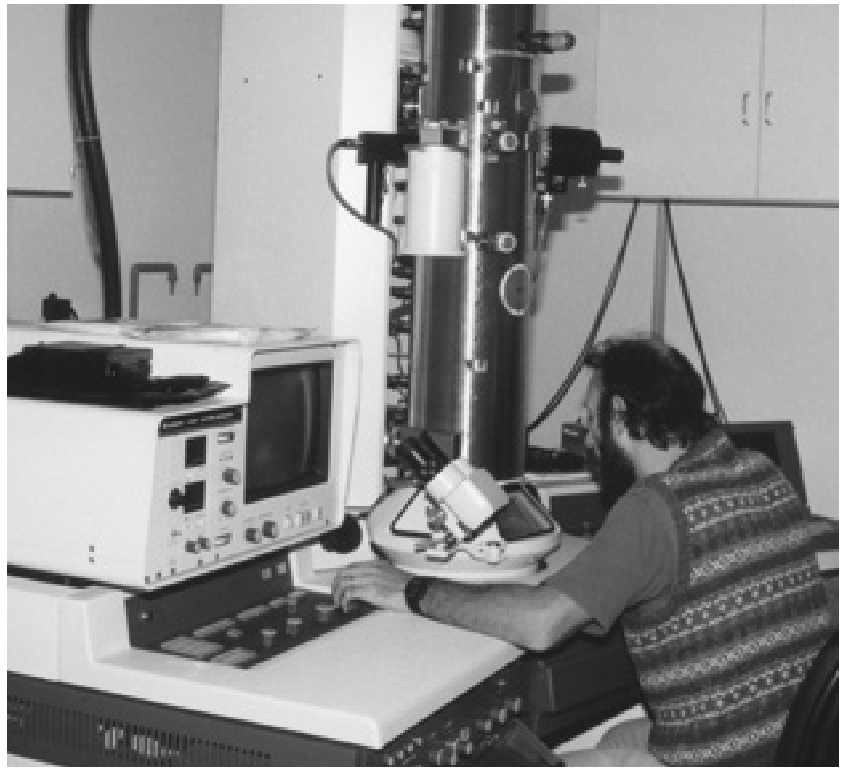
When Professor Eduard Kellenberger set about establishing the Biozentrum in Basel in 1971, his expertise in biophysics was not all that he brought with him from his former place of work in Geneva – just as important was his knowledge of electron microscopy. The electron microscope (EM) works in a similar way to the optical microscope, but delivers a significantly higher resolution by using electrons rather than light waves. Kellenberger relied on the EM primarily to investigate the structure of bacteriophages – viruses that infect bacteria.

In the 1970s and 1980s, the main variant in use was the transmission electron microscope. Professor Werner Arber used this device to study bacteria infected with viruses, paving the way for the groundbreaking discovery of the restriction enzyme. Electron microscopy underwent constant refinements at the Biozentrum. A key focus was the preparation of biological samples, which presented particular challenges for electron microscopy – in which the electrons move in a vacuum – in view of their high water content.

Not all researchers shared Kellenberger's passion for electron microscopy. Nevertheless, in retrospect the technique can be regarded as the methodological centerpiece of a 50-year success story. An enduring boost came in 1986 with the establishment of the Maurice E. Müller Institute for High-Resolution Electron Microscopy. "For us, electron microscopy was not just another service, but a cutting-edge technology for top-level research," explains the Institute's former director, Professor Ueli Aebi, who used the technique for structural analysis of the cytoskeleton, among other applications.

Working alongside Aebi, Professor Andreas Engel developed a novel EM designed to determine the mass of biomacromolecules and their supramolecular complexes. The device, known as a STEM, combines elements of the transmission electron microscope (TEM) and the scanning electron microscope (SEM), which uses a thin electron beam to scan the sample. Today, it is the research group led by Professor Jan Pieter Abrahams that is pursuing further developments in the field of microscopy by merging different technologies. "Research projects in cellular and molecular biology have become so complex nowadays that the only way to succeed is to use a combination of complementary methods," explains Ueli Aebi.

The latest innovation in the field of transmission electron microscopy is cryo-TEM, a technique that has become the gold standard of the life sciences. Using this technology, biomacromolecules can be observed at the nanometer scale – in other words, at near-atomic resolution. The cryo-TEM was created by combining three technological innovations: first, three-dimensional image reconstruction employing images of the sample captured from different angles; second, the use of an innovative electron camera, and finally the use of cryogenics to shock-freeze samples to a temperature of around minus 200°C. Special cooling technology freezes the water in the samples into a vitreous state, avoiding the formation of ice crystals. This allows the samples to be studied in their natural state. The foundations for this cooling technology were laid by Jacques Dubochet in the 1980s after completing his doctorate at the Biozentrum. In 2017, he and two other co-creators of cryo-TEM were awarded the Nobel Prize in Chemistry.



“A gift suddenly fell at my feet”

Interview with Professor em. Jacques Dubochet, 2017
Nobel laureate in Chemistry: Benedikt Vogel

Professor Dubochet, you came to the Biozentrum in 1971 with your doctoral supervisor Eduard Kellenberger. What was the mood like here?
Dubochet — There was a wonderful, extraordinarily dynamic atmosphere! We – the electron microscopy group – used a row of theater seats to set up a small café at the end of the corridor. This was a kind of heart of the Biozentrum, and a hive of social activity.

In 1978 you moved to the European Molecular Biology Laboratory (EMBL) in Heidelberg, where you developed cryo-electron microscopy. This earned you the Nobel Prize in Chemistry in 2017. How did that happen?
Dubochet — My instrument of choice to understand life processes was electron microscopy. A key challenge was preparing the samples. Rapidly cooling them in a hydrated state led to vast improvements.

This idea came to you while you were still at the Biozentrum. How important was your time in Basel for your Nobel Prize?
Dubochet — Are you familiar with the concept of serendipity? It means finding something without searching for it. In Basel there were not many people who were highly skilled in my field of research. In Heidelberg, a new world opened up for me. Thanks to serendipity, chance, bam! – a tremendous gift suddenly fell at my feet.

What nuclear spin can tell us

Text:
Benedikt Vogel

Nuclear magnetic resonance (NMR) spectroscopy is one of the most important analytical methods in structural biology today. It works by measuring the resonance of nuclear spin. With this technology, molecules can be examined in their original form in an aqueous solution at room temperature – at atomic resolution.

NMR spectroscopy at the Biozentrum Basel was established from 1999 onward by the structural biologist Professor Stephan Grzesiek, building in part on groundwork laid by the biophysicist Professor Joachim Seelig. With the help of this technique, Stephan Grzesiek was able to describe how certain receptors in the cell membrane (GPCRs) transmit signals to the interior of the cell. This was a major breakthrough, as numerous pharmaceutical agents bind to cells via GPCRs. A second NMR expert, Professor Sebastian Hiller, came to the Biozentrum in 2011 after completing a doctorate at ETH Zurich under the guidance of the Swiss Nobel laureate Kurt Wüthrich. Hiller used NMR spectroscopy to study the membrane protein VDAC, which is linked to cancer and the autoimmune disease amyotrophic lateral sclerosis. In 2019, he used the same method to demonstrate the importance of the membrane protein BamA for the effectiveness of two new classes of antibiotics (Darobactin and OMPTA).

In the last decade, NMR spectroscopy has evolved considerably. Aside from the structure of molecules, it is increasingly able to provide information on their dynamics, interactions and functionality. An example of this are chaperones, which support the folding of proteins inside cells. In 2013, Sebastian Hiller’s research group was able to image a chaperone with its bound client protein at atomic resolution for the first time ever. It emerged that the client protein is highly dynamic; rather than binding to the chaperone like a conventional protein complex, it is kept in a fluidic state by the chaperone. The researchers also demonstrated that chaperones can take over the functions of other chaperones. Another study in early 2020 shed light on how chaperones interact with alpha-synuclein, a protein associated with the onset of Parkinson’s disease.

“A virtually endless domain”

Interview with Professor Sebastian Hiller: Benedikt Vogel

Professor Hiller, magnetic resonance imaging (MRI) is an invaluable tool in medical diagnostics. Is it correct to say that your method of examining biomolecules – NMR spectroscopy – operates on the same principles?
Hiller — We do indeed work with the same principles as MRI. In both cases, what we are measuring is the resonance of nuclear spins that occur when certain atomic nuclei are placed in a magnetic field and excited by means of radio frequency pulses. MRI uses this phenomenon to examine a particular region of the body, while we use it to study the characteristics of proteins. Our samples have a volume of around half a milliliter. This is far less than with MRI; however, we work with a much higher resolution. By measuring the distance between individual nuclear spins in the sample and processing the measurement data accordingly, we can understand the relationship between the atomic components of a molecule, and how the molecules function.

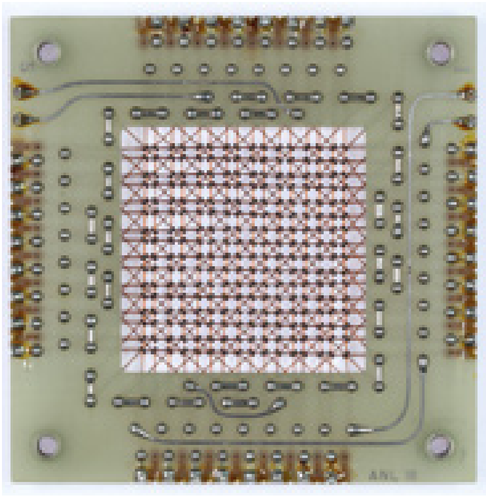
Does NMR spectroscopy work for any given protein?
Hiller — There are around 25,000 different proteins in the human body. A huge number of them can in principle be studied using NMR spectroscopy. Then there are numerous other organisms such as bacteria, plants and fungi with proteins of their own. In other words, it allows us to study a virtually endless domain of biological topics. This variety is truly fascinating, besides harboring enormous potential for advances in medicine.

In spring 2021, the Biozentrum began operating an 800 MHz NMR spectrometer, and next year an even more powerful 1,200 MHz device will go online at the University of Zurich. What impact do you anticipate that these two instruments will have on top-level research?
Hiller — We’re delighted to have had the opportunity to team up with the University of Zurich and ETH Zurich to form the Swiss Ultra-high-Field Solution NMR Facility, which operates these spectrometers. Devices in this performance range are beyond the financial scope of individual universities. This instrument will give us the fantastic opportunity to study molecules that are not currently accessible to us due to their size. In Basel we operate five spectrometers with high and medium field strengths, offering basic measurements to researchers across Switzerland. These are complemented by individual high-precision measurements performed with the ultrahigh-field device in Zurich. In this way, the two sites complement each other perfectly.

Bioinformatics – life sciences in the dry lab

Text: Benedikt Vogel

Exactly 30 years after it came into being, the Biozentrum added a new methodological string to its bow in the form of a dry lab: With the appointment of Professor Torsten Schwede in 2001, bioinformatics was established as a new field at the University of Basel. In his previous job in the pharmaceutical industry, Schwede – who trained as a chemist and structural biologist – had modelled protein structures, and was accustomed to using information technology in the service of molecular biology research. “At the Biozentrum, bioinformatics was not meant to be an end in itself – from the beginning, our aim was to use it to answer questions in the life sciences,” Schwede explains.



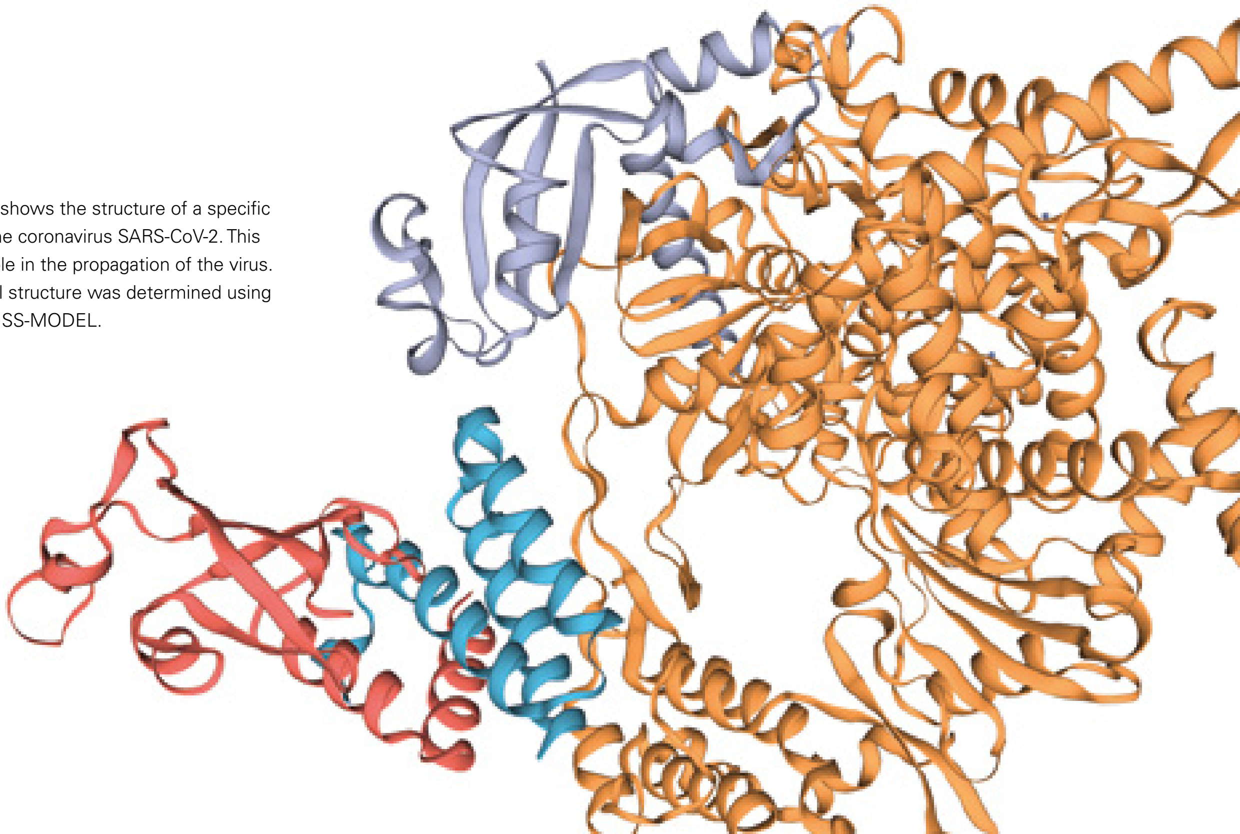
Understanding the function of proteins within a cell in molecular detail involves determining their three-dimensional molecular structure. This is achieved by experimental methods such as X-ray crystallography, NMR spectroscopy and, more recently, cryogenic electron microscopy. With the sequencing of the human genome, as well as that of many other organisms, the number of known protein sequences increased dramatically – much faster than the corresponding 3D structures could be experimentally determined. This raised the question of the extent to which the 3D structures of these new proteins could be predicted using computational methods. The most reliable method to this end is known as homology modeling, which involves large databases of amino acid sequences and experimental 3D structures. Based on the experimental structures of evolutionarily related proteins, a 3D model is generated for the new protein.

As these computer models deliver results much faster than experimental methods, researchers often use them to speed up their experiments. Structural modeling helps them to formulate hypotheses about the molecular basis of diseases, simulate how new pharmaceutical agents bind to target molecules, or plan selective modifications of proteins. As with all computer-assisted predictions, however, a key question concerns the reliability of the models. This question can be answered by means of systematic comparisons between the predictions and experimental structures. The CASP (Critical Assessment of Structure Prediction) experiment set a global standard for the development of benchmarks in numerous other research areas.

Automating methods for the prediction of protein structures is an important prerequisite for determining the reliability of the models and enabling the application of these methods by researchers in a broad range of disciplines. Over the last two decades, Biozentrum researchers have continually worked to improve the algorithms. "In the early days, our algorithms were only able to predict the structure of individual protein fragments with around 50 percent accuracy, whereas today the technique works for complexes consisting of multiple proteins," says Schwede. Building on groundwork completed in the 1990s, he and his team refined the SWISS-MODEL web platform. With the support of the Swiss Institute of Bioinformatics (SIB) and the State Secretariat for Education, Research and Innovation, the Biozentrum offers access to the platform to researchers from all over the world. It is now used by around half a million scientists to determine the structure of proteins. Every minute, two to three queries are answered in a fully automated process. Over the years, the results have made their way into some 20,000 scientific publications.

Operating such a service, with users all over the world, requires professional-grade supercomputers. The "[BC]2 Basel Computational Biology Center" set up for this purpose was available to all Biozentrum researchers, and helped new bioinformatics research groups become established in Basel. Since the merger with the cluster of the university's computing center in 2014, sciCORE – a center of competence for scientific computing – has provided computing power, software and consulting for all of the University of Basel.

Scientific techniques to leverage large volumes of data in the life sciences have made great strides in recent years, thanks in no small measure to the contribution of the bioinformatics research groups led by Professor Mihaela Zavolan, Professor Erik van Nimwegen and Professor Richard Neher. With a newly-created "Center for Data Analytics", the University of Basel supports researchers in the use of machine learning methods. "Today, deep learning algorithms are able to predict protein structures with an accuracy that we could not have dreamed of in the last 50 years. A minor revolution is unfolding," says Torsten Schwede.



This computer model shows the structure of a specific RNA polymerase of the coronavirus SARS-CoV-2. This enzyme plays a key role in the propagation of the virus. The three-dimensional structure was determined using the web platform SWISS-MODEL.

“For 50 years, we have been training top scientists and laying the foundation for future careers.”

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pp. 2, 13, 27–31, 36–38 Martin Friedli
p. 9 Erich Meyer, Luftaufnahmen
pp. 14–15 Daisuke Hirabayashi
pp. 17, 24, 51, 112 Nano Imaging Lab, SNI
pp. 18–21 Biozentrum and Nano Imaging Lab, SNI
p. 33 picture Silvia Arber, pp. 94–96 Matthew Lee
pp. 56–57 Annette Roulier
p. 71 Markus Dürrenberger

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