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N°19

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Just a few years after its inception, the Institute of Molecular and Clinical Ophthalmology Basel (IOB) is on the cusp of a medical revolution.

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Translating scientific insights into therapies

Dear Readers,

Two major developments in the eye-care sector had converged in 2017 when we decided to set up the Institute of Molecular and Clinical Ophthalmology Basel (IOB): First, technological and scientific advances made it possible to gain a deeper understanding of the genesis of many eye diseases and work on new treatments. Second, Basel had the academic, personnel and industrial infrastructure to close the gap between basic and clinical research, which had been growing apart over the years given the absence of convincing medical breakthroughs.

The University of Basel, the University Hospital Basel, and Novartis took the opportunity to create an institute which would bridge this gap. The goal was to increase the touch points between scientists and clinicians and take advantage of the recent breakthroughs in genetic research and organoid science. Combined, these developments provided the basis for much-needed new insights in the ophthalmology space that had lagged the innovation power of other scientific fields.

The venture has proved a success so far. The IOB not only made rapid progress in its research and clinical efforts. The institute also carved out a leading position within the scientific community, becoming one of the pre-eminent translational research centers in the world. Since its foundation, the IOB has attracted more than 140 scientists from over 30 countries, won almost 80 awards and has increased its publication output from 13 papers in 2018 to over 500 in 2023.

More importantly, its research strategy of focusing on disease areas that lend themselves to the development of new treatments has proven the right way to go. Not even seven years after launching its activities from a small office in Basel with a few people, the IOB has already spun out one of its first key research projects in the realm of cone optogenetics, which will be pursued further by RhyGaze AG and has received fresh funding from venture capital companies. Other projects may follow suit in a similar or different form – but all with the view to developing efficient treatments for patients with impaired vision or vision loss.

There is a major need for this work. According to the World Health Organization, more than 2 billion people worldwide have a near or distance vision impairment, triggering annual global costs of more than 400 billion US dollars. According to a survey published in the *International Journal of Ophthalmology,* doctors cited wide-spread eye conditions such as dry age-related macular degeneration, wet age-related

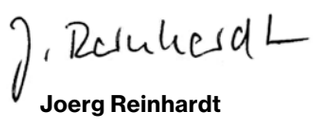
macular degeneration, glaucoma, diabetic macular edema, and dry eye among the biggest immediate medical needs.

But there are many other diseases for which the medical community has found no answer to date. Many of these conditions lead to blindness, signifying a devastating verdict for the patients and their families. And although some rare, hereditary forms of blindness can be treated today with the help of novel gene therapies, the field has only made its first, very humble steps. The scientific community will need to up its efforts forcibly to develop innovative treatments that can make a visible difference for patients.

The IOB has what it takes to make an impact. Currently, more than seven groups at IOB are working on an array of research projects that include novel approaches to tackle myopia, Stargardt disease, retinal dystrophy, and Usher syndrome, to name but a few. At the same time, the IOB is also working hard to develop new technologies that can help accelerate the development of new treatments. Among others, it has worked on state-of-the-art organoid, protein engineering and virus platforms, which are crucial to gain a deeper understanding of disease mechanisms.

The speed at which the IOB is working reflects the dedication of its scientists and clinicians, a diverse team of high-caliber researchers ranging from computer scientists and optical engineers to clinical experts who have daily contact with patients and their immediate needs. It is this combination that makes the IOB stand out within the ophthalmology field, which is receiving important impulses from the efforts undertaken here in Basel's Klybeck quarter – once the headquarter of Novartis predecessor Ciba.

Looking ahead, I am convinced that the IOB will create substantial value over time, not only in the realm of ophthalmology. It will also benefit the Basel research community and Switzerland in general. Much like the foundation of the Friedrich Miescher Institute in 1970, when Novartis predecessor companies Ciba and Geigy combined their forces with the University of Basel to build what is today one of the foremost research institutes in Europe, the IOB will contribute to the country's leading research position and uncover insights that can be translated into novel treatments.



Joerg Reinhardt
Chair of the Board of Directors of Novartis (until March 2025)

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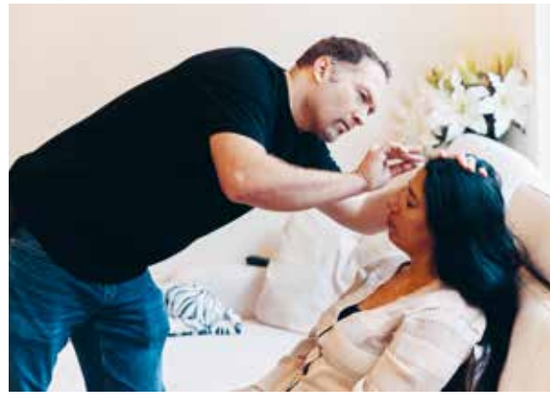

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The cover image shows an artificial human retina from the IOB platform of Magdalena Renner. The image was produced by Martin Oeggerli for *live* magazine.

“The ultimate metric of success is that we change people’s lives”

Interview with Botond Roska, Director of the Institute of Molecular and Clinical Ophthalmology Basel (IOB), and former IOB Co-Director Charles Gubser. The interview was conducted by **Goran Mijuk,** photos by **Laurids Jensen.**

It was already a few minutes past 10 a.m. in the morning. We were waiting for Charles Gubser to join us shortly, when Botond Roska received a message that he would be delayed for another few minutes as he was still on a call to nail down some details on an important transaction that had kept him busy for the last few weeks.

The deal in question, which led to another 20-minute break in our interview later that morning, was a key achievement for the Institute of Molecular and Clinical Ophthalmology Basel (IOB). It revolved around the transfer of an optogenetic project to a new company, RhyGaze AG, that would continue the work to develop a novel treatment for a hereditary form of blindness.

The closure of the agreement, which was only a few weeks away, not only reflected the fast-paced approach of the IOB, which had been founded some six years earlier. It also showed how it could leverage its research efforts to generate funds and translate some of its key research insights into breakthrough therapies.

In a nutshell, the deal exemplifies the vision that inspired Novartis, the University of Basel, and the University Hospital Basel to join forces in 2017 to create the IOB. The hope was that by combining basic research with the work done at the Eye Clinic, the IOB would be able to develop new ophthalmologic treatments and overcome what was a dearth of new eye-care treatment options at the time.

"I have high expectations for this new scientific center. Uniting our expertise in ophthalmologic research and clinical development and using new technologies such as gene therapy, I am sure the Institute of Molecular and Clinical Ophthalmology will change the practice of medicine and help patients around the world improve vision and quality of life," former Novartis Chairman Joerg Reinhardt, who was among the key drivers to create the institute, said at the time.

That the IOB would generate palpable results so fast was a positive surprise for all involved. At the beginning, the institute was no more than just an idea supported by a handful of people who had the courage to pave the way for a research and development center that could help ophthalmology out of its crisis mode.

Much of the initial hope was resting on the work of Director Botond Roska, a former group leader at the Friedrich Miescher Institute in Basel, who had published several seminal papers that dived deep into retina research and looked at the opportunity to treat eye diseases with emerging gene technologies.

While his research opened a new avenue to treat some severe eye conditions, several breakthrough developments were needed to help turn some of his basic research ideas into reality. One was the development of gene therapies per se, which hit an impasse around the millennium. Another one was the realization that eye disease research relied too heavily on animal models, which gave researchers the wrong clues.

All of this changed several years back with the advent of more efficient gene technologies, the emergence of organoid research and the further advance of eye research. "Innovation in ophthalmology has been a great challenge, partly because our understanding of the eye on the molecular and cellular level has been slow to emerge," said former Co-Director Charles Gubser.

"One area that needed advancement was formulating an understanding of how the retina picks up information, computes it, and sends it to the brain. This is something where Botond and only a few other scientists have really delved in and been able to understand, and then manipulate how that system really works," Gubser added.

For Roska, besides the basic science insights, other key developments included the realization that animal eye models were not sufficient. "People started to recognize, both in industry and in basic science, that translation from mouse models to human is very difficult," Roska said. "And most of the diseases, especially the common diseases, are not represented in a mouse, because a mouse is lacking the most important structure in our retina, the fovea or macula, which is important for vision."

As these strands converged, the time was ripe to create an institute such as the IOB that brings clinical and basic research together, said Roska. Also, he added, that with the inclusion of Charles Gubser, who joined from Novartis, where, among

others, he had been working in the global drug development unit, the IOB gained the translational skills needed to work towards new therapies.

Hence, for Gubser, while the basic research efforts at the IOB are important, the institute needs to stay focused on its research efforts to create outcomes that can benefit patients. "One aspect is to acknowledge that academic publishing is an important driver and metric of success at the IOB. But the real ultimate metric of success is that we change people's lives. To do that, it takes a more intense focus on optimization and the creation of insights that can be translated into medicines," he said.

Mr. Roska, was the creation of the IOB a dream come true for you?

The genesis of the IOB was based on a notable gap in ophthalmology. While the eye is uniquely accessible for treatments and diagnostics, there was a striking lack of therapeutic options compared to the wealth of anatomical and cellular knowledge we had. This disparity between knowledge and treatment effectiveness drove us to establish the IOB, aiming to harness this untapped potential to develop real solutions. For me personally, as I was already active in the field for more than two decades, it was a dream come true.

Mr. Gubser, which other factors were important?

Advances on the molecular and cellular level made it possible to finally do predictive science and work on projects that can be potentially translated into therapies. On the other hand, what stands out with the IOB is the ability to work collaboratively between clinicians and molecular-level researchers. From a funding perspective, it was the right moment in time to invest in ophthalmology innovation through the IOB. And maybe what we'll see from that is a real change in the way we approach the science of the eye, clinical practice in the eye, and then hopefully the therapeutic approaches.

Did it take courage on the part of the founders?

I believe that, from the point of view of the founders, which includes Novartis, the University of Basel, and the University Hospital Basel, it looked like all the advances in the ophthalmic space constituted a turning point, which prompted them to take the risk and create the institute. But it still took courage to do it since there was no guarantee that it would work.

Mr. Roska, in terms of research you have made strong advances in rare disease areas. Where do you go from here?

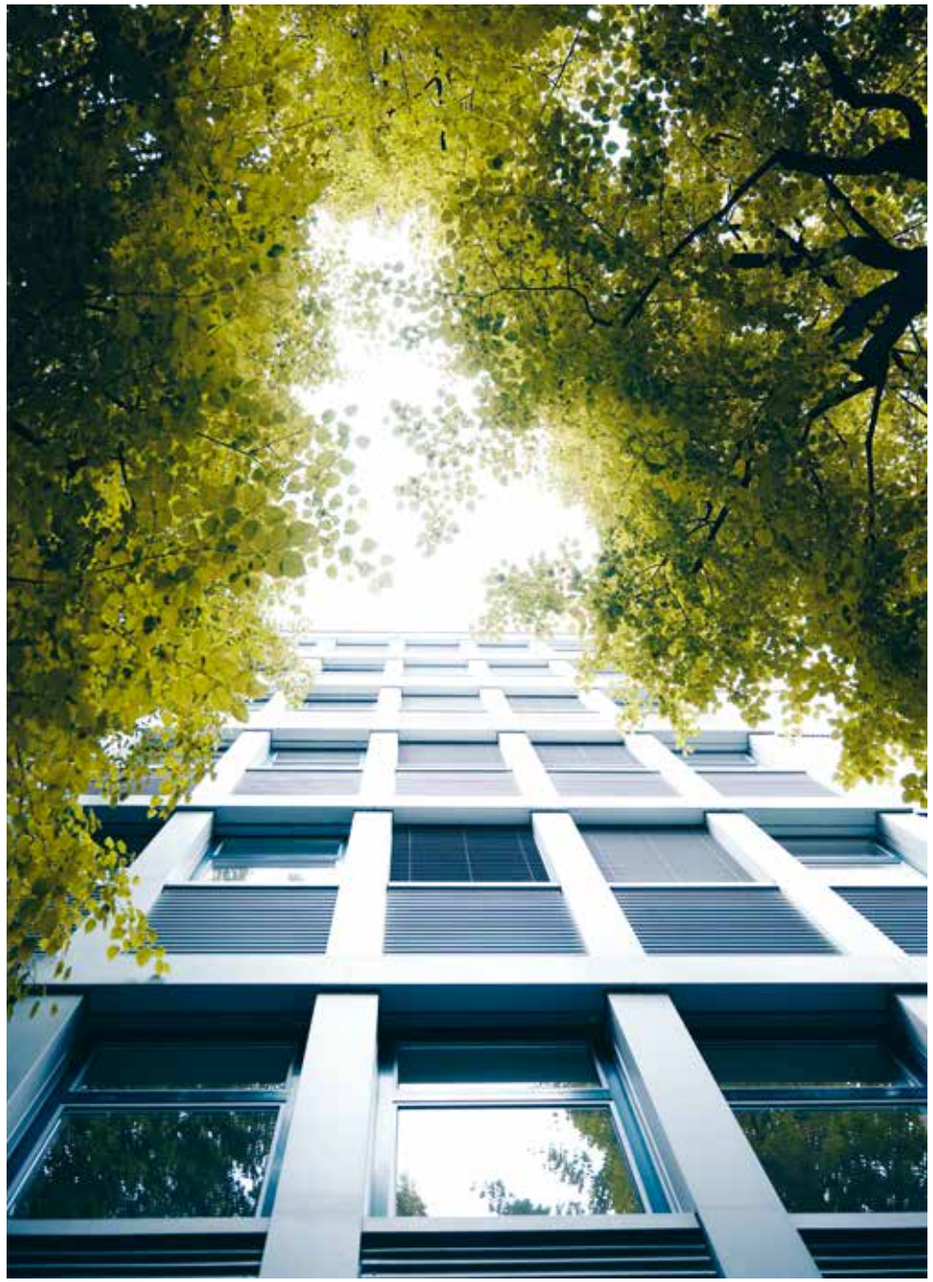
I think from the point of view of science, the initial focus on rare diseases made sense, since we had animal and human models of disease and we could work out gene-dependent and independent therapy approaches. But, of course, we also want to work in larger indications such as myopia – in fact there is no larger need than myopia. Going forward, the molecular mechanism and treatment for myopia will be a major theme for the IOB, and our goal is to approach it from different angles to slow myopia progression.

What were some of the other lessons learned after the first six years of the IOB?

I believe in the beginning we were very much determined to work on the basic science and make advances there. But we certainly had some challenges in how to translate our findings into potential medicines. With the engagement of Charles Gubser and scientists such as Bence György, the IOB was able to attract the translational skills needed and to start to develop an expertise in translation. Compared to the work of a basic scientist, who is led sometimes purely by his personal curiosity, and the work in the clinic, which is focused on care, the translational skill is something that we needed to develop.

Mr. Gubser, can you talk a little bit about this translational mindset and the skills that are needed?

In a nutshell, it boils down to understanding, on a quantitative level, how a potential therapy and its mechanism works. In the most advanced program we have, in the optogenetic approach to vision restoration, one of the central efforts has been to gain a clear understanding of the whole chain of events that makes up a therapy. Without that quantification,



Some green can even be found in Klybeck, a former industrial site.

it's very difficult to tell if what you're doing is just a gimmick or luck, or something that has the potential to translate.

What does this mean for basic science?
Without excellent basic science, you cannot do good translation. So, if you don't understand the system in depth, you won't really be able to manipulate it reliably. And, having said this, much of that basic science depends on the premise that we work with the right models, not exclusively with animal models as in the past, but with human tissue as well as with organoids. Here, the IOB has also made massive progress. Furthermore, the collaboration with our colleagues from the clinic is and will be crucial going forward.

Mr. Roska, do you agree with this observation?
Very much so. First, the collaboration with the clinic really makes the IOB unique in the ophthalmology space. Also, in terms of quantitative skill, we are making inroads. To just give you one example: One of our group leaders is a professor of theoretical physics, who came to us for the very idea that our approach is so data-driven and that we want to generate a meticulous understanding of the processes we are researching.

Is this also reflected in your Ph.D. program?
Yes. A strong focus of our Ph.D. program is on this quantitative approach. For example, it's obligatory for the students to take courses in programming and statistics and various other subjects that lend themselves to developing these specific skills.

Mr. Gubser, with the focus on driving quantitative research with a strong bias on data-driven skills, how important is skill diversity at the IOB?
I think the diversity of scientific backgrounds at the IOB is unusual. We have physicists, mathematicians, biologists, chemists, people who can build microscopes, people who can manipulate biological systems. This is very diverse. But it's deliberately composed to support a range of different efforts, all focused on the eye. Also, the cultural diversity is high. We have colleagues from Kazakhstan, Portugal, the United States, and Brazil and many more. Their backgrounds and interests are extremely diverse, and this is generally a good thing, because people are brought together by what they really want to do, which is doing great science.

Mr. Roska, given this diversity, could the IOB have its headquarters elsewhere?
The genesis of the IOB is closely linked to Basel. Not many other places in the world had the know-how, the courage, and the financial means to create such an institute. But then, Switzerland has many other advantages too. It's a very open place from a cultural point of view. It has a strong scientific community, and it has a funding system that allows researchers to work on top-notch science. All of this makes Switzerland and Basel a very strong place.

Mr. Gubser, can you also talk about funding?
Fundraising is always a challenge in the academic world. We have been very privileged to have strong support from our founders. That support was time-limited when we initially created the IOB. And I'm optimistic that we'll be able to raise the next round of funding from the same founders, and possibly some other participants, to carry the IOB forward. But, of course, it will also depend on our work – but here I am optimistic given our success with the cone optogenetic project.

With the transfer of your optogenetic assets you have found a way to not only translate scientific insights into a potential therapy, but also secure future funding. How do you plan to proceed from here?
We're open to different approaches. But fundraising for an asset that will go beyond the boundaries of the IOB, and potentially become a medicine, that too is challenging. And you know, it takes work, effort, and explanation. So, I think we will do some of that work. But we are open in terms of what the right model is. In the instance of our cone optogenetics efforts we have been able to secure venture funding. The next transactions might look different.

A sweet spot between academia and industry

When Director Botond Roska asked Bence György to join the Institute of Molecular and Clinical Ophthalmology Basel (IOB) in 2018, it was a perfect match for both. György was looking for a scientific and medical challenge and Roska had a research project he wanted to speed to the clinic. Fast forward six years and the IOB has its first gene therapy candidate. György explains the feat with the institute's ideal position between academia and industry.

Text by **Goran Mijuk,** photos by **Moritz Schermbach**

Bence György has few regrets about leaving Boston's big and busy academic world for the tranquility of Basel and the modest size of the Institute of Molecular and Clinical Ophthalmology Basel, which is located in a former Ciba-Geigy research building in an industrial city quarter on the banks of the river Rhine.

In fact, this is exactly what György was after. Equipped with a degree in medicine and molecular genetics from the Semmelweis University in Budapest, and post-doctoral stints at Harvard Medical School and the Massachusetts General Hospital, he was more than familiar with the world of academia, both its possibilities and its limits.

What he wanted was a place where he could leverage his expertise in gene therapy and work on research projects that could potentially be translated into therapies. He was looking for neither an ivory tower career in academia nor the frenzy of a biotech start-up, avenues he could have easily pursued in Boston.

"In the United States, the translation of technologies to therapies often occurs in small companies that lack economic freedom and rush experiments to satisfy investors," György said, when I met him at the IOB in late spring in 2024. "Academia, on the other hand, which is focused on basic principles and is under constant grant and publication pressures, is ill-suited for large, goal-oriented projects that exceed traditional academic scopes and budgets. I was looking for a third way."

Bence György

When Director Botond Roska asked him to join the IOB, the new route opened clearly before his eyes. “When I discussed my plans with Botond in Basel, he confirmed that the IOB, which offers academic freedom and is equipped for structured, goal-oriented translational programs, would be an ideal place,” György said.

Furthermore, he also appreciated that the institute, which was founded in 2017 by Novartis, the University of Basel, and the University Hospital Basel, was closely collaborating with clinicians. “In addition, the institute’s engagement with practitioners and patients was another important element in the translation efforts I was pursuing, which attracted me to Basel,” György said.

The right model

The first research project on which György embarked at the IOB was focused on optogenetics. It was a field in which Roska had made major inroads a decade earlier when he found that patients suffering from retinitis pigmentosa, a hereditary eye disease that affects the light-sensing retina and leads to blindness, could benefit from a gene therapy intervention – findings he had published in a paper in *Science*.

Roska’s research showed that by genetically altering cone photoreceptor cells to produce light-sensitive proteins he could restore vision in mice. While the results showed great promise in the early research phase, it was György’s task to develop a therapy that would work in humans. But he would soon find that the early research obtained in mice results would lead to a dead end.

What worked in mouse models, on which the initial research was based, did not work in humans. “The same constructs that worked very well in the mouse did not work at all in the human retina. In the first year, it was almost shocking because we didn’t get a single cell expressing what we wanted them to express,” György recalled.

While the mouse model served as a successful proof-of-concept demonstrating the potential of the approach in treating blindness, a series of other questions remained unanswered and required creative solutions.

First, it was unclear how to adapt the therapy for the human retina. Second, it was uncertain whether all blind patients could benefit from this therapy or if it would be suitable only for specific patient populations.

Optimization, optimization, optimization

In a first step, György started to work with human retina models as well as with retina organoids, retina-like structures that are produced through induced pluripotent stem cell technology from human skin cells – a technology the IOB was among the first to master in large scale. This strategic pivot was decisive to move on with the project.

But the task at hand was far from easy as György and his team had to redo most of the processes outlined in Roska’s original research paper from 2010, but now focusing on human systems.

Regarding the therapy, the team had to develop the entire process from scratch. This included testing gene regulatory elements such as the promoter, the control switch that turns on the activity of a specific gene, or the capsid, which refers to the protein shell of a virus that is used to deliver therapeutic genes into human cells. It was both a complex and exhausting effort, which György summed up as “optimization, optimization, optimization” to develop a potential therapy. “You can imagine how much iterative optimization there was until we got to a construct that worked robustly – and when I say robustly, I don’t mean for an academic publication, but for a clinical therapy.”

A big breakthrough came when György and his team not only replicated Roska’s original proof-of-concept in human retinas and in retinal organoids but also devised a novel method that allowed the functional assessment of optogenetic tools in human retinal explants. For this, they developed a bespoke, electrode-array system that would be able to recognize whether the optogenetic gene therapy had reactivated the electrical activity of human retina.

“We were able to establish a functional readout by recording from the ganglion cells,” György explained. In a nutshell, when the team stimulated the human retina with light, the ganglion cells, which are the bridging neurons that connect the retinal input to the visual processing centers, showed activation, much like they would do in a normal eye. “This, for us, was the breakthrough.”

Clinic expertise

But this was not the end. To make the therapy as efficient as possible, György also decided early on to start with patient stratification, adding Lucas Janeschitz-Kriegl, an ophthalmologist and Ph.D. student, to the team, who joined from the Eye Clinic of the University Hospital Basel to help them find out which patients would benefit most from the therapy.

For this, the team gathered eye scans and functional data from blind patients around the world, including centers such as Budapest, Miami, and London, making it one of the largest cross-sectional studies in the world. The team, Janeschitz-Kriegl said, used artificial intelligence to analyze the data and determine the number of targetable cones in the retina.

The retina consists of two types of photoreceptors: rods and cones. The rods are responsible for vision in low-light level conditions, while cones are being used for high-resolution color vision. The light-sensitive part of these photoreceptors is the so-called outer segment, a part of the cells, which functions like an antenna. The outer segment contains the critical proteins to detect light.

In inherited retinal disease as well as in age-related macular degeneration, rod photoreceptors degenerate. As a result, in certain patients, cone photoreceptors lose their outer segments, but the cone cell bodies do not degenerate. In other words, cones become “dormant.”

How frequently these dormant cones are present in blind patients has been completely unknown, but this is of critical importance when it comes to vision restoration therapies targeting these cells.

“As the therapy aims to restore vision in these dormant cone photoreceptors by delivering a light-sensing protein using a viral vector, we wanted to find the patients who possess targetable cones,” Janeschitz-Kriegl said. “To our surprise, it was found that two-thirds of blind patients still retained dormant, non-functional cone photoreceptors.”

This meant that the therapy would be helpful to a potentially large number of patients suffering from inherited retinal disease as well as age-related macular degeneration, increasing the chances for its potential successful application in the clinic.

This finding is crucial, as it may help the team avoid the pitfalls of other ophthalmic trials where strong proof-of-concepts failed to translate into meaningful patient out-

Lucas Janeschitz-Kriegl

comes. In those cases, the disease biology and the specific aspects of the disease that the therapy impacts were not studied in parallel, Janeschitz-Kriegl said.

For György, the clinical study was yet another key differentiator for the work conducted at the IOB and another sign that his decision to join the institute in Basel to make an impact in translational science was the right choice as the collaboration with the clinic made a big difference.

Thinking big

Thanks to the IOB's collaborative and skill-divers set-up, György and his colleagues traversed a big field and uncovered many firsts: They were the first to develop a vision restoration therapy directly in human systems and they were the first to determine the fraction of blind patients with targetable cone photoreceptor cells.

"We had the ability to investigate this therapy from every angle," György said. "This is also because we put a lot of focus on teamwork. So, instead of being fragmented to independent projects, which is typical academia, we focused strongly on collaboration between the various expert fields and especially between the clinic and the lab," he said.

For Janeschitz-Kriegl this teamwork is likely to create palpable results in future. "Although ophthalmology has made great inroads in terms of diagnostics and the understanding of the eye, we still lack major breakthroughs for many eye diseases. Sometimes, as a clinician, you can't offer much to patients."

The collaborative approach could change this. "The IOB can make further progress because clinicians understand patient needs and our researchers have the insight to work on innovative gene therapies," Janeschitz-Kriegl said. "Once the human trials can start, it could bring a benefit to many patients."

The early breakthroughs bode well for the entire field, which is in dire need of new medicines. Worldwide, more than 2 billion people are suffering from some sort of vision impairment. The number of blind people is estimated to stand at around 43 million people, and this is forecast to increase to 61 million by 2050.

Among other areas, the IOB, under the leadership of György, is working on a gene therapy project focused on Stargardt disease, a rare genetic eye disease that occurs when fatty material builds up on the macula. Since the disease is caused by a single faulty gene, György and his team are working on a base-editing approach that could correct the mutant gene sequence in question.

Currently, Janeschitz-Kriegl explained, doctors, for example, try to treat Stargardt disease by reducing vitamin A influx to the eye. "The IOB and Bence, together with his team, are working on a gene therapy to correct the faulty genetic code. This would be a welcome alternative and it would be the most optimal solution," he said.

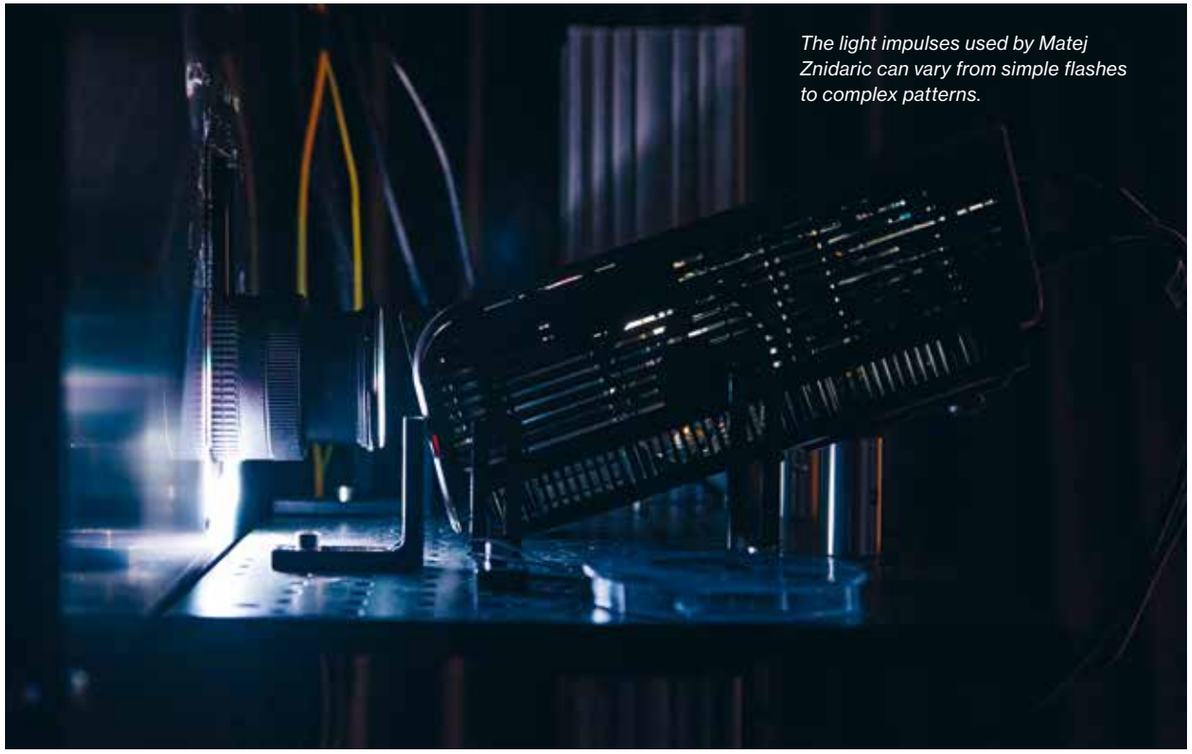
Six years down the road at the IOB, Bence György is far from exhausted, and he doesn't long to go back to Boston's academic circles or join a biotech. The IOB, for him, is a sweet stop that brings the best of two worlds together and could help potentially millions of patients receive new treatment options.

"The main aim of the IOB is to solve problems, whether it be understanding why a disease is being caused or developing a therapy for it," György said. "For this, we need brilliant people and to give them a big goal. That is what sets IOB apart and what is set to drive its future trajectory."

In the searchlight

Matej Znidaric works closely with Bence György in establishing one of the first optogenetic therapy models for the treatment of retinitis pigmentosa, an eye disease that affects cone photoreceptor cells and can lead to blindness.

Text by **Goran Mijuk,** photos by **Laurids Jensen**



The light impulses used by Matej Znidaric can vary from simple flashes to complex patterns.

When Matej Znidaric is working with retina samples and exposing them to light impulses in the IOB physiology lab, he does this in almost complete darkness. Only a red light provides him with guidance.

Znidaric works both with human and animal retina samples. He receives human eye samples from partner hospitals in Budapest and Basel.

A trained physiologist and biologist, he prepares the tissue samples by cutting the retina into tiny pieces before measuring the behavior of genetically altered cone photoreceptor cells under artificial light conditions.

Before the measurements can start, the cone photoreceptors in the retina, which degenerate in certain diseases, are treated with special light-sensing proteins that are induced through a viral vector.

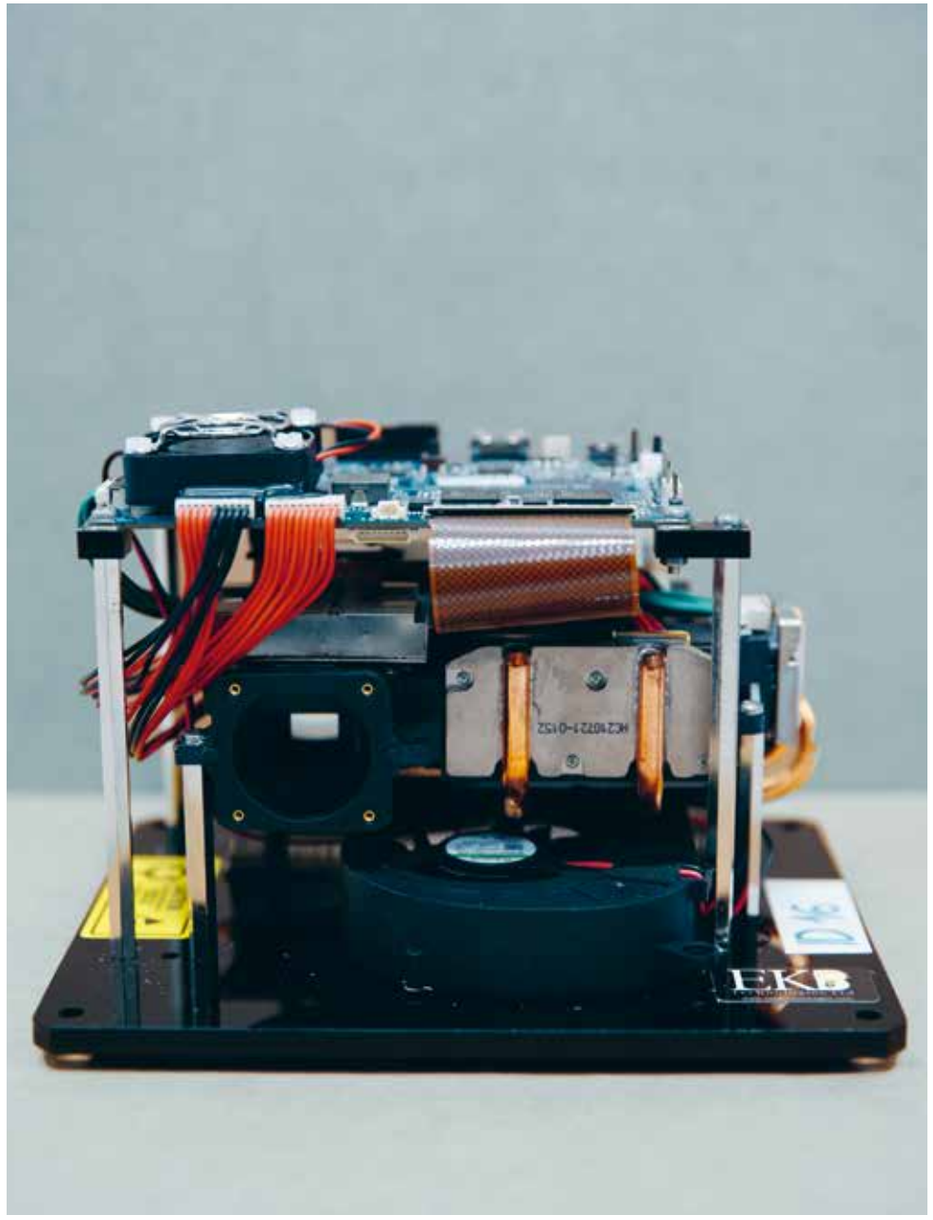
The light-sensing proteins, which take four to five weeks to express in tissue, can capture light and send these impulses to other retina cells. These cells then transfer the signals to ganglion cells, which connect the retina with the brain.

Znidaric uses highly specialized tools for his delicate sample preparation.

What for non-experts may look like a microscope because of the visible eyepieces is in fact a bespoke sensor apparatus that allows for extensive and exact cell behavior testing.

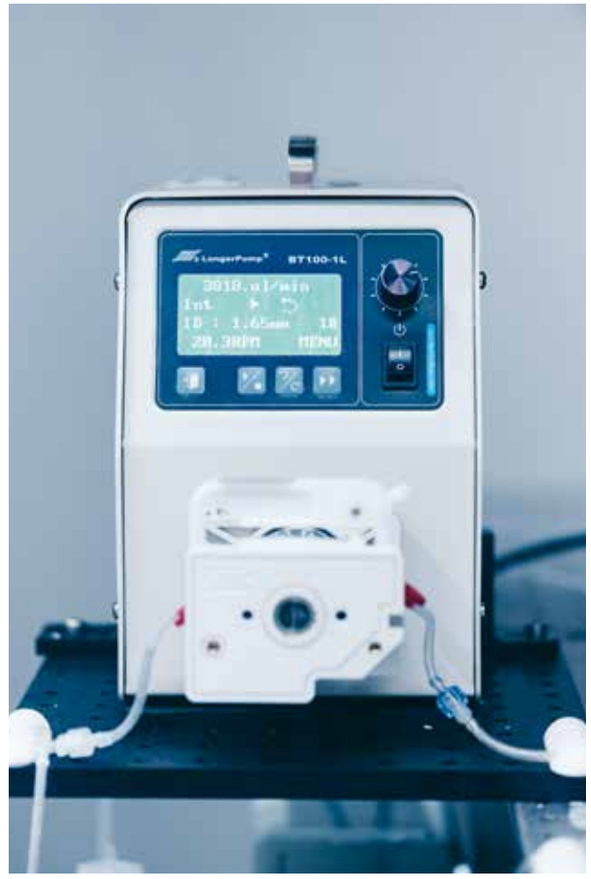
Znidaric has designed and assembled the apparatus himself, using devices such as chips and software from several third-party providers.

The front includes an array of instruments that help keep the sample tissues alive, register voltage changes, and connect these electric signals to a software.

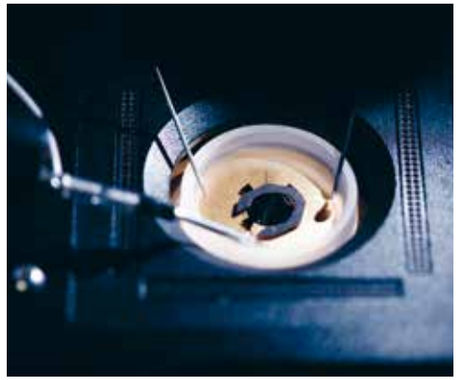


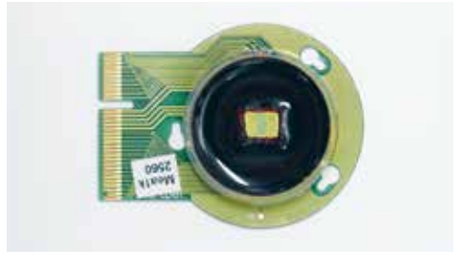
The light projector (shown in the picture is a new version that is currently not in use) is installed in the back of the apparatus.

To keep the samples alive while the experiment runs, the retina samples receive nutrients and oxygen.



The flow rate, with the outflow managed by a pump, is at a constant 4 to 5 milliliters per minute.

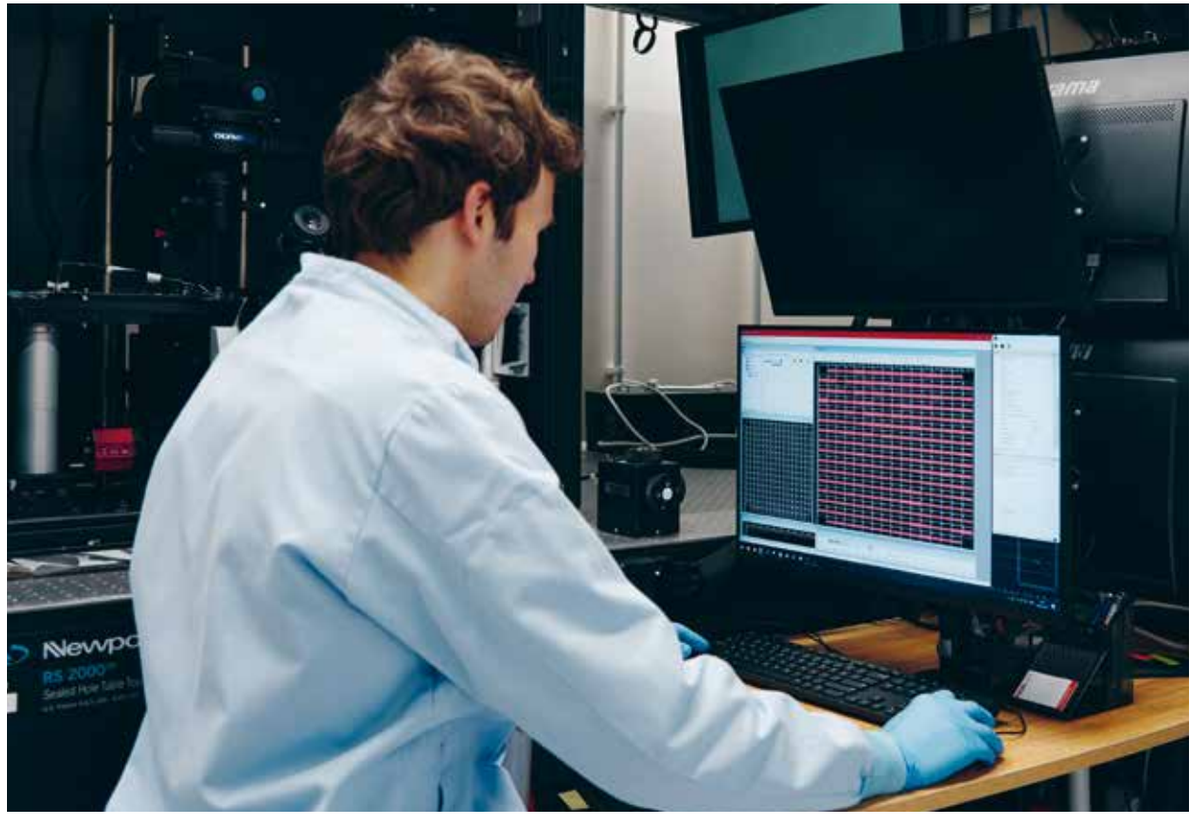




The pieces of a cut retina are stored in six-well culture plates, where they are attached to a thin membrane. The tissue samples are kept in these wells for four to six weeks, during which time their medium is regularly changed. Once Znidaric starts with the experiment, he takes the samples from the wells, detaches them from the membranes and transfers them to a chip. On the chip the samples get “covered” by a metal harp with thin wires to hold the tissue in place.

The microelectrode array constitutes the core of the apparatus. It is a sensor with electrodes. The array currently used by Znidaric (shown in the picture through the microscope under red light) is equipped with 16 x 16 electrodes, each spaced 100 micrometers apart. The IOB is also using arrays developed by the ETH (green chip), which has 25,000 electrodes.

For the measurement, the cone photoreceptor cells, which lie on top of the tissue, receive the light impulses directly. From there, the signal travels through a cascade of cells in the retina until it reaches the ganglion cells at the bottom of the tissue. As part of this process, the ganglion cells change their membrane potential, which results in a change of voltage registered by the electrodes. The electrodes then transmit the signal to the computer.



The setup of an experiment is complex and data-intensive. One computational line registers the light impulses, while the other identifies the electric transmission from the electrodes. Both lines need to be aligned in time to have a correct data read-out. The process needs to run with the maximum possible precision given that the time difference between the light impulses and the voltage changes in the ganglion membrane is counted in milliseconds. The amount of data coming from a single experiment can easily reach a terabyte.

The software registers the voltage change in the ganglion cells. The sensor fields of the chip are represented as a grid on the screen. Matej Znidaric needs to establish how many of the retina cells respond to light stimulation and what the response properties are. If the ganglion cells show a spiking behavior on the screen, it means that they are receiving impulses from the “rescued” photoreceptor cells and that the retina is once again able to process light. In a potential optogenetic therapy, this means that a person can have their vision restored. After the experiment, the retina samples are stained with a fluorescent protein to identify the cone photoreceptors. The team at the IOB also takes high-resolution images with the help of a spinning disk confocal microscope. L.

Fit for the future

In 2019, the Institute of Molecular and Clinical Ophthalmology Basel (IOB) moved into an old Ciba building, injecting fresh life into the Klybeck district, which was once the sprawling heart of Switzerland's heavy chemical industry. While the building might not have been a perfect fit from the start, it is fit for the future now, also thanks to Tamas Szikra.

Text by **Michael Mildner,** photos by **Laurids Jensen** and **Moritz Schermbach**

Once the welcome area during chemistry's hey-day, the visitor gate has since been ripped down.

The gate at Klybeckstrasse 141 in Basel, where hundreds of employees were greeted day in and day out by sometimes grumpy staff, has long been deserted; electronic access control has taken over their duties.

It is a sign of the times. Klybeck, where color dye production started in the 19th century and chemical and pharmaceutical companies reigned supreme during the last 100 years, is redefining itself after Novartis sold the area to city developers, who aim to attract start-ups and private residents to the place.

One of the recent arrivals to the quarter, next to artists, small manufacturers and biotechs, is the Institute of Molecular and Clinical Ophthalmology Basel, which moved into a seven-story building from the early 1970s.

Tamas Szikra, a neuroscientist, who has been an IOB associate since its foundation in 2017 when Botond Roska, a former researcher at the Friedrich Miescher Institute co-founded the organization, was instrumental in helping the IOB settle here some six years ago after the group had initially opened shop on the Novartis Campus.

The early days were full of excitement. “We packed a truck full of our laboratory equipment that we had bought from the FMI, and off we went from the Rosental site to the other side of the Rhine,” Szikra said recalling the first move to the Campus. “Soon after, we moved to Klybeck.”

Their new home became building WKL-420 – WKL stands for Werk Klybeck, or site Klybeck in English –, which originally served as a quality assurance facility for Ciba, including laboratories and archives. When Szikra first visited the building, he was struck by the huge paper archives in addition to the many chemistry laboratories. These were clear signs of a different era.

Setting the scene: Agile thinking

Neuroscientist Tamas Szikra was instrumental in getting the IOB up and running.

Hot days stuck in a lift

The move from the Novartis Campus to the Klybeck site took place in the middle of the pandemic. “The renovation of our new site began at the start of 2019, and the first employees were able to move into floors 3 to 6 in September of the same year,” Szikra said.

By that time, the IOB, which started off with only a handful of team members and co-director Botond Roska, already employed around 60 associates and intended to grow further. “We were very happy that we still had some space in reserve at the new location, which we were then able to expand floor by floor,” Szikra explained.

However, renovating the former chemistry and archive building to meet the high requirements for biosafety laboratories was challenging. “The ventilation and air conditioning in particular gave my team and me sleepless nights in the first few years,” Szikra said. The tension from that time can still be clearly heard in his voice.

The hot summers were a big challenge. “During the first two years after the move, I went to the institute every evening at 10 p.m. in the heatwaves of the summer to open all the windows and then put ice cubes in front of the fans. I was back again at 6 a.m. to close everything in the hope that these measures and the air conditioning system, which was still quite rudimentary at the time, would get us through the hot days,” he detailed.

After the ventilation and cooling systems were fixed, the team struggled with the elevators. “In the initial phase, we had visits from the company fire department practically every week, who had to rescue people from the elevator,” Szikra remembered as he walked me through the building. The elevator was so old that not even the manufacturer’s specialists knew how it could be repaired. After long negotiations with the new owner of the building, Swiss Life, a modern elevator was finally installed.”

Modern workplace

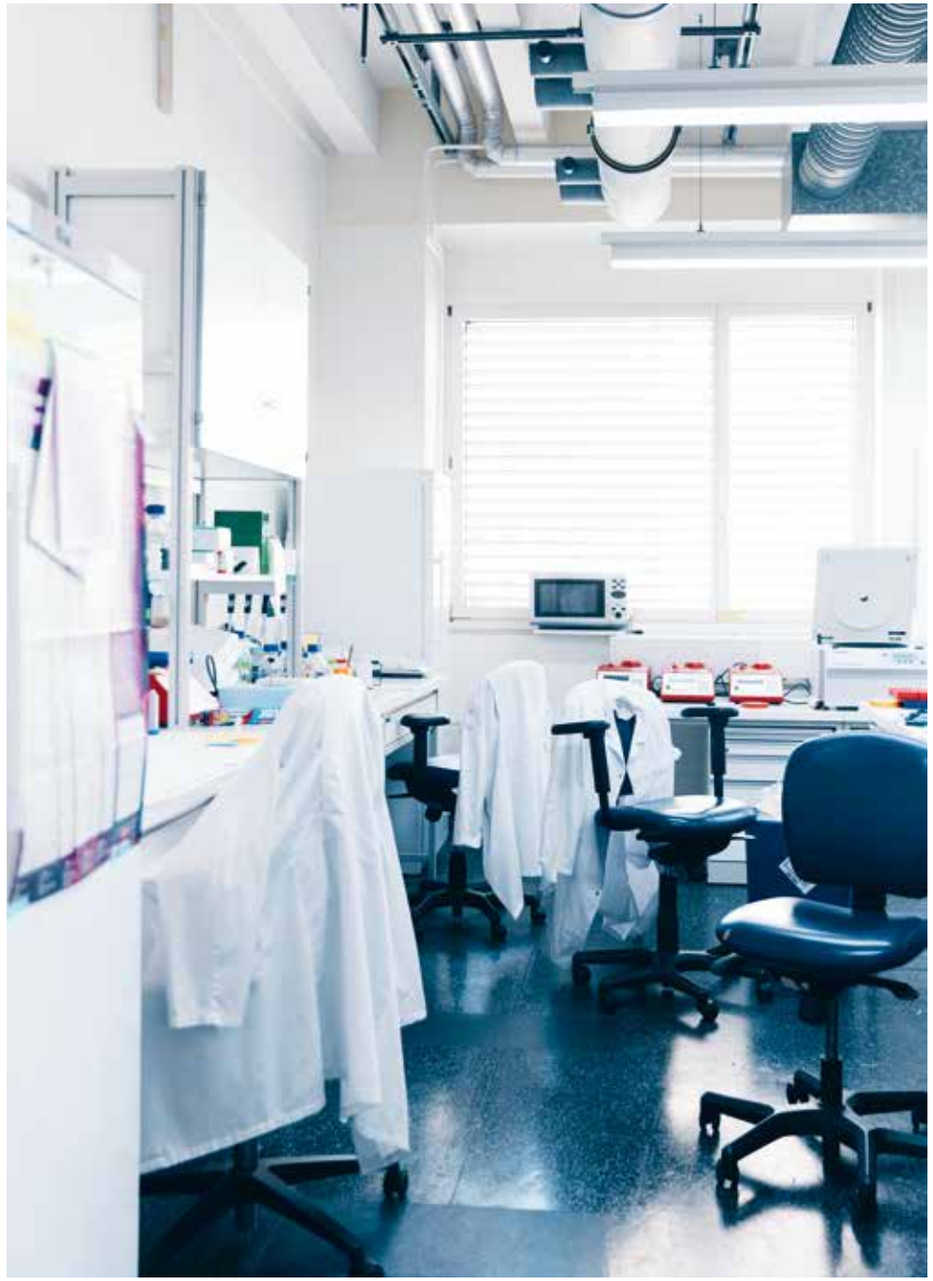
Such hectic days are long over. Today, associates can enjoy a wonderful vista over the city of Basel from the roof terrace on the seventh floor, which also includes a coffee area and meeting rooms. From there, Tamas Szikra led me through the building, floor by floor.

“On the sixth floor, there are workspaces for more than 60 people,” Szikra explained. “They were designed as an open space from the outset. Our employees move between the laboratories on the lower floors and the offices on this floor so that there is always enough space for everyone.”

On the lower floors, the IOB entertains a series of top-notch labs, including bespoke microscopes and analysis instruments that help scientists shed light on how the eye functions in health and in disease.

Only the second floor is not yet in use, serving as a kind of reserve for future growth. Here, the original Ciba vibe is still felt. “During the

On the second floor of the building, the IOB has some reserve space, which is currently still clogged with old stuff from the Ciba-Geigy days.



Lunch break.

Art on the wall.

conversion, we kept as much from the originally existing lab arrangement as possible to save costs," Szikra said, pointing to the cupboards and other furniture.

Not perfect, but purposeful

While the building is not perfect, Szikra is happy with how the IOB was able to repurpose K-420 and how researchers find what they need for their work. Some of them have even found niches that make them feel like they are in their home office.

"What we are particularly proud of is the opportunity to unite all competencies in one building in a small space: from molecular biology to cell biology, to electrophysiology, modeling and translational, and clinical aspects," Szikra said. "There are not many places in the world where clinicians and biologists, engineers and mathematical modelers work so closely together to develop new therapies for vision loss," he added.

For the city developers of Klybeck, which was the breeding ground for inventions such as Ferrari Red, Voltaren, Gleevec and Araldite, the addition of the IOB bodes well for the future of the district: Innovative spirits, now in biology, are still attracted to this place. L.

A moonshot that landed multiple breakthroughs

Aspiring to change the practice of ophthalmology is the thread that holds the Institute of Molecular and Clinical Ophthalmology Basel together. In one such effort, a small team of researchers worked on a moonshot program to tackle mitochondria-driven optic nerve diseases. Their findings could not only pave the way for the treatment of optic neuropathies, but also help create a new class of drugs to address neurological and other disorders that are associated with mitochondrial dysfunction.

Text by **Goran Mijuk,** photos by **Laurids Jensen** and **Moritz Schermbach**

Temurkhan Ayupov was stuck in Oxford during the early stages of the coronavirus pandemic, when he got a call from Botond Roska in April 2020 to discuss potential projects he could pursue as part of his doctoral thesis at the Institute of Molecular and Clinical Ophthalmology Basel (IOB).

"It was a typical call for Botond," said the energetic 26-year-old researcher from Kazakhstan. "He suggested several projects, among them some risky moonshots, as is almost normal for him, that I should start working on while in Oxford."

For one of the projects, Ayupov was tasked with developing new ways to tackle diseases triggered by dysfunctional mitochondria. Previous studies had revealed that mitochondrial impairment is involved in various eye diseases, such as glaucoma or inherited optic neuropathies.

"This led us to consider mitochondria as a primary target, aiming to develop a universal tool to protect retinal ganglion cells," Ayupov said. "From that point, we began focusing on screening different approaches to improve mitochondrial function."

For Ayupov, who had studied at universities in Helsinki, Zurich, and Oxford, where he finished his master's thesis, the project initially looked like a major career switch as he had previously worked in the plant biology space.

But the jump to which he was aspiring as he wished to move into human biology was not as big as it seemed. Before, Ayupov had mainly concentrated on chloroplasts – plant

Thinking out of the box pushed the IOB researchers to test new ways to work on mitochondria. While using standard equipment, their approach was unique in the sense that they aspired towards a bold goal.

cell organelles that are responsible for photosynthesis. Although different, they share some functional and structural similarity to mitochondria, which are responsible for energy diffusion in the cell.

"My first research projects focused on plant-pathogen interactions, and after that I worked on chloroplasts," Ayupov said, explaining that "both chloroplasts and mitochondria are considered symbiotic organelles that were once independent entities but became integral parts of the cell."

"One fascinating aspect of these organelles is that they have their own DNA, which makes chloroplasts and mitochondria unique. My early research focused on understanding how chloroplasts function and the mechanisms that regulate their quality control," he added.

Despite these similarities, the mitochondria IOB project, which became his Ph.D. thesis, was a real moonshot and anything but an easy ride, as the idea was to transplant healthy mitochondria to specific cell types of patients.

A viral idea

Previous studies, Ayupov explained, had shown that mitochondria can move naturally from one cell to another. For instance, it had been demonstrated that during ischemic injury, astrocytes, glial cells found in the brain, can secrete mitochondria.

"When we started our work, a few studies had already attempted to apply mitochondria to cells, but these had low efficacy and were not targeted to specific cell types," Ayupov said. "They reported some potential, suggesting it could improve mitochondrial function in those cells."

In human body, mitochondria are transferred through secretion, or via the formation of nanotubes, which create a bridge between cells, allowing them to transfer mitochondria.

Applying this principle, Ayupov isolated healthy mitochondria and injected them into eye samples. But not much would happen. "What we observed was a lack of targeting specificity and overall therapeutic inefficiency," Ayupov said.

Then, following a line of thought that Roska had developed earlier, he and Ayupov started to think about how viruses travel through the body, jumping from cell to cell by using specialized proteins that allow them to break through the membranes of cells and infuse the viral core into the cells.

"Our inspiration came from viruses and how they infect cells. Viruses interact with cell surface proteins, binding to them in a way that allows them to enter the cell. By modifying either the mitochondria or the target cell's surface proteins, we thought it might be possible to address these targeting inefficiencies," Ayupov explained.

Creating binders

The idea was to create specific binders that would help transport mitochondria to specific cells, breaking through the membrane and then releasing the healthy mitochondria to trigger a therapeutic effect.

"We already knew that we could alter the surface of target cell types, but it wasn't clear what the best therapeutic approach would be. Should we modify the surface of mitochondria, the target cells, or perhaps do nothing at all and instead use specific binders to engage different receptors? This led us to explore all three possibilities for manipulating mitochondria."

Simon Hansen

Breakthrough beats: Multiple targets

Temurkhan Ayupov

For this type of work, they needed a specialist, which they found in the person of Simon Hansen, who joined the IOB as Head of the Protein Engineering Platform, where he works with several teams on new therapeutic proteins.

Starting out in food science, Hansen said that he was drawn early in his career to fundamental research and that it was the "moonshot mentality" that attracted him to the IOB. "I've always worked on *in vitro* selections of engineered proteins, which is fast and cost-effective – fitting well in a fast-paced research environment like this. When I was hired, they needed someone with my background, and I felt it was a good match," said the 39-year-old researcher.

"Previously, I worked in industry, but I missed the innovative side of research – finding creative solutions and collaborating on out-of-the-box ideas. Here, I not only get to work on cutting-edge technology, but I also see it applied to meaningful projects, particularly in the field of ophthalmology," Hansen explained.

When starting his work, Hansen tinkered with several different approaches, but would soon use so-called nanobodies, which looked to be the most suitable type of binders for the goal they wanted to achieve.

In essence, nanobodies are small antibodies. In contrast to traditional antibodies, which are made up of two heavy and two light chains, nanobodies are composed of only a single heavy-chain variable region. Today, nanobodies are used for various therapies, the first drug having been approved back in 2019.

"These proteins are much smaller in size, which is an advantage because it makes them easier to work with," Hansen said. "Being a single protein domain also makes it simple to integrate them into systems."

System breakthrough

Once Hansen was on board in 2023, the research that Roska and Ayupov had been conducting for several years further accelerated. "Especially in the early stages of fundamental research, speed is crucial. Since we create many different proteins, each one needs to be cost-effective to work with," Hansen said.

The team, which also included Verónica Moreno-Juan and others, devised a new system that would allow them to transport healthy mitochondria to the cells they envisaged. Called MitoCatch, the system can deliver mitochondria to specific cell types using different types of protein binders, which either bind to the mitochondria, the target cell, or both.

By using MitoCatch, the team was able to show that donor mitochondria are efficiently transported, internalized, and undergo fusion and fission inside target cells. "This is really the breakthrough," said Botond Roska, who oversaw the project. "We were not the first who had the idea to transplant mitochondria," Roska added. "But our system is able, for the first time, to target specific cells and efficiently bring healthy mitochondria into the cells. This has potentially many applications across many different fields of medicine."

The three different approaches of mitochondria delivery not only allow the team to fine-tune the delivery efficacy of the healthy mitochondria. They also showed that the system works in the optical nerve cells and many other cell types. Furthermore, MitoCatch itself could be the basis for a new class of therapies.

"In terms of size and complexity, our approach bridges the gap between biologics and cell therapies by using cell organelles as therapeutic moiety," Hansen said. "As a novel class of treatment, there's significant potential here, especially given the clear link between mitochondrial dysfunction and various diseases."

Beyond the eye

The IOB is convinced that MitoCatch stands a chance to become a universal strategy to efficiently target disease-affected cell types with mitochondria in organs affected by diseases associated with mitochondrial dysfunction.

This would move the mitochondria field another step forward and could even prove to open a new avenue when it comes to the treatment of many elusive disorders which are believed to be partly triggered by mitochondrial dysfunction.

While the fundamental functioning of the mitochondria was established in the 20th century, recent advances in the field include mitochondrial replacement therapy, in which defective mitochondria is displaced. Other research is looking into the role of mitochondria in cancer, immune response, and metabolism.

The findings at the IOB could add to this roster. "There are two types of mitochondrial diseases. The primary type occurs when a protein involved in mitochondrial function is impaired, directly affecting the mitochondria and leading to cell death, like in retinal ganglion cells," Ayupov explained. "The secondary type happens when mitochondria become dysfunctional due to factors such as oxidative stress or disrupted quality control, without a direct genetic cause."

The repercussions could be most felt in the neurology space, since most common neurodegenerative diseases, such as Alzheimer's and Parkinson's, are linked to mitochondrial impairment. For instance, mutations in the Parkin gene, which is involved in degrading damaged mitochondria, lead to cell death. "Our therapy, which is aimed at improving ganglion cell function to help them survive during stress, could potentially benefit both primary and secondary mitochondrial diseases."

For Ayupov and his colleagues, the sky is the limit as they are intent on helping the millions of patients suffering from mitochondrial diseases. "There isn't a single approved therapy for primary mitochondrial diseases yet, although several are in clinical trials," Ayupov said. "People have tried to improve mitochondrial function and even to target mitochondria in cancer therapies to kill cells, but these approaches have led to severe side effects and haven't been very successful. We hope our approach can change that."

Before any such step can become possible, Ayupov and his colleagues have much more work to do to prove that the concept can be translated into a robust clinical process. This might be years away. But, nevertheless, their multiple breakthroughs – including a potential class of new drugs that could be used in optic nerve neuropathies and other disease areas – are most likely to create significant industry interest in the mitochondria space, potentially accelerating future development.

Dissecting the cellular mechanics of myopia

With the number of myopia diagnoses steeply rising worldwide, new medical treatments are urgently needed to correct nearsightedness in millions of patients. By studying the individual cell and gene pathways that appear to cause the condition, the IOB has carved out new targets that could give rise to innovative medicines.

Text by **K.E.D. Coan,** photos by **Laurids Jensen**

“We think that our findings will dramatically change the way the scientific community thinks about myopia,” says Tiago Rodrigues, an ophthalmologist who is pursuing a Ph.D. at the Institute of Molecular and Clinical Ophthalmology Basel, or the IOB.

Since its formation in 2018, one of the core missions of the IOB has been to better understand myopia and to use that knowledge to lay the groundwork for future therapies. Under the lead of Cameron Cowan, Head of the Scientific Computing Platform, and Botond Roska, Director of the IOB, Rodrigues and his colleagues have been working for the past few years on elucidating what is known as the myopia mystery, which is notable both for its steep rise in prevalence, as well as the fact that the reasons behind the condition are shrouded behind a seemingly complex veil.

Myopia is one of the most common eye diseases, affecting more than 30 percent of people worldwide. But despite its frequency, there are no effective treatments available that target the molecular and cellular changes that cause myopia – largely because the genesis of the disease is still poorly understood.

Over the last five decades, researchers have uncovered fundamental insights about how myopia can be induced or prevented in model organisms using lenses and other optical techniques. One of the most important discoveries from this research has been that visual processing within the eye drives the distorted growth of the eye in myopia.

Building on this accumulated experience, Rodrigues and Cowan are tackling this medical challenge from a fresh angle by using new technologies that study individual cell types and genes, providing a deeper molecular understanding of this phenomenon.

“Until our work, there have been many unanswered questions about which cells

and genes are involved," Cowan said. "To develop effective, targeted therapies, we need this basic mechanistic understanding – and this is the sort of research we specialize in at the IOB. We're hoping that this will serve as a resource for many decades of myopia research, as well as a foundation for building therapeutic strategies at the IOB and elsewhere."

Striking the vision of the young

A one-of-a-kind research center, the IOB is dedicated to exploring the mechanistic basis of a range of eye diseases by looking at the cellular circuits in the eye and brain and incorporating those insights into the preclinical development of new treatments. Beyond myopia, other eye diseases, particularly those associated with aging, are also on the rise. However, few have as broad a societal impact. This is because myopia frequently begins in infancy or childhood and goes on to diminish people's vision throughout their most productive years.

Myopia is commonly associated with factors of our modern environment, such as prolonged focus on nearby objects, like computers and phones, and time spent indoors. These conditions were further exacerbated during the COVID pandemic, accelerating the disease's prevalence and course. It is projected that myopia will affect 50 percent of the global population by 2050.

"Concerningly, approximately 10 percent of people with myopia will progress towards high myopia. In these patients, the excessive growth of the eye causes mechanical instability, which can lead to retinal tears, retinal detachment, optic nerve atrophy, and/or myopic macular degeneration," says Rodrigues. "So, a sizeable chunk of the population could be at risk of becoming blind because of myopia."

Environmental interventions are effective at reducing the risk of developing myopia, for example spending more time outdoors and less time performing near work (e.g., use of electronic devices and reading). But once myopia develops, it is difficult to reverse. Similarly, although glasses and contact lenses make it possible to correct vision changes, they do not slow further progression of the disease.

"To date, existing strategies have pursued empirical, environmental interventions, but there's no clear understanding of the biological mechanisms involved," says Cowan, who specializes in how the eye processes the visual information it communicates to the brain. Cowan has also previously led the development of an atlas of human retinal cell types.

"So, our first objective was to discover which cells and genes show changes during the onset and development of myopia," says Cowan.

Growing understanding

The many unanswered questions about myopia are not for a lack of effort on the part of researchers and clinicians around the world. But the eye is a complex organ, with over a hundred cell types, each a part of different biological circuits that serve specialized functions.

Although Rodrigues and Cowan began with the daunting task of looking for changes across all of these different cell types, they had two important clues that helped narrow their search. First, previous research showed that, upon detecting blurred images, the eye can compensate by growing so that objects are brought back into focus. In myopia, the feedback underlying this system goes haywire, and the eye keeps elongating uncontrollably. Typically, the more severe the myopia, the larger and more misshapen the eye, and the higher the risk of vision loss.

"It is truly phenomenal and unique – there is no other organ in the body in which

growth is regulated by a sensorial perception," says Rodrigues. "This understanding paved the way for the empirical approaches available today and also for our own work."

The second clue was the fact that this mechanism – the elongation of the eye in response to prolonged defocus – is conserved across a wide range of species. This meant that the team could refine their search by looking for gene and cell patterns that consistently appeared in different species.

With these clues in hand, the team set out on their ambitious, interdisciplinary project to discover the biological mechanisms behind myopia.

One cell at a time

All visual cues are received and processed by the cells at the back of the eye. So, Rodrigues and Cowan began their search by comprehensively measuring which of these cells showed changes during the process of excessive eye elongation and myopia development.

"We started with a baseline measurement of all the cell types in the back of the eye," says Cowan. "Then, by inducing the eye to undergo a myopic shift, we had a global view of what cell types and genes could be driving this response."

To do this, they collected samples of eye tissue from a variety of model species and separated the individual cells that composed these tissues. Once they had the isolated cells, they performed RNA sequencing one cell at a time to measure which genes were expressed normally and then also following defocus.

The rationale for looking at RNA changes rather than DNA stemmed from the knowledge that myopia is generally weakly associated with genetic (DNA-based) variations. Although DNA contains the genetic template for producing cellular components, like proteins, RNA levels show how much certain proteins are being produced at any given time, or if they are being produced at all.

"It made much more sense for us to look at the RNA level because, through regulation of RNA transcript levels of different genes, biological systems can respond very fast and dynamically to changes, whereas the DNA is more static," explains Rodrigues.

From this information, the team identified which cell types showed the biggest changes. They also identified which genes were specifically behind those changes. After this, they prioritized their findings based on the cell types and genes that showed consistent changes across all species that they had tested.

Sorting through all of these cells was meticulous and challenging work, but the team eventually identified a shortlist of cellular and genetic candidates, offering new mechanistic insights into myopia.

But the team still needed to confirm whether any of these candidates indeed caused myopia.

Confirming causation

"The single-cell studies showed that there were many changes in gene expression, but just because these were correlated with eye elongation didn't mean they proved causation, so we needed to validate which of these induced myopia," says Rodrigues. "And for this we needed to develop a model system closer to replicating what is happening in the human eye."

Some of the models closest to human biology are engineered miniature organs, called organoids. Typically less than a millimeter in size, these simplified organs are grown from human stem cells, making them the closest model for testing in humans, without the need for human volunteers.

Breakthrough beats: The end of short-sightedness

For their study, Cameron Cowan and Tiago Rodrigues often worked in laboratories in the United States, which had the necessary equipment.

Shredding the cells to pieces and analyzing the DNA was akin to a massive puzzle.

In this case, the team had to miniaturize the tissue involved in the downstream effects of the genetic and cellular changes that they were testing. The tissue in question, the sclera, forms the outer casing that surrounds the eye and controls the eye's shape during normal development, or abnormal development as in myopia. The sclera does this by changing its biomechanical characteristics, such as its stiffness or elasticity.

"No one had made scleral organoids before, so we were really starting from scratch," says Rodrigues. "In addition to the challenges of growing the organoids, we needed to design a way to measure scleral changes and we spent about three years developing and optimizing this model."

The solution was a method called nanoindentation, which uses a minuscule probe that lays gently against the scleral organoid. This probe presses on the organoid surface, causing small strains, which makes it possible to measure a variety of biomechanical properties. None of these characteristics are visible through imaging.

The team made the organoids by transforming human stem cells into sclera cells and then growing layers of this model tissue. Once the organoids were formed and ready for experiments, the next question was whether any of the team's prioritized gene and cell candidates indeed affected the biomechanical properties of the miniaturized sclera tissues.

"We know that the sclera's biomechanical properties change during the development of myopia and so these organoids helped us to confirm that several genes, and the proteins they encode, appear to trigger these changes and have a causal role in this disease," says Rodrigues.

"Although we're not at the stage of developing therapies yet, we expect that these sclera organoids will also be a useful model for testing molecules that might eventually lead to treatments in the future," adds Rodrigues.

A foundation for the future

"It's been a huge effort to accomplish what we've achieved, but the resulting datasets are extremely high quality and we think we'll be able to make strong conclusions from these findings," says Rodrigues.

The team has already tested a variety of predictions based on their initial findings and many of these experiments have successfully validated their hypotheses.

"So far, our results are already surprising and impactful," says Cowan.

Cowan and Rodrigues are quick to note that the unique setting of the IOB was instrumental in their ability to construct such a comprehensive dataset. Their team included specialists in optics, molecular biology, cell engineering technologies, single-cell genomics, computational models, and, of course, experts in myopia. They also credit the contributions of their collaborators at universities in New York and Texas.

"This research required many techniques and different types of expertise, and we are lucky that the IOB fosters an environment that brings this all together," says Rodrigues. "It was all of these different pieces coming together that made our work possible and this is a really uncommon setting, especially in the myopia field."

"We really hope that the new mechanistic insights from our research will accelerate progress towards better myopia treatments," he adds.

Magdalena Renner

A scientific suspicion and serendipity

Tasked with producing retinal organoids in high enough numbers to provide researchers with high-quality study samples, Magdalena Renner from the Institute of Molecular and Clinical Ophthalmology Basel (IOB) hit a wall early in the process. But once she questioned the reigning production protocol, she put the institute in a leadership position when it comes to organoid research and production.

Text by **Goran Mijuk,** photos by **Laurids Jensen**

Magdalena Renner was skeptical and frustrated. For months she had been trying to produce retinal organoids in high enough quantities that would eventually help spur the basic research efforts at the Institute of Molecular and Clinical Ophthalmology Basel (IOB). But things did not turn out as she had wished.

While she and her team were able to produce high-quality organoids that allowed scientists to study the function and disease genesis with the help of these artificial photoreceptor tissues, the number of organoids her lab could create reached a maximum of several dozen.

This, she knew, was too little to make a difference and support scientists in being less dependent on difficult-to-acquire human retinas, as well as mouse retinas, which are not perfect research organisms in ophthalmology because they differ in important physiological traits. Unlike human eyes, for example, mice have no fovea, which is responsible for sharp vision.

She needed to change something but was unsure what. Yet, she had a hunch, which would not only help boost production of these important research samples, but also unleash the IOB's ability to do basic research at scale. Together with her colleagues, she was also able to pave the way to start the first large compound screening with retina organoids.

Organoid pioneer

Renner was well acquainted with organoid research. She had already focused on this emerging field early on in her career when she joined the lab of Juergen Knoblich at the Institute of Molecular Biotechnology in Vienna, which paved the way in this domain by induced pluripotent stem cell technology in neurology more than a decade ago.

Among other things, she was a co-author of a seminal paper that detailed the development process of such minibrains in 2013. In parallel, while doing her Ph.D. in Austria's capital, she was also one of the first scientists to work on the question on how to use minibrains as disease models.

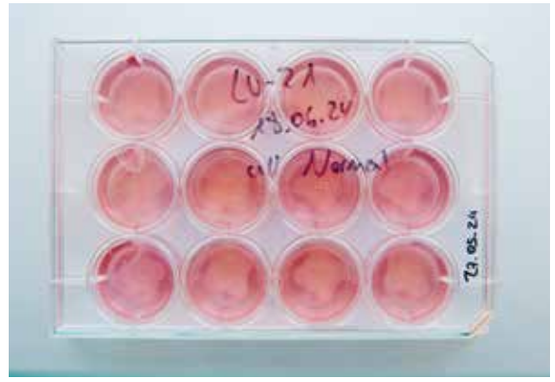
After her stint in Vienna, where she also worked with emerging gene technologies such as CRISPR/Cas9 that allows for precision gene manipulation, Renner joined Novartis and the Friedrich Miescher Institute. There, IOB co-founder and today's director Botond Roska asked her in 2017 to join the freshly founded IOB to work on retinal organoids – a little-explored field back then which needed to be set up from scratch.

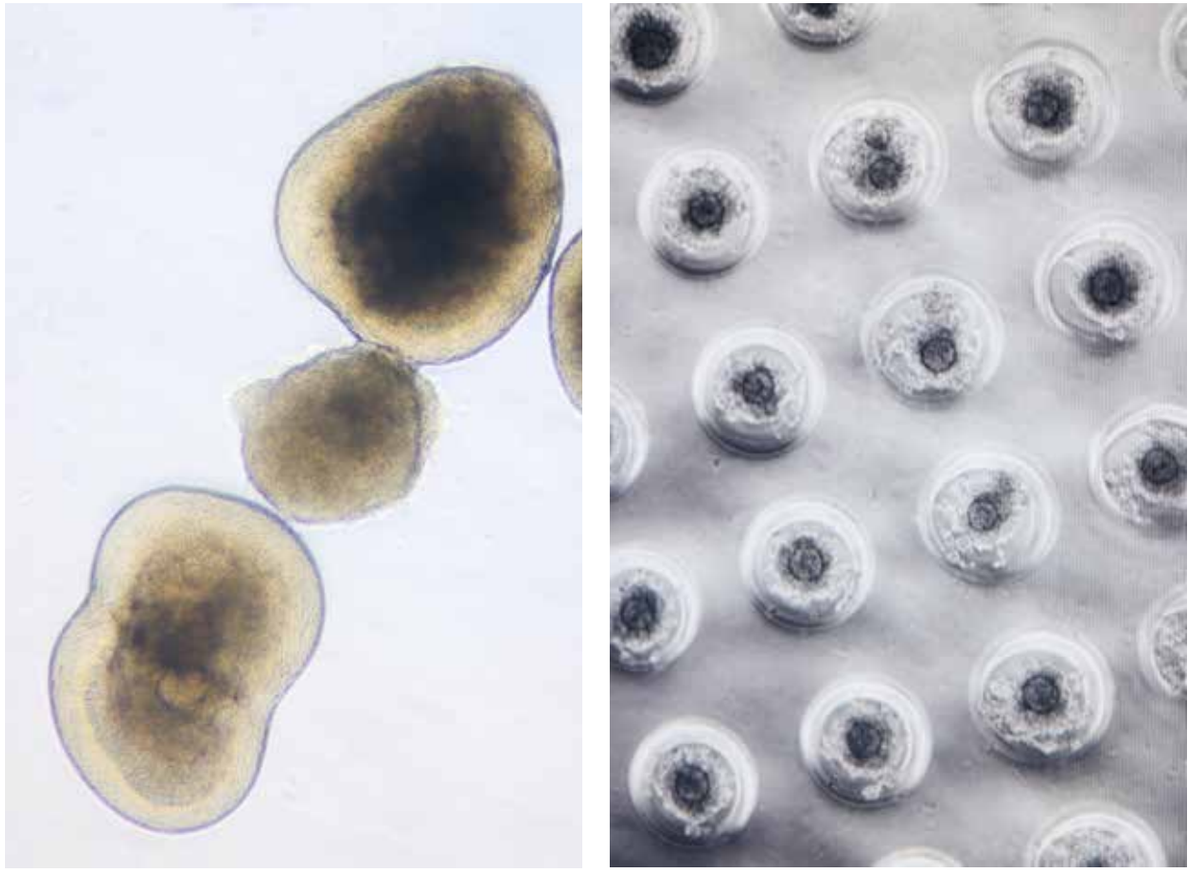
"The retina is part of the brain," Renner said. "So, for me, the switch from brain organoids to retinal organoids was not huge. There are many parallels in the protocols, and the challenges are similar."

Step by step

As part of the production process involving induced pluripotent stem cells, Renner would take human cells and revert them back into stem cells – a cell type that can develop into any other cell type of the body. From there, she would try to develop them into retina organoids. As part of this technology, skin or blood cells are reprogrammed into an embryonic-like state. During

Before Magdalena Renner started to scrape off artificial retinas, she and her team were only able to produce a dozen of retinas per trial. Today, her team is producing thousands, thus helping boost research.





Artificial retinas seen through the microscope.

this reversal process, the cells maintain a donor's genome. This allows researchers to later study either healthy or diseased organoids. They can also genetically design organoids with specific mutations to better understand a biological process or an aspect of a disease.

After the transformation into stem cells, Renner would initiate the growth process by putting the cells on small plates, add a cell culture medium and wait until the retinas became visible under the microscope – showing a horseshoe-like structure.

Renner would then use a needle to scoop them out of the plate and transfer them to another nutrient vessel, where they would form into full organoids. As was industry standard back then, Renner would only take those organoids out of the plate that fit the horseshoe shape and discard the others.

The net result of this process was that six months down the road, she and her team would only count a few retinas in the growth vessel. This was too little to make a big splash or even consider a compound screen to test a treatment or understand the genetic makeup of an organoid or cell type.

Following a hunch

"The process takes a very long time, which is frustrating," Renner said. While she was struggling to accelerate it, she was also questioning the established development protocol. "What made me suspicious was that there were no good criteria as to which organoids are fit for further processing," she explained.

One day, she decided, instead of painstakingly fishing out the horseshoe-shaped organoids, she would dissect all the organoids that were on the plate and transfer them to the nutrient vessel. "Instead of individually cutting off those structures from the cell culture dish, I took a pipette, drew a grid with it and scraped off all the cells on my dish, without worrying about what they looked like," Renner said.

The intuition to follow this route was not only due to the fact that she was not fully convinced by the established method as it lacked clear criteria beyond the organoids' form. She had in fact observed that when she was taking out the horseshoe organoids – a process that often took days – organoids on the plate would form where she did not expect it.

She took a leap of faith and decided to test a new procedure. "I was going to discard the plate anyway. So, in a sense, it cost me nothing to just scrape off everything and see what was there. To my astonishment, we suddenly went from 20 organoids to hundreds in almost no time."

The serendipitous moment took her by surprise. And while she concedes that much of the organoid development process remains in the dark and that even scientists marvel at the fact that induced pluripotent stem cells can develop into miniature organs, her luck was based on a scientific decision to test another route as the established one seemed ineffective.

The move not only paid high dividends. It also showed that the IOB, just shortly after its inception, lived up to its ambition to attract leading talents who were willing to transform ophthalmology and change the status quo.

A researcher analyzes virtual retinas. Their sheer number was deemed impossible just a few years back.

High quality

Meanwhile, the quality of the organoids Renner's team produced was also high. "We compared them to the human adult retinas. And the cells, especially cone photoreceptors, were amazingly similar," Renner said.

Although organoids are minuscule compared to real organs, in order to be efficient, they need to include the vital parts that are important to study. This helps scientists deepen their understanding of the underlying biology. Furthermore, they can also use the organoids to do genetic testing, which has improved rapidly since the advent of precision gene technology.

Induced pluripotent stem cell technology and CRISPR/Cas9 gene technology have been a boon for science, helping researchers reduce animal testing and stay off controversial stem cell research. Besides minibrains and minikidneys, scientists are working on a series of new types of organoids around the world.

For Renner, organoids have a huge capacity to spur scientific research if the quality of the organoids meets the necessary criteria. "In our organoids, there are five layers resembling those found in the adult human retina, including three nuclear layers where the retinal cell bodies reside, and two synaptic layers facilitating cell communication," Renner said.

Given the high quality and functional resemblance to the human retina, researchers now readily switch to organoids and have even embarked on large compound screens. One of the first such effort was a project led by Stefan Spirig from the IOB, who tested about 3,000 compounds with about 20,000 organoids from Renner's lab.

Other scientists at the IOB are following suit.

New horizons

For Renner and her colleagues, the work continues, as they are now focusing on new model organisms such at retinal pigment epithelium, an important cell type that the team is trying to grow in a very pure way. "These are crucial cell types for interaction and play an important role in disease. To have them as organoids is important."

The team has succeeded in developing a new protocol that allows the generation of such cells to be used in high-throughput screens, much like in the case of the retina organoids that have been used by Spirig.

The team has also developed a method to determine whether these cells can be used as a gene therapy prescreening tool to select the best candidates for validation in human explant cultures, which are difficult to obtain.

"We try many things in parallel," Renner said, "to develop model organisms that can help scientists reduce their dependency on both the human retina and the mouse retina. The overall goal is to build a better model of the eye and thus help researchers even more to advance our understanding of ophthalmology." L.

A side project with impact

Just a few years after its inception, the Institute of Molecular and Clinical Ophthalmology Basel managed to do its first large compound screen with self-developed retinal organoids, leading to fresh clues on how to tackle degenerative eye diseases and paving the way for potential treatments with either small molecules or gene therapies.

Text by **Goran Mijuk,** photos by **Adriano A. Biondo**

Stefan Spirig was behind the steering wheel, while a colleague of his was holding a vessel in his lap that held a rare and precious content: a couple of thousand retinal organoids that had been painstakingly prepared for months at the Institute of Molecular and Clinical Ophthalmology Basel.

Spirig had to transfer the material from the IOB headquarters in Klybeck to the Novartis Campus in Basel's St. Johann quarter to continue with his project, which entailed a large compound screen. He and one of his colleagues had to make the short trip several times since they had to transport a total of around 20,000 organoids.

Once on the Campus, Spirig would start to test the organoids against around 3,000 molecules from the Novartis compound library with the intention of establishing whether any of the therapeutic molecules had an impact on degenerated cone photoreceptors, which are often the cause of severe diseases such as macular degeneration or retinitis pigmentosa.

It was one of the first such screens at Novartis with 3D tissue samples, which have emerged as valuable alternatives to difficult-to-obtain human cells or animal samples, which often give researchers the wrong clues when they aim to work on human therapies later – a fact that has held up the field of ophthalmology for a long time.

The screen was a culmination of events that had started a few years earlier when Spirig was looking to pursue a gene therapy project for his Ph.D. after completing his studies in Zurich. He received an opportunity to work at the IOB, where Director Botond Roska assigned two projects to him.

"I was able to work on a gene therapy project right away, but Botond also assigned me to do a compound screen," Spirig said, adding that he was less interested in the screening project because it was initially not focused on gene technology.

"Both projects were risky and, a few months down the road, the gene technology project hit a dead end," Spirig said. "But as is often the case in science, the side project suddenly showed huge potential and I got extremely interested in working with organoids. As an extra, the project led to a gene therapy venture in the end."

Preparing the screen

Although Spirig had little acquaintance with organoids before he joined the IOB, he got quickly up to speed after collaborating with the lab of Magdalena Renner, who was not only an expert in the field but was the first scientist to generate retinal organoids in large numbers and whose method was instrumental to produce the 20,000 organoids needed for the screen.

While the retina development process is lengthy and complex, Renner's lab can produce thousands of them today. When she and her team started out a few years back, they usually could generate only a few dozen high-quality organoids.

When asked by Botond Roska how many they could prepare for a compound screen, Renner and Spirig calculated that 10,000 could work. Botond suggested doubling the amount. "This was so typical of him," Spirig and Renner said laughingly. "It's the ambition with which he wants to move things ahead."

After brainstorming with Roska, Spirig said that they decided to pursue a compound screen to test potential therapies for conditions that cause blindness due to cone photoreceptor degeneration and for which there are no therapies yet.

"Our goal was to develop a therapeutic intervention to slow or halt this kind of degeneration," Spirig said. "We envisioned a large-scale experiment using organoids to simulate cone photoreceptor degeneration – a condition mimicking age-related macular degeneration and retinitis pigmentosa, common causes of blindness."

By depriving them of glucose, which is the primary energy source for these organoids, Spirig was able to induce a state of starvation and observed rapid cell death, particularly in cone photoreceptors. "This model," he explained, "enabled us to test drugs that could potentially extend the survival of these crucial cells."

As part of the experiment, they would starve all the cone photoreceptors in the organoids, and later add the compounds to find out if some of the therapeutic molecules could prevent those cells from dying or prolong their life by as much as possible.

Collaboration with Novartis

At Virchow 16, where Novartis stores its massive compound library with more than 1 million potential therapeutic molecules and has automated high-throughput screening technology in place, Spirig's team started to prepare the test and worked together with colleagues from Novartis.

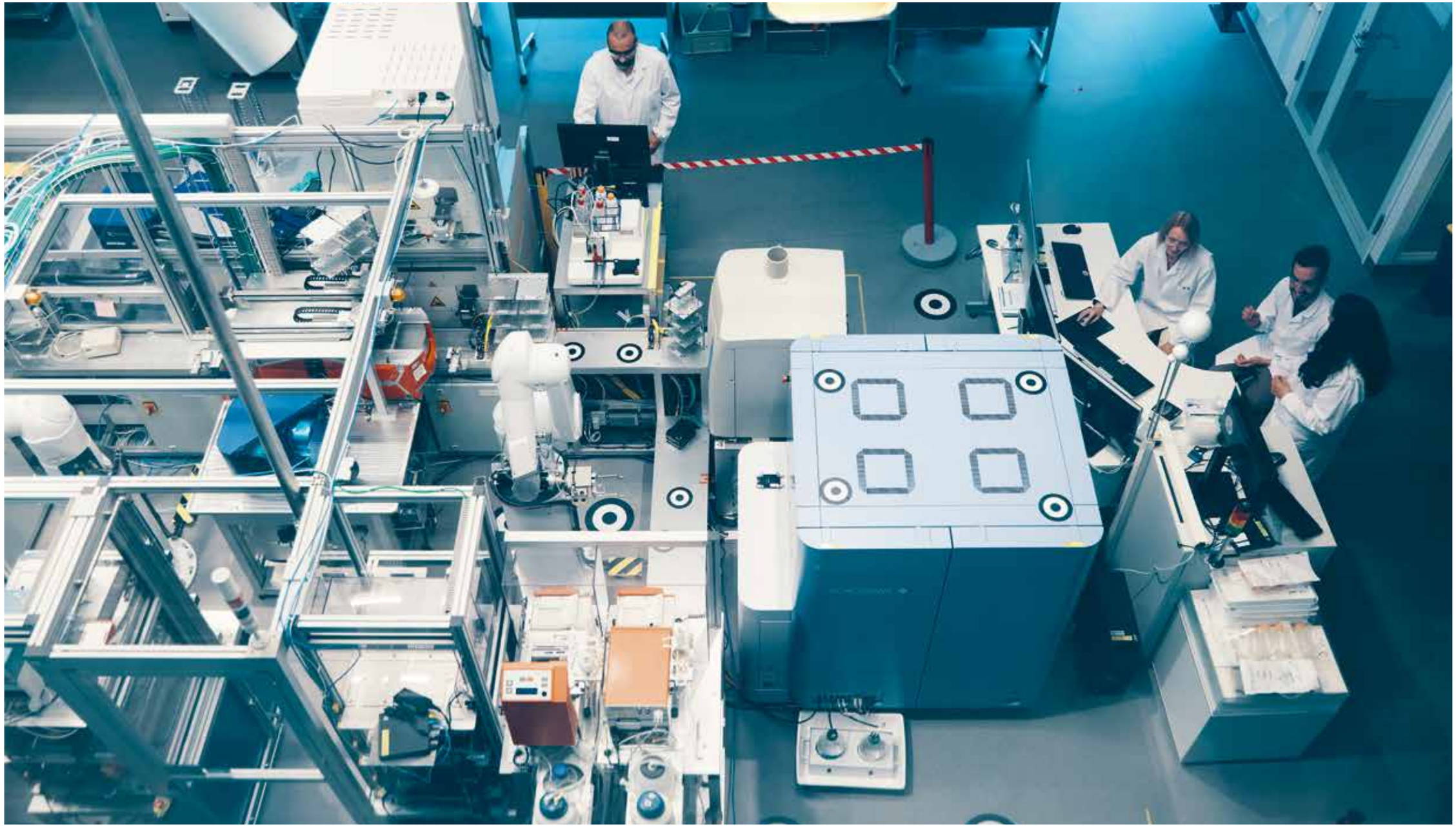
Using the equipment and molecule library at Virchow 16 was key. Although Spirig was able to prepare the experiment setup at the IOB, he needed the technological framework at Novartis to proceed with the screen and use the compounds.

Novartis researcher Daniel Baeschlin, who oversees the company's compound library and automated high-throughput screening, said that not only was the collaboration good, but he and his team were impressed by the setup of the screen and the energy of Spirig and his colleague.

"You could really feel how extremely motivated they were," Baeschlin said. "From our point of view, it was a very ambitious program and by far one of the most complex organoid screens that we had to perform here because it involved such a large number of artificial retinas."

Unlike in automated high-throughput screens in which compounds are tested against 2D cells, the team had to do a lot of manual work with their 3D organoids for which no fully automated system was in place yet.

Breakthrough beats: Collaboration writ large



Teamwork between the IOB and Novartis Biomedical Research was paramount for this project.

True milestones can only be achieved together.

"We started from scratch by creating a screening setup with well plates, each containing a single organoid exposed to different drugs. So, 20,000 organoids had to be put into these wells individually," Spirig said.

Once the organoids were prepared in the wells, the team added one of the 3,000 compounds in each well. "Novartis sometimes screens a million compounds in one go," Spirig said. "But for us that was impossible."

First, the team did not have as many samples. Second, because organoids are so variable, they had to test the same compound multiple times on multiple organoids. Adding the compounds also included partially automated steps. "Usually, I had to press some buttons," Spirig said.

Several hits

After starving and colorizing the cone photoreceptor organoids with a green fluorescent protein, the team took high-resolution images of the organoids with the help of a spinning disk confocal microscope that can take pictures fast.

A week later, they would add the compound and after that take another high-resolution picture to see whether the cone photoreceptors were degenerated or still intact. The whole process, which took around two years to develop, screen and evaluate all 20,000 organoids, led to several hits.

"I am very happy that we were able to identify several compounds," Spirig said. Two of the molecules were kinase inhibitors, which protected the cones from degeneration in both the short and the long term. Another group of molecules initially protected the cells, but later damaged them. Other inhibitors also showed interesting activity.

Through the project, Spirig's research has helped to create a large database, which the IOB will make accessible to researchers worldwide through the website https://conetargetedcompoundscreen.iob.ch/. It could one day form the basis for the development of new treatments that can slow down or even prevent the progression of diseases such as macular degeneration.

Gene therapy project

For Spirig, the journey meanwhile goes on. It is even coming full circle as the project is now evolving into a gene therapy venture, which he had been looking for since he joined the IOB more than five years ago.

As Spirig was working to identify the exact protein targets, he also took a closer look at the genes that are involved in the creation of these proteins, allowing him to understand the underlying genetic process that can cause cone photoreceptor degeneration.

"Now, as we know the genetic targets, we can start to look at gene therapies that can down-regulate these genes," Spirig said. "Thus, we can actually work on a potential gene therapy that prevents the degeneration of these cells."

While this leg of the research journey may also take a few years, the IOB has what it takes. Less than a decade after the institute was created, researchers here have already gained substantial new insights and have paved the way for an optogenetic gene therapy designed to treat a hereditary form of blindness and are working on a similar project to treat Stargardt disease, which affects the macula.

"It is really exciting, and while I may have been less interested in organoids at the beginning, I have to admit that I grew really fond of them, much like when I was on the lookout for a gene therapy project," Spirig said.

An opportunity to be seized

The founding of the Institute of Molecular and Clinical Ophthalmology Basel (IOB) in 2017 was a stroke of luck for the regional and national research hub. The institute's partnership model could also prove promising in other areas of medicine.

Essay by **Werner Kübler,**
Hospital Director and Chairman of the Hospital Management of the University Hospital Basel and former member of the Board of Trustees of the IOB

When we at the University Hospital Basel were approached by Novartis about seven years ago and were asked if we were interested in setting up a new research and development institute in the field of ophthalmology together with the University of Basel, my answer could only be yes. For successful research – today more than ever before – is driven by the interaction of different scientific fields.

This collaboration is vital in medicine. This is due not only to the rapid pace of technological development calling for more intensive interdisciplinary dialogue, but also to the fact that medical practice and research often operate in silos.

On the one hand there are hospitals, clinics, and medical practices that are primarily dedicated to the needs of patients, while on the other hand there are high-tech laboratories where scientists try to understand biological processes at the molecular level. An institutional hinge that connects the two worlds with their different focal lengths is usually lacking.

Filling this gap has been one of the mainstays of the IOB: not only conducting pure research but developing laboratory work in collaboration with experienced clinicians and linking it closely to the medical needs of patients. The IOB aims to work on practical solutions for the development of new therapies.

This vision is not only inspiring, but also an opportunity to reflect on how to advance medical research in the future. Basel may be one of the world's suitable cities for such a venture given that it sports two world-leading pharmaceutical companies, Roche and Novartis, in the same place.

This idea is neither arrogant nor ingratiating but is intended to express the extraordinary potential when the best of academia, industry, and clinics are brought together in a city that is already home today to more than 800 companies in the life sciences sector.

The knowledge that is developed at these companies, research institutes, and in medical practice needs to be enhanced through creative collaboration.

Creative collaboration and the courage to break new ground have always served as the best conditions for advancing research and gaining pioneering insights. This was already the case at the Roche-funded Basel Institute for Immunology, which produced three Nobel laureates from the time it was founded in 1969 to its closure at the turn of the millennium: Georges J. F. Koehler, Niels K. Jeren, and Susumhu Tonegawa.

The special spirit that prevailed at the institute spawned a generation of researchers who shaped Basel's research environment for decades, including Marcel Tanner, former director of the Swiss Tropical and Public Health Institute (Swiss TPH).

Tanner's experience at the institute, where, he said, "you could really let your mind run wild and do research at a very fundamental level," not only inspired his work in the lab and in the field, but also helped him establish a robust leadership and work culture at the rapidly growing Swiss TPH.

The Friedrich Miescher Institute (FMI), which was founded by what was then Ciba-Geigy and the University of Basel in 1970 to advance basic research and build a bridge between industry and academia, has experienced a similar development. This has been further strengthened this year: The FMI is now at home on the Novartis Campus, giving it the opportunity to create a new framework in which academic and industrial research can support each other.

The IOB, which conducts its research in Klybeck, and the Eye Clinic in the St. Johann district may be geographically separate. However, the institute strives for close integration when it comes to bringing clinicians and researchers together and promoting intensive dialogue. In addition to regular meetings between scientists and clinicians, the institute is also designed to promote translational medicine. Using the findings from basic research, it develops robust processes that can be transferred to medical and pharmaceutical practice.

Just seven years after its founding, the IOB has already carried out its first spin-off, with a gene therapy developed at the institute for treating a hereditary eye disorder now being continued by the start-up RhyGaze AG. In addition to developing a compelling proof-of-concept study, the IOB has advanced the technology and biology of this gene therapy to the point where RhyGaze AG will soon be able to begin clinical trials and give patients hope for a new treatment.

Similar transactions are likely to follow in the future, as researchers at the IOB have one big goal in mind: They wish to give new impetus to the field of ophthalmology, which has fallen behind in recent decades compared to oncology and cardiology. The development of new therapeutic approaches in the field of biotechnology and genetic engineering should make it possible to treat and perhaps even cure diseases for which there are currently no or only insufficient therapeutic options.

I have every confidence that the young researchers who have come to Basel from all over the world will not only revolutionize ophthalmology with their work. Above all, they will also strengthen Basel as a research hub and provide an argument for closer collaboration between academia, industry, and medical practice. Every success they achieve will not only benefit patients directly, but also create new forms of collaboration that advance medicine and help patients. This is an opportunity for Basel and Switzerland to seize.

Sharpening vision through the centuries

The history of ophthalmology is marked by a growing understanding of the structural, molecular and genetic eye functions. Surgical interventions dominated the field for much of the 19th and early 20th century before small-molecule drug development set in. With the advent of biologics and gene therapies, eye disease treatments have seen a dramatic improvement, which is expected to continue as basic and translational research efforts accelerate.

Text by **Goran Mijuk,** illustrations by **Lehel Kovács**

Renowned as the first physician in recorded history, **Imhotep** (c. 2650–2600 BC) contributed to the advances in medicine with early surgical techniques, which likely encompassed treatments for eye diseases.

The **Code of Hammurabi** (2250 BC) included one of the earliest references to medical treatments for eye conditions, specifying rewards and penalties for successful and unsuccessful eye surgeries.

Aristotle (384–322 BC) advanced the understanding of eye anatomy through **animal dissections,** describing the optic nerve and various eye layers.

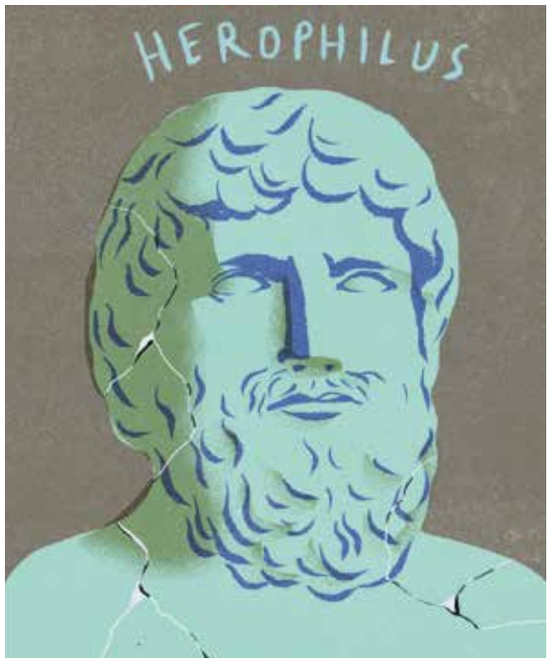
Herophilus (330–260 BC), also known as the **father of anatomy,** conducted extensive dissections and described the eye's internal structures, including the optic nerve and the lens.

The Canon of Medicine by Avicenna (980–1037 AD) details numerous ophthalmic conditions and treatments, influencing medical practice for centuries.

The invention of **eyeglasses** in Italy (c. 1286) helped improve vision for millions and is considered one of the greatest advancements in the history of vision correction.

Andreas Vesalius (1514–1564) pioneered modern anatomy, including **detailed studies of the eye,** which provided a foundation for future anatomical research.

Georg Bartisch (1535–1607), often considered the father of modern ophthalmology, published the first comprehensive book on eye diseases and surgery, **Ophthalmodouleia.**



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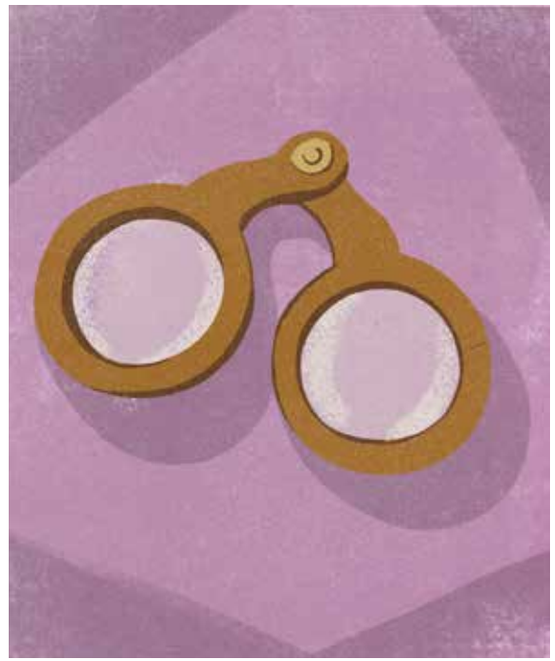


The invention of eyeglasses is considered one of the greatest advancements in the history of vision correction.

Sir Isaac Newton's (1643–1727) work on **light and optics,** particularly his theories on the nature of light and color, revolutionized the scientific understanding of vision.

Benjamin Franklin (1706–1790) invented **bifocal lenses** in the 18th century, allowing for improved vision at multiple distances.

German physician Hermann von Helmholtz (1821–1894) invented the **ophthalmoscope** in 1851, a groundbreaking instrument that allowed doctors to look inside the living eye.

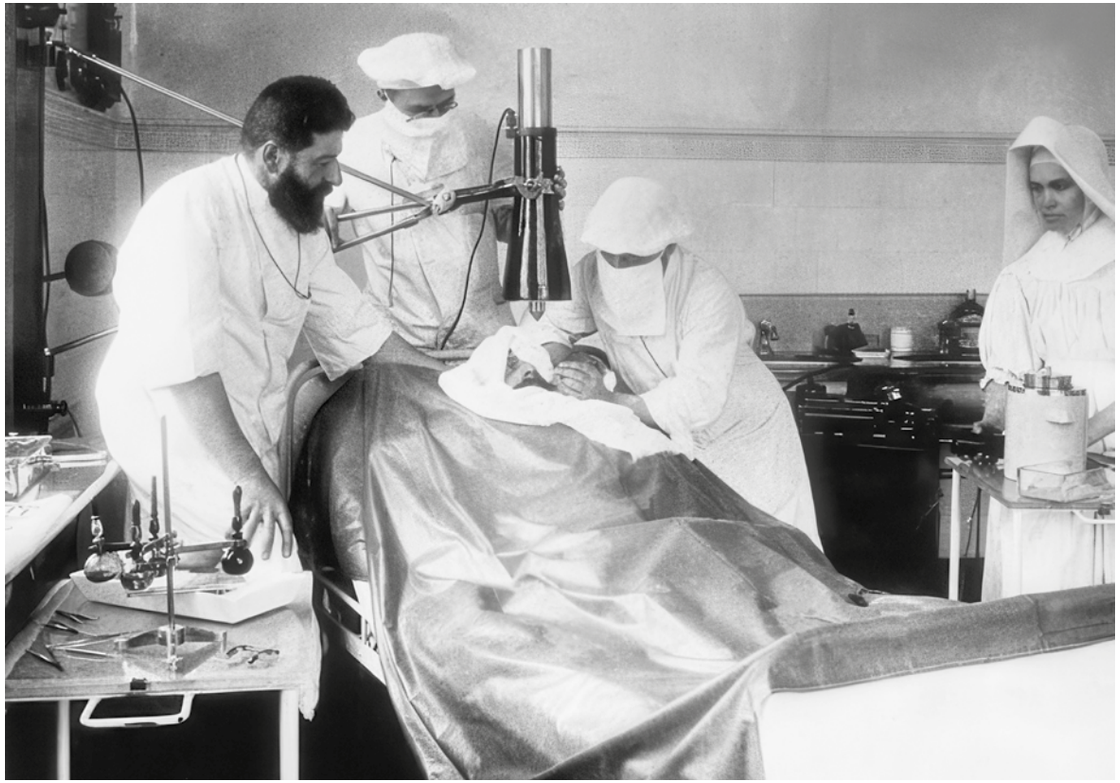
Ferdinand Ritter von Arlt (1812–1887) made significant contributions to the study and treatment of refractive errors and was the first physician to prove that myopia is a consequence of excessive axial length of the eye.

Albrecht von Graefe (1828–1870) developed new surgical techniques for treating glaucoma and cataracts and founded the first specialized eye clinic.

Karl Koller (1857–1944), an Austrian ophthalmologist, introduced the use of cocaine as a local anesthetic in eye surgery in 1884.

Allvar Gullstrand (1862–1930), a Swedish ophthalmologist and the only Nobel laureate for ophthalmology, made significant contributions to the understanding of the optical system of the eye and the development of **corrective lenses.**

Eduard Zirm (1863–1944) performed the first successful **human corneal transplant** in 1905, paving the way for modern corneal transplantation.



Eduard Zirm performed the first successful human corneal transplant in 1905.

Shinobu Ishihara (1879–1963) created the Ishihara **color test** in 1917, a breakthrough in diagnosing color blindness.

In the 1920s, pilocarpine, a medicine **derived from Pilocarpus,** was introduced for glaucoma, marking a significant breakthrough in reducing intraocular pressure.

Harold Ridley (1906–2001) performed the first **intraocular lens implant** in 1949, which laid the groundwork for modern cataract surgery.

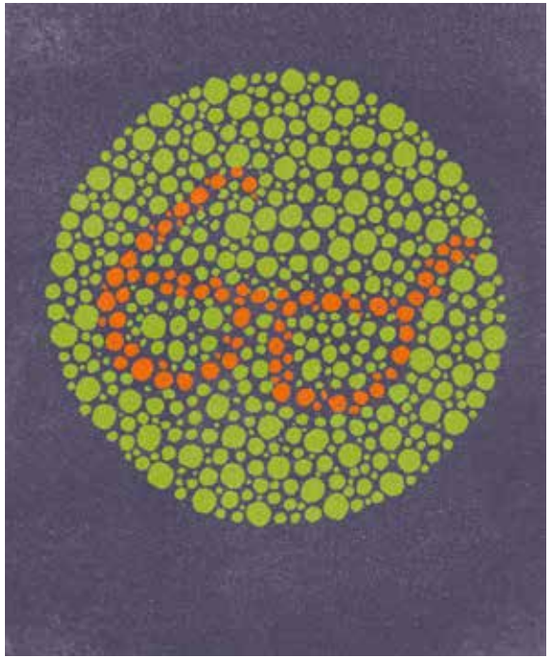
Charles Schepens (1912–2006) developed the **binocular indirect ophthalmoscope,** enhancing the ability to diagnose the back of the eye and treat retinal diseases.

Antibiotics, first introduced in the 1940s, revolutionized the management of bacterial eye infections.

The introduction of **corticosteroids** in the 1950 became vital for treating inflammatory eye diseases such as uveitis and allergic conjunctivitis.

In 1961, **fluorescein angiography,** in which a fluorescent dye is injected to highlight blood vessels, improved the diagnosis and management of retinal conditions.

The development of **beta-blockers** in 1978 provided the basis for new therapies for glaucoma, in which the optic nerve is affected.



The Ishihara color test by Shinobu Ishihara.

Antibiotics revolutionized the management of bacterial eye infections.

Anti-vascular endothelial growth factor (VEGF) therapy in 2004 transformed the treatment of wet age-related macular degeneration, in which abnormal blood vessels grow in the back of the eye and damage the macula.

The development and widespread use of **OCT technology,** which allows for sub-surface images of the eye, provided high-resolution imaging of the retina, starting in the 1990s.

The advent of **ultrasound bio-microscopy,** which uses high-frequency waves to produce detailed images of the anterior segment of the eye, including the cornea, iris, ciliary body, and lens, added further clout to diagnostics.

In 2017, the FDA approved the **first gene therapy** for an inherited retinal disease, marking a significant advance in treating genetic causes of blindness.

Ongoing research in gene editing technologies such as **CRISPR** offer hope for curing previously untreatable genetic eye disorders and potential cures for conditions like retinitis pigmentosa and Stargardt disease.

Rocking vision

Unlike large pharmaceutical companies, which employ thousands of researchers and clinicians and are highly hierarchical, the Institute of Molecular and Clinical Ophthalmology Basel (IOB) is small but very rock'n'roll. Small is also important because the IOB's leaders believe that true excellence in ophthalmic research can only be achieved by the most talented people working together. This not only helps to produce compelling results that enhance the IOB's reputation. It is also important in attracting the industry's mavericks and creates a special dynamic and team spirit that is both fun and competitive.

Photos by **Moritz Schermbach**

Quantitative visual physiology group (Group head: Felix Franke). From left to right front: **Annalisa Bucci, Felix Franke;** back: **Marc Büttner, Federica Bianca Rosselli, Matej Znidaric.**

Eyes on the future: Teams at work

Ophthalmic translational research group (Group head: Bence György). From left to right, front: **Jane Matsell, Wibke Schwarzer, Simon Hostettler;** back: **Tiana Koottungal, Duygu Sigurdsson, Lucas Janeschitz-Kriegl, Jay Zoellin, Beryll Klingler, Matej Znidaric, Bence György.**

Central visual and human retinal circuits group (Group head: Botond Roska). From left to right, front: **Michael Altermatt, Rei Morikawa, Serena Curtoni, Akos Kusnyerik;** back: **Hannah Stabb, Fiona Muellner, Temurkhan Ayupov, Sarah Nadeau, Miklos Boldogkoi, Tamas Dalmay.**

Eyes on the future: Teams at work

Central visual and human retinal circuits group (Group head: Botond Roska). From left to right, front: **Ilaria Gregorio, Nicole Ledergerber, Veronica Moreno Juan, Tania Marzolla, Elsa Sigle;** back: **Mohammad Khani, Botond Roska, Tiago Rodrigues, Alex Fratzl, Dimitri Rey, Andrea Tóth, Giuseppe Vaccaro.**

Eyes on the future: Teams at work

Ophthalmic genetics group (Group head: Carlo Rivolta). From left to right, front: **Francesca Cancellieri, Dhryata Kamdar, Sandrine Wallerich, Mukhtar Ullah;** back: **Elifnaz Celik, Karolina Kaminska, Maria Cuadrado-Vilanova, Mathieu Quinodoz, Marc Folcher, Abigail Moye, Ji Hoon Han, Ana Iglesias-Romero.**

Human Organoid platform (Platform head: Magdalena Renner). From left to right: **Patricia Galliker, Larissa Utz, Magdalena Renner, Natasha Whitehead.**

Clinical trial center platform (Platform head: Nicolas Feltgen). From left to right, front: **Nils Schärer, Ursula Hall;** back: **Daniela Hauenstein, Nicolas Feltgen, Petra Rossouw, Georg Ansari.**

Scientific computing platform (Platform head: Cameron Cowan).
From left to right: **Duygu Sigurdsson, Sarah Nadeau, Cameron Cowan, Susana Posada Céspedes.**

Single cell genomic platform (Platform head: Simone Picelli).
From left to right, front: **Sara Crausaz, Mariana Ribeiro;** back: **Svitlana Malysheva, Rebecca Siwicki, Simone Picelli.**

Complex Viruses Platform (Platform head: Josephine Juettner). From left to right: **Josephine Jüttner, Jannick Imbach, Adrienn Volak** (seated), **Philipp Timo Kleindienst.**

Myopia Research Group: **Léa Ingrassia, Frank Schaeffel** (Group head).

Eyes on the future: Teams at work

Theoretical and Computational Neuroscience Group (Group head: Rava Azeredo da Silveira). From left to right, front: **Luke Ewig, Taniya Channa;** back: **Rava Azeredo da Silveira, Junjie Huang, Harper Wallace.**

Visionary talent

A key ingredient to the future success of the Institute of Molecular and Clinical Ophthalmology Basel is its ability to attract top talent, for example through its Ph.D. program. Part of the institute's edge is that is offers young scientists a chance to understand eye diseases in unprecedented molecular detail and also to translate those discoveries into new treatments.

Text by **K.E.D. Coan,** photos by **Moritz Schermbach**

"During my bachelor's training, I became fascinated with how neurons work in ensembles to essentially make us who we are," says Hannah Stabb, a neuroscientist who began her Ph.D. training in 2023 at the Institute of Molecular and Clinical Ophthalmology Basel (IOB).

"I was always interested in fundamental questions like, what is the nature of intelligence and how can I develop a computational model for the mechanisms behind how we think?" says Junjie Huang, another recently joined student of the IOB's Ph.D. program who left his home in Beijing, China, to train here in Basel.

These are the voices of the young scientists who come from around the world to pursue their doctoral training in the IOB's Ph.D. program in Translational Visual Neurosciences. Each of these students has come to the IOB for the unique opportunities offered by the institute – namely its groundbreaking advances and rare blend of both fundamental research on eye diseases and the application of those insights to the development of new medicines to treat those diseases.

Although the Ph.D. program is only a few years old, the student body has been steadily growing. It has so far attracted over 20 students of 18 different nationalities, including students from Europe, North America, Asia, and Africa.

Many of these students have been drawn to the IOB by the institute's field-leading research, the reputation of the institute's faculty, and the one-of-a-kind education offered by the program.

"The uniqueness of our program lies in providing students with both practical and theoretical immersion in modern approaches to translational ophthalmology," says Lobna Maaroufi, who coordinates the Ph.D. program. "Our program strives to bridge the gap between basic research and clinical applications in visual neuroscience – and so do the Ph.D. candidates who join us."

An uncommon blend

The IOB itself was created in 2018 by the University of Basel, the University Hospital Basel, and Novartis to advance basic eye disease research and develop innovative therapies to restore lost vision. With all of the liberties of an academic institution, the IOB officially launched its Ph.D. program in 2022 to train the field's next generation of researchers.

"The program's title, *Translational visual neurosciences,* refers to the field of research aiming to bridge the gap between basic scientific knowledge about the visual system and practical applications for improving human vision or treating visual disorders," says Maaroufi. "Research at the IOB covers the entire spectrum of vision research, from basic science to patient-oriented clinical research, and we are aware of only two or three other institutes that offer such a blend of basic research and clinical application in ophthalmology."

In ophthalmology and most other specializations, basic and clinical research are often kept separate due to the vast expertise needed by each field. But there has been a growing realization that closer collaboration between these specialties can guide more patient-centric research and spark innovation.

"It's so important for clinicians and scientists to collaborate closely to improve patients' quality of life," says Jay Zoellin, a self-described aspiring physician-scientist who began his Ph.D. at the IOB in 2024. "This is one of the aspects that drew me to the IOB."

The IOB's Ph.D. program also welcomes early-career medical doctors who wish to obtain a research degree, and Zoellin received his M.D. in 2024 from the University of Zurich. Zoellin has been determined to pursue both an M.D. and a Ph.D. since he started his training and he has been fascinated by the eye since he took a clinical elective in ophthalmology at medical school.

All IOB students are officially enrolled at the University of Basel, where they have access to the university's full catalogue of courses in addition to the specific training they receive through the IOB.

The IOB's groups and platforms combine insights from neuroscience, ophthalmology, genetics, molecular biology, protein engineering, cell biology, biomedical engineering, data science, mathematics, and computational biology, as well as preclinical and clinical drug development.

"I was intrigued by the really well-planned, methodological research happening at the IOB, and the computational and mathematical aspects seemed like an important complement to the clinical setting," says Zoellin. "This was something I wanted to be a part of."

Attracting talent

The high-impact research of the IOB staff is another aspect that brings many students to the program.

"Botond Roska is quite famous for his pioneering research in optogenetic vision restoration," says Hannah Stabb, the student who came to neuroscience to understand how neuronal networks form our character.

Hannah Stabb

Eyes on the future: Young mavericks

Junjie Huang

Jay Zoellin

Although Stabb originally learned about Roska's research through her master's program at the University College of London, she also heard his name often in the media of their shared home country, Hungary.

"Everyone in Hungary is very proud of him and, during my master's, I followed his papers, and I knew of his reputation as a good supervisor," Stabb says. "I knew that I wanted to come to his lab."

Junjie Huang, the student interested in computational models of thought, was also drawn to join the program by the research of one of the IOB group leaders. While Huang was pursuing a degree in math and physics at the Tsinghua University in Beijing, he was fascinated by the summer school presentation of a visiting professor. This professor was Rava Azeredo da Silveira, the leader of the IOB's Theoretical and Computational Neuroscience Group and now also Huang's Ph.D. mentor.

Although they joined different labs, Stabb and Huang are working on a shared topic, which is the mechanism behind how a special class of neurons, called head direction neurons, compute orientation. Consistent with the IOB's interdisciplinary expertise, Stabb and Huang are tackling their projects with quite different, yet complementary approaches.

"Our projects are deeply connected," says Huang. "On Hannah's side, their focus is the experimental and molecular lab work, and then in da Silveira's group, we develop theories and models to explain the lab results and also to make new predictions that they can test to see if our predictions are correct."

"In many of the other Ph.D. programs where I applied, I would have had one project limited to one field, but I was really seeking an interdisciplinary view on science," adds Stabb. "Here at IOB, we have everything available for doing interdisciplinary research."

Winning recognition

Besides the unique research opportunities, interdisciplinary methodology, and reputations of the IOB's group leaders, the IOB has also gained recognition through the earliest graduates of its Ph.D. program.

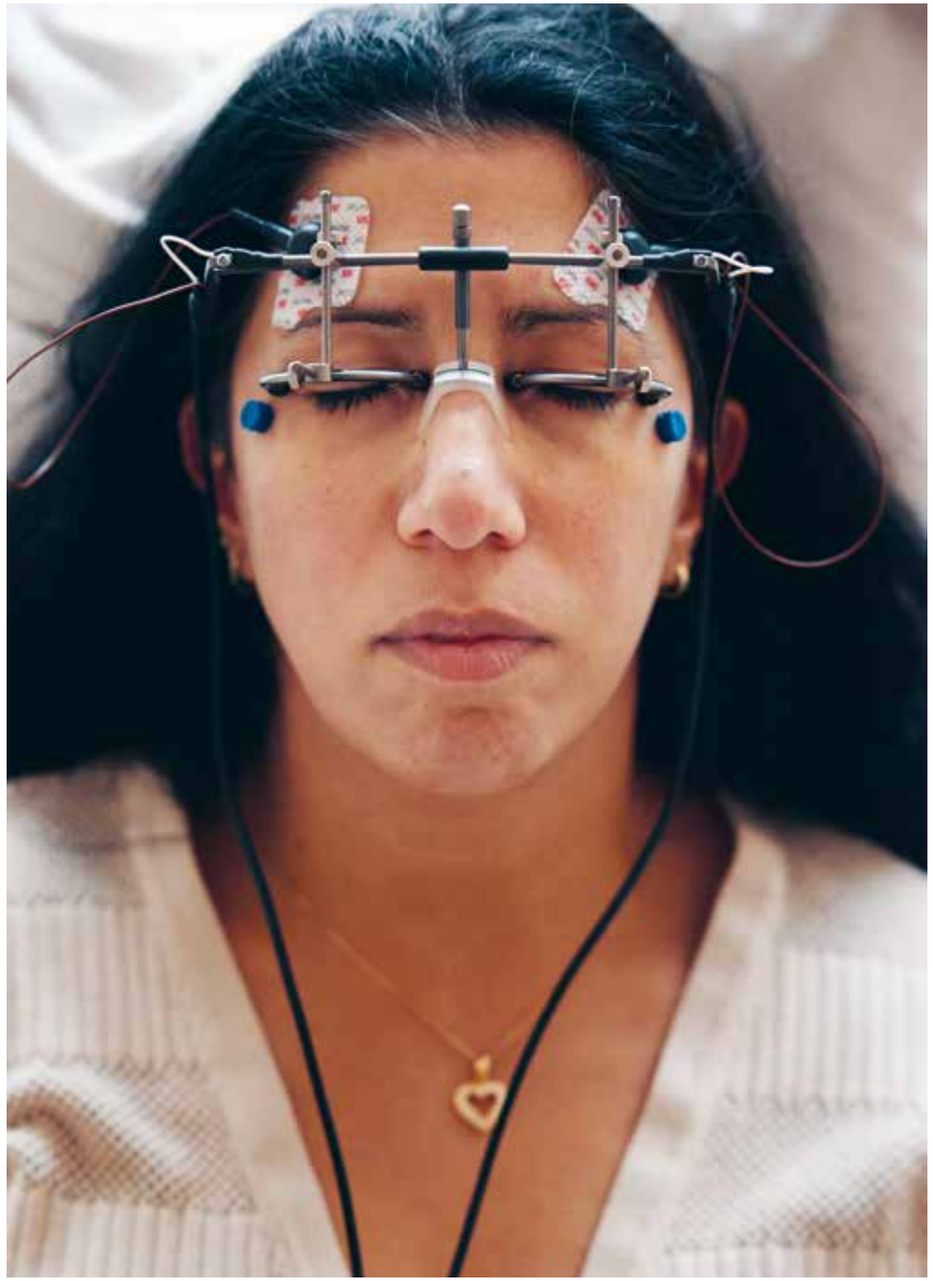
"Our former Ph.D. student, Dasha Nelidova, developed an innovative technology that could potentially pave the way for restoring central vision in patients blinded by macular degeneration," says Maaroufi.

Nelidova was jointly a graduate of the IOB and the Friedrich Miescher Institute for Biomedical Research, also in Basel, where Botond Roska held a position before creating the IOB. Her research has already earned 25 international awards, including the Pfizer Research Prize 2021, one of the most prestigious biomedical research awards for early-career scientists in Switzerland.

"I am really excited to see if we can get to a point where my research could be translated into the clinic – that would be incredible, but it's still a bit far," says Stabb, who is also working on a project to restore color vision.

"I think it is always important to keep in mind that if you're doing biomedical research, one of the ultimate goals, if not the ultimate goal, is of course always to improve quality of life for patients," adds Zoellin.


“I live in hope
of a cure”



Electric eye stimulation is considered to help Hanna Renner to manage the disease and help her save what is left of her vision.

Ever since she was a teenager, Hanna Renner has suffered from retinitis pigmentosa, a retinal disease that has reduced her vision almost to the point of complete blindness. She is in acute danger of losing her sight for good, but hopes that treatment will one day help her lead a normal life again.

Text by **Goran Mijuk,** photos by **Laurids Jensen**

Hanna Renner smiles as we arrive in the German town of Enkenbach after a journey of some three hours. Her family home, a new build painted in white, is easy to find among its neighboring buildings in this small suburb of Kaiserslautern, occupying a prominent spot next to a striking village church made of characteristic Palatinate red sandstone.

"Come in," she says, arms wide open. At first I am a little confused. We have only been in contact by phone and via WhatsApp, and I have been unable to get a proper idea of what she is like until now. The videos she sent me from her time as a dancer and fitness trainer in Hamburg reveal little or nothing about her current state. Is she blind or not?

I must have unconsciously assumed that she relies on a mobility cane and sense of hearing to find her way around. But Hanna is different. She looks into our faces, shakes our hands, and moves naturally as she leads us around the house before we sit in the garden to interview her. Only later does she tell me that she hasn't learned to walk with a cane yet, and that she can use the little sight she still has to get around the house.

Hanna's home is conspicuous for its bare walls and almost clinical tidiness – I assume because she and her family have only recently moved to Enkenbach. Her spacious garden, which we can see from the living room, contains the remnants of the walls of a demolished house. Next to the freshly laid lawn is a fallow, weed-ridden spot with stones and slabs piled up here and there. It looks like there is still work to be done on the property, both inside and out.

As we go upstairs, Hanna explains to us that the walls have been intentionally left bare. "I used to like having decoration everywhere, but now I want the house like this." In addition to the bedroom, which consists of only one bed, there is also a closet room, which can be accessed from two sides. The house has a large bathroom that is just as uncluttered and hotel-like as the other rooms.

But her daughter's room is out of bounds. "She's 17 – a proper teenager and a bit shy too," says Hanna. "Her room is the total opposite of the rest of the house. In fact, it would be dangerous for me to enter." She explains that there could be something on the floor, and that she could slip and injure herself.

This is the very reason why the whole house looks so plain and unadorned. Nothing blocks the way, and all the things that tend to be left lying around in other homes are neatly stowed. "I need order in my life. It keeps me safe."

Hanna later points to a small scar on her forehead. She says she was fumbling around her shoe cabinet and had not realized that one of the doors had been left open. On another occasion, she reached into the sink and almost cut her finger open on a knife that is normally kept in one of the drawers.

Life came to a standstill

As we sit down in the garden, Hanna tells us how her eyesight deteriorated dramatically over four years ago. Back then, shortly before the COVID pandemic, she was still living with her family in Hamburg, had two jobs and led a fulfilling life.

She already knew she had retinitis pigmentosa (RP), a hereditary disease in which parts of the light-sensitive retina slowly die off, possibly leading to complete blindness. While learning to drive at the age of 18, she had noticed a dark line in her field of

The home of the Renner family looks as clean and ordered as if it were new.
For Hanna Renner the empty space is life-saving.

Digital assets such as Siri help Hanna Renner to cope with the challenges of everyday life.

vision when checking her rear-view mirror, whereupon she went to a hospital that diagnosed the condition.

"It was nowhere near as bad as it is now," says Hanna. "I could still do everything on my own – drive a car, ride a bike, go to work, write letters. There was just a tiny, wafer-thin black line. Otherwise, I could see clearly. It took years for the black line to start getting thicker. Things only came to a head three or four years ago. Then I thought: OK, you are going blind."

Hanna's world came crashing down during the pandemic. Not only did she lose her job at the employment office in Hamburg, but she was also barely able to give dance and fitness lessons. With her eyesight getting rapidly worse, her life came to a virtual standstill overnight.

The family subsequently decided to move to Enkenbach, where Hanna's husband already owned a piece of land. The intention was to build a house and settle in Germany's Palatinate region. Hanna's husband found work at the nearby Philippsburg nuclear power plant, and her daughter also got set for the move. But relocating was not easy.

Even today, Hanna still struggles to hold back the tears when recounting her story. "And now I am almost at the end of my tether already," says the 43-year-old. "I smile, but I am falling apart inside." Although she would never dream of committing suicide, she keeps questioning the point of life.

But then she gives us her own quick-fire riposte: "I live in hope of a cure. I know there definitely is one. I know that someone somewhere has the answer, and I am waiting for it. And I always tell myself that I will get through this. Just wait and see."

New life, new challenges

You can immediately imagine what Hanna must have been like before the onset of RP. A straight-talking bundle of Berlin-born energy who is unafraid to speak her mind, she will persistently question doctors to learn more about her condition and possible ways to treat it. Or she will champion a charity event in aid of RP-related research.

Hanna says she first danced at the age of 13 with friends in Berlin. Her gang would often let off steam at the disco. They later went on to dance in front of audiences, even earning some money to help buy their dancing costumes. All this stopped when Hanna started training for a job, but a fortunate twist of fate allowed her to eventually pursue her passion. She soon began to work part-time as a dance teacher, giving lessons to large groups.

These days, Hanna stays at home most of the time. She has yet to learn how to use a mobility cane. Her future guide dog is currently in training. Hanna likes and enjoys family life with her husband and daughter within her own four walls, where everything is familiar and organized to a tee. But the lack of work or a social life means she often feels lonely.

Be that as it may, Hanna has no intention of throwing in the towel. She wants to give dancing lessons (to children) on a regular basis again – and campaign for wider sidewalks in Enkenbach. It is almost impossible for her to go outside alone anymore. Too many cars, she says. While the narrow sidewalks make even a short stroll impracticable.

Only with her husband and daughter does Hanna venture far beyond the front door. When she does go outside, she particularly enjoys riding with her husband on the tandem they recently bought. "We are the perfect power couple on our bike," she laughs. "We regularly strike up conversations with people who keep saying how surprised they are that I am blind."

Few people realize straight away that Hanna can hardly see anything. Her movements – perhaps because she was such a good dancer – are as natural as those of a sighted person. This also poses problems, as Hanna's husband can testify. When they park their car in a disabled parking space, it is not uncommon for other members of the public to confront them. "People have directed abuse at us on numerous occasions because they thought Hanna wasn't blind," her husband says. "That is when I lose my cool."

Everyday life is hard enough as it is. A taxi driver once refused to drive Hanna home from a doctor's appointment in Frankfurt because he wouldn't recognize the certificate entitling her to a free ride. Her husband had to clock off work in Philippsburg

On the way to the gym.

Moments of joy. When giving classes, Hanna Renner feels like her old self.

to come and pick her up. “I was alone on the street and unable to go back into the practice because the building was already locked. It was terrible.” Eventually, another taxi driver agreed to drive her home.

Waiting and hoping

But it takes more than that to throw Hanna off her stride. She knows what she wants and is determined to regain at least part of her eyesight and return to some kind of bearable normality.

Hanna currently uses special eye-cam glasses to “see” things. If she holds a banknote in front of her eyes, the device’s built-in camera will be able to tell whether it is a 10- or a 20-euro note. Furthermore, the German Federation of the Blind and Partially Sighted will soon be providing her with computer training.

Siri, Apple’s AI chatbot, also helps her to stay connected, allowing her to listen to messages and surf online. This is also how she keeps track of the latest medical findings, which give her hope when it comes to innovative ways of treating her disease.

There is reason for optimism, because more than 100 clinical trials to treat RP are currently ongoing around the world. Apart from developing new gene therapies, scientists are also looking to use existing drugs or food supplements like N-acetyl-L-cysteine to mitigate or even cure the disease, which affects some 3 million people worldwide.

Time is running out for Hanna, who currently uses an electrical stimulation device called OkuStim to contain the condition. Hanna is completely blind in one eye and can only see a bit with the other. And the little she does see is blurred. “I can really only see through a tiny hole and have to try very hard to identify anything at all. But I am clinging on to that dot of light so that I can live independently without too many aids. I am doing everything I can to avoid turning completely blind. Because I simply don’t want to believe that worse is to come.”

Hanna receives support from doctors not only in Germany but also in Switzerland at the Eye Clinic of the University Hospital Basel, which is collaborating with the Institute of Molecular and Clinical Ophthalmology Basel (IOB) to develop a novel gene therapy. “It’s good to know that research is continuing and that the doctors in Basel are doing so much to help me get better,” she says.

The groundbreaking therapy, for which the IOB laid the groundwork, achieved an important milestone in summer 2024 when the research project was outsourced to RhyGaze AG, the start-up now entrusted with advancing clinical trials. If everything goes according to plan, the method of injecting light-sensitive genetic material into damaged retinas could help Hanna and thousands of other affected patients to regain some eyesight.

Hanna has been waiting for little cures like this. “You could say that blind people are waiting all the time. We are waiting and hoping for something to happen. Our life consists of waiting,” she says, with more than a hint of gallows humor. “Certainly, there are worse diseases. But I will be the happiest person in the whole world if I get some of my eyesight back.” L.

Eyes on the future: Waiting for a breakthrough

Hanna Renner is waiting for a treatment. In the meantime, she is doing everything to live a fulfilled life.

Cataract surgeons, slit lamps and the Basel Eye Clinic

The history of ophthalmology goes back more than 4,000 years, when specialists in eye treatment were already working in the advanced civilizations of the Middle East. However, ophthalmology only developed into a scientifically based medical discipline over the last few centuries, through the work of oculists and cataract surgeons in the Middle Ages. The founding of the eye hospital, the forerunner of the Eye Clinic, by Dr. Heinrich Schiess-Gemuseus in 1864, laid the foundation for an internationally renowned treatment, teaching and research center in Basel.

Text by **Michael Mildner**

Anyone who passed themselves off as an ophthalmologist in ancient Babylon could make a fortune, as reported in the more than 3,600-year-old Code of Hammurabi. A successful treatment was rewarded with 10 shekels. At that time, a shekel had the purchasing power of 50 kilograms of flour, 360 fish or 2 liters of date syrup. However, the consequences of failure due to medical malpractice were drastic: The doctor's hands were chopped off.

Over the following centuries, ophthalmology retained the reputation of being a somewhat shady profession, as the complexity of the human eye and the inadequate instruments for examining it hindered scientific progress for a long time. The anatomy and functioning of the eye remained unclear until the 18th century, and it was only with the advent of the microscope that it became possible to see details and use the knowledge gained for therapies. Although ancient Indian medicine and many Greek scholars such as Hippocrates were concerned with the anatomy and treatment of the eyes, their findings were based essentially on studies of animal eyes and were hardly transferable to humans.

Above: The first "Sanatorium for Poor Eye-Patients in Basel" was opened in 1864 at Missionsstrasse 45 with eight beds.
Below: The Basel Eye Clinic at Mittlere Strasse about 1925.

The starling and its piercers

This unsatisfactory state of knowledge did not, however, prevent practicing doctors from treating one of the most widespread eye conditions with surgery: cataracts. As early as 140 AD, there was a report of such a surgical procedure being performed by a Greek doctor. In the Middle Ages, extensive theoretical works were written that described observations and findings such as the pupil's reaction to light or the absorption of light by the retina. At that time, the practical tasks were performed by specialized artisan surgeons, who were also referred to as cataract surgeons and oculists. Dr. Eisenbarth, who was famous in the Middle Ages, performed cataract operations using a special knife to push the cloudy lens into the interior of the eye.

The situation at that time is described by the German oculist Georg Bartisch in his 1583 book *Ophthalmoduleia:* "Eyes should be held in high regard and cataracts should not be allowed to develop. The oculist should be pious, have studied anatomy, have subtle hands and fingers, and be agile on both hands, not greedy for money, not a drunkard, not boastful; such oculists are few and far between."

Friedrich Rintelen, former director of the Basel Eye Hospital, gives us an insight into conditions in Basel at the time in his essay *Ophthalmology in Basel during the Baroque Period*. Here, too, cataract surgeons were in practice until the 18th century, and the most successful of them enjoyed a high reputation. Towards the end of the 17th century, the city physician of Basel, Bernhard Verzascha, recommended the following eye lotion for the medicinal treatment of cataracts: "Eyebright spirit, fresh valerian root, fresh bellflower root, fresh vervain and rosemary, nutmeg and cinnamon, fresh rue, fennel and aniseed, fresh eyebright; mix everything together, leave it to stand overnight, distill it on the balneo Mariae and keep it in a well-protected glass. This water can be used both internally and externally."

Rintelen concludes his treatise by stating that ophthalmology in 17th-century Basel and in the first quarter of the 18th century was a very peculiar but typical mixture for the baroque cultural period: 'The faculty taught outstanding work in the fields of anatomy and physiology and probably also medical-clinical knowledge, which the masters of the faculty taught and had their doctoral students express; we may assume that some skilled surgeons and cataract surgeons were at work. And alongside this, a worryingly primitive, botched therapeutic practice flourishes, worthy of a caustic Molière comedy.'

The Basel Eye Hospital

When the founder of the Basel Eye Hospital, Dr. Heinrich Schiess-Gemuseus, a doctor from eastern Switzerland, settled in Basel in 1861, the level of knowledge in the field of ophthalmology had already developed considerably. Schiess, for his part, had extensive ophthalmological knowledge, which he had acquired during his studies in Basel,

Wuerzburg, Munich, and Vienna. He specialized in the field of ocular histopathology and published around 60 studies on clinical and histopathological topics during his lifetime. Schiess was also the ophthalmologist to Friedrich Nietzsche and a lecturer in ophthalmology in Basel.

It was at the Basel University that the medical professor C.G. Jung had given his first lectures on eye diseases as early as 1823, and it was Jung who encouraged Schiess, a practitioner, to open a clinic exclusively for eye diseases in Basel after his arrival in Basel. However, the municipal hospital and curatorship provided so little support for this project that Schiess only managed to acquire sufficient funds and land for his project with the help of the public. In 1864, Schiess founded the "Sanatorium for Poor Eye-Patients in Basel" with eight beds in a small house at Missionsstrasse 45. Nursing care for the patients was provided by nurses from the Bern Deaconess House.

The need for competent treatment of eye diseases and the possibility of inpatient care was immense, not only in the city of Basel but also in the surrounding areas, leading to the rapid expansion of the eye hospital. In 1877, the main building of the present-day eye hospital on Mittlere Strasse was already in use; at that time, at that time, the clinic had as many as 48 beds, a permanently employed assistant, a head nurse and an administrator. In 1900, the first polyclinic was set up in the garden area, and with the invention of the slit lamp, developed by the Swedish physician Allvar Gullstrand in 1911, the hospital's doctors now also had a modern examination device at their disposal. The slit lamp can be used preventively during a routine examination, but also to diagnose existing complaints.

Heinrich Schiess was succeeded by Carl Mellinger, Alfred Vogt, and Anton Brueckner, who took over the post of head physician at the eye hospital between 1896 and 1948. Friedrich Rintelen then ran the hospital for almost 30 years, from 1948 to 1974. During his term of office, the current Eye Clinic and the still-used ward block were built between 1950 and 1953. The new polyclinic building, which currently hosts more than 80,000 consultations a year, was completed in time for the 500th anniversary of the University of Basel in 1960. The polyclinic is the center for outpatient ophthalmological care and for the training of medical staff.

During Rintelen's term of office, particularly in the 1950s and 1960s, ophthalmology also became highly specialized, which ultimately meant that the diverse subject areas could no longer be covered by a single head physician.

Integration and innovation

In the 1960s, the first research laboratory of the Eye Clinic was set up, headed by a newly appointed scientist specializing in basic research. Initially, the focus was on research into corneal physiology problems;

In the 1950s the dormitory was rebuilt (view from the garden).

in the 1980s, this area was abandoned and the focus was now on vitreoretinal surgery. Under Balder Gloor, who was head of the clinic from 1974 to 1985, ophthalmic surgery became a high priority, and with the opening of the new surgical wing in 1980, the number of operations also rose sharply.

When Josef Flammer took over as director of the clinic, having been its senior consultant from 1987 to 2013, research work changed again, this time towards the physiology and pharmacology of the eye, with a focus on glaucoma. Flammer introduced several teams for basic research, but also for clinical research, and intensified scientific exchange. To this end, contacts with nearby institutes such as the Biozentrum, but also with international partners, were expanded, and in 2006 an additional department for diagnostics, teaching and research was opened at the clinic.

The integration into the University Hospital Basel (USB) opened up exciting new perspectives for the Eye Clinic in the field of interdisciplinary cooperation with internal medicine, neurology, and surgery. For example, the USB is the Swiss center for a recently approved gene therapy for the treatment of inherited retinal dystrophy, a rare disease that affects one in 3,000 people in Switzerland and can cause blindness in early adulthood. The gene therapy drug is applied microsurgically under the retina, which requires not only the necessary instruments but also considerable knowledge and skill. On March 10, 2021, a 12-member team from the Department of Ophthalmology successfully performed the first such operation in Switzerland.

Another example of the Eye Clinic's forward-looking approach is its partnership with the Institute for Molecular and Clinical Ophthalmology Basel (IOB), with which the Eye Clinic has been working closely since 2017. Both partners represent a unique innovation chain in ophthalmology – from basic research to patient application. The motto of this translational research is "from bench to bedside," i.e. from the laboratory to the patient as quickly as possible. Since the IOB was founded, every effort has been made to accommodate both basic researchers and clinicians under the same roof so that they can work hand in hand to gain a better understanding of eye diseases.

Today, the management of the Eye Clinic is in the hands of Nicolas Feltgen. A polyclinic is available for patients to provide basic care, with a 24-hour emergency service. In addition, the Eye Clinic offers all specialist ophthalmological consultations. In order to remain at the forefront of medical innovation, the Eye Clinic's surgical facilities are currently being fully converted to digital microscopy. This will also enable live imaging of the retina during operations. For operations, the clinic can draw on experienced specialists and state-of-the-art technology. If required, a ward is also available in addition to the outpatient area.

Research and clinic at eye level

The basic researchers at the Institute of Molecular and Clinical Ophthalmology Basel (IOB) and the physicians at the Eye Clinic of the University Hospital Basel are connected not only by the short distance between the sites, but also by their joint translational approach. This approach transfers research results for the development of new, innovative therapies into clinical practice as quickly as possible. The intensive collaboration between the two partners thus offers unique perspectives for patients and science.

Text by **Michael Mildner,** photos by **Laurids Jensen** and **Kostas Maros**

During his training as an optician, Nils Schaerer learned that retinitis pigmentosa, a hereditary eye disease that often leads to blindness, cannot be treated. Later in his studies in optometry at the University of Applied Sciences, the disease was discussed in more detail and with different variants, but the conclusion remained the same: There is nothing that can be done. It was only after his employment at the IOB and his work as a study coordinator at the Eye Clinic of the University Hospital Basel that he learned the first genetic therapies already existed offering treatment options for one of the disease variants – and that research was working at full speed on further innovative approaches.

This perspective and the daily collaboration with patients and physicians at the Eye Clinic are still fascinating and motivating for him today – more than five years after his decision to change his profession as an optometrist and work daily as a study coordinator at the interface between research and the clinic.

Broad portfolio of projects

IOB employees, study coordinators and ophthalmologists from the Eye Clinic meet regularly to implement promising research approaches in clinical practice and to benefit patients as quickly as possible. For Nicolas Feltgen, Chief Physician a.i. of the Eye Clinic since April 2024, these meetings are a valuable element of collaboration. “The IOB presents its research projects, for example in the field of socially relevant retinal diseases, and we report on issues from the clinical field. The most important current topics are myopia research and new options for preventing scarring after eye operations. These intensive discussions provide both sides the opportunity to gain new insights and make further progress. Above all, however, this creates a unique opportunity for patients to benefit from the latest and most innovative treatment options.”

Feltgen and his team of 24 physicians have formed various clinical groups, each with 4 to 12 participants, which they assign to the IOB’s main research areas. In addition to epidemiological projects or widespread diseases such as short-sightedness, the collaboration also focuses on retinal dystrophies, a malformation of healthy tissue that is caused by genetic defects, among other things. “Close collaboration between basic researchers and the medical team is particularly important in this very special, still little-researched area. This is where the IOB’s Ophthalmic Genetics research group is doing pioneering work,” explains Nicolas Feltgen. Meetings between the IOB and the Eye Clinic take place at various intervals and on various occasions. For example, the planning group meets every two weeks, the dystrophy working team every four weeks and there are at least four medical-scientific training events in the lecture hall of the Eye Clinic each year. In addition, there is a retreat lasting several days once a year.

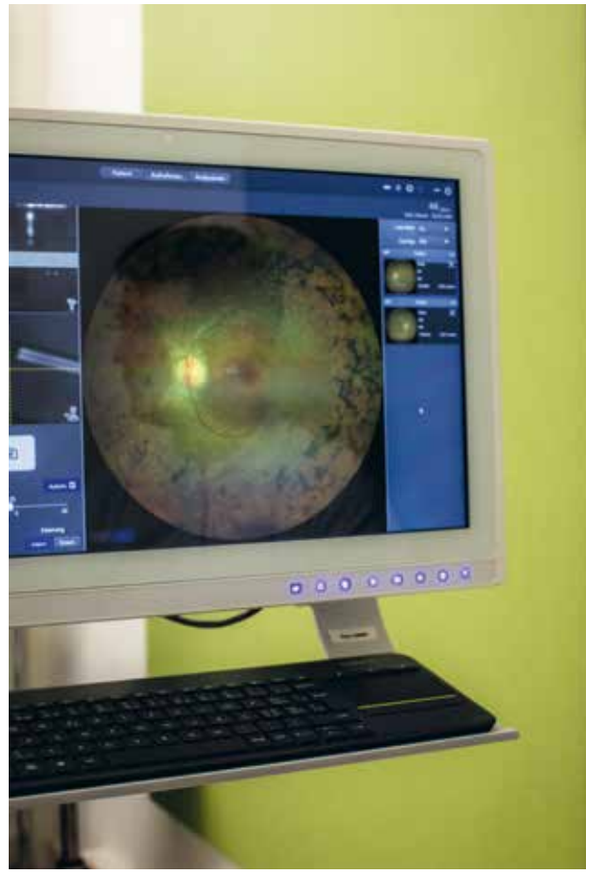
Genetic beginnings

These regular meetings and the exchange of data between the clinicians at the Eye Clinic and the IOB’s ophthalmic genetics researchers have already helped advance the field and patient care.

“It’s so important that clinicians and scientists work together because every new treatment needs both worlds,” says Lucas Janeschitz-Kriegl, one of a handful of clinician scientists at the IOB who splits his time between his roles as a clinical ophthalmologist at the Eye Clinic and as a Ph.D. research student in the group of Bence György. “We need to understand the molecular details of a new pharmaceutical approach and we need to know how well that will meet the patient condition in the clinic – the success of many treatments relies on close collaboration between these disciplines.”

There are over 80 different known genetic variations of retinitis pigmentosa and one of the most valuable benefits of these collaborations is the high probability of identifying exactly which variant a

Eyes on the future: Diligent collaboration



Although old, the Eye Clinic in Basel is equipped with top-notch surgical and analytical instruments.

Nicolas Feltgen in the lecture hall of the Eye Clinic in Basel.

patient has. The IOB offers a variety of genetic analyses using the latest testing methods, including tools developed at the IOB, as well as complementary state-of-the-art methods through collaborations with external companies. As a final step in any diagnosis, all of these findings are confirmed through a clinically certified external lab.

From this information, the research team additionally offers predictions of the likely molecular consequences of each genetic variant.

"Our high success rate is made possible by these innovative methods combined with our close discussions with the clinicians," explaineds Janeschitz-Kriegl. "For example, we can compare genetic findings with clinical symptoms until we are confident in the genetic diagnosis, which can lead to new discoveries as well as a higher level of accuracy and quality for our patients compared to what is available through normal labs."

One of the biggest benefits for the IOB is the amount of patient data, which is strictly coded, that the clinicians can share with the genetic research teams to help them develop stronger predictions and confirm hypotheses about the roles of specific genes and gene variants. The clinicians also have the most detailed insights into how the disease presents in patients and what treatments might be the most beneficial.

In most institutes, these exchanges rarely occur in real-time, if they occur at all. But at the IOB, these monthly meetings provide a forum for vibrant exchange of new treatment ideas, patient results, and patient treatment needs.

"These face-to-face discussions are very fruitful and really facilitate the flow of questions and results between the researchers and physicians," says Janeschitz-Kriegl. "It's a win-win-win for clinicians, researchers, and patients."

Between two chairs

At the heart of all these joint projects are clinical studies that are conducted in the Eye Clinic, as well as at other clinics across the globe, with the IOB acting as sponsor/initiator. The IOB is not granted access to personalized patient data for regulatory reasons. Therefore, the results of the studies must be collected by employees of the University Hospital Basel, to which the Eye Clinic belongs, and processed and coded before forwarding to the IOB.

The team of four study coordinators and one study doctor, who perform dual functions, are the ones who make this happen. "We are employed by the IOB, which also pays our salaries. As we have our offices in the Eye Clinic and the patient contacts also take place here, we are also employees without a salary at the University Hospital Basel – with the same duties as all employees there," explains Nils Schaerer. He is keen to describe this unique arrangement as follows: "It's like football. We are employed by one club but have been loaned

The old building still serves its purpose and belongs to the city's silent architectural gems.

out to another club for certain tasks and with a different role. There is always a need for explanation so that the matter of the two different hats is properly understood."

Nils Schaerer and his four colleagues therefore are taking on tasks and contacts with patients as part of the studies that IOB employees are not permitted to do. When they leave their office to go to the clinic and see patients, they put on the white coat or metaphorically the Eye Clinic hat and they shed their IOB identity.

Alleviating patient suffering

Patients suffering from diseases such as retinitis pigmentosa have come to the Basel Eye Clinic for regular check-ups every six months for several years now. During these routine appointments, their visual field is tested and images of the retina are taken. The results are then analyzed and discussed in the clinic.

The team of study coordinators provides a link between the clinic and the research institute. "As clinic staff, we receive the patients and, together with a clinician, inform them about the studies. We also carry out eye tests, collect the patients' genetic samples, and take over the study questionnaires from the doctors, which they have filled in by hand during the examinations of the patients," explains Nils Schaerer.

Back in the office, depending on the project they are working on, the study coordinators resume their role as IOB again, they prepare study applications for the ethics committee, de-identify and transfer data and images for storage in a database, optimize processes, and answer questions from group leaders and Ph.D. students or support recruitment for new studies.

In their dual role as part of the IOB and the Eye Clinic, the study coordinators play an integral role and they are actively engaged in joint meetings between the two departments. They bring their expertise to such meetings as soon as it is needed. "We are happy to leave the scientific and clinical discussions to the specialists from the IOB and the Eye Clinic. However, we are eager to join the discussion when it comes to study planning, regulatory aspects or details of the Human Research Act and Good Clinical Practice," Nils Schaerer asserts.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