IOB Institute of Molecular and Clinical Ophthalmology Basel

ANNUAL REPORT 2022

IOB in numbers

People

Groups

11

Platforms

6

Nationalities

31

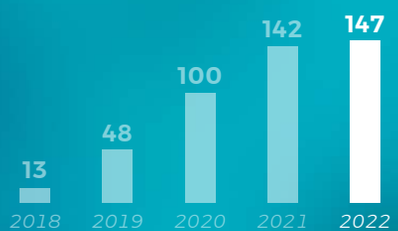
Awards

since 2018

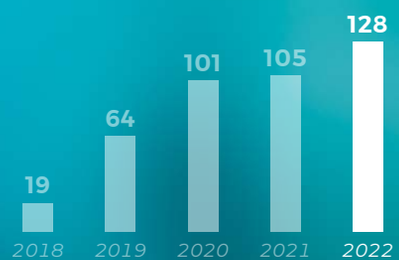
69

Publications

per year



Partner institutions



Funding

m CHF/year

Groups and platforms at IOB

	MOLECULAR	+	CLINICAL
11 Groups	› Central Visual Circuits Group › Human Retinal Circuits Group › Theoretical & Computational Neuroscience Group › Quantitative Visual Physiology Group › Visual Cortex Plasticity Group		› Ophthalmic Genetics Group › Ophthalmic Imaging & OCT Group › Ophthalmic Translational Research Group › Myopia Research Group › Genetic Epidemiology of Ophthalmic Diseases Group › Ophthalmic Epidemiology & International Ophthalmology Group
6 Platforms	› Human Organoid Platform › Complex Viruses Platform › Single-Cell Genomics Platform › Scientific Computing Platform		› Clinical Trial Center Platform › Visual Neurophysiology Platform

Contents

Directors' letter

Dear Reader,

It is now five years since the Institute of Molecular and Clinical Ophthalmology Basel (IOB) was founded with the aim to better understand eye diseases and to develop treatments for affected patients. What started with the simple idea of bringing researchers and clinicians together to strengthen translational research has evolved into an established and internationally recognized institute.

We are very proud to have reached this important milestone and are grateful for all the support IOB has received over these years, especially for our strong partnerships and collaborations with institutions around the world, and the continuing support of our founding partners and generous donors.

In our fifth year of operations, we were delighted to return to normality after the more than two years dominated by the COVID-19 pandemic. Our labs, hallways and offices are again full of scientists and clinicians meeting, discussing and exchanging ideas to jointly create excellent science.

These efforts have been acknowledged worldwide: In 2022, IOB scientists published key contributions to global scientific exchange and received internationally recognized awards and grants. We were able to make important breakthrough discoveries regarding the function or dysfunction of the eye and the visual brain that will lead to the development of radically new therapies for eye diseases.

2022 also marked the start of our new PhD and MD-PhD Program on Translational Visual Neurosciences. This program opens the door for scientists to participate in world-leading vision research, offering an exciting variety of lectures on vision, eye diseases and therapy as well as practical training in state-of-the-art physiological, molecular, and translational technologies.

With this program and our established reputation, we are convinced that IOB will continue to attract talented researchers from all over the world, thus further strengthening our teams and our goal to combine outstanding research with clinical excellence.

Sincerely,

Botond Roska

Director Molecular Research

Hendrik Scholl

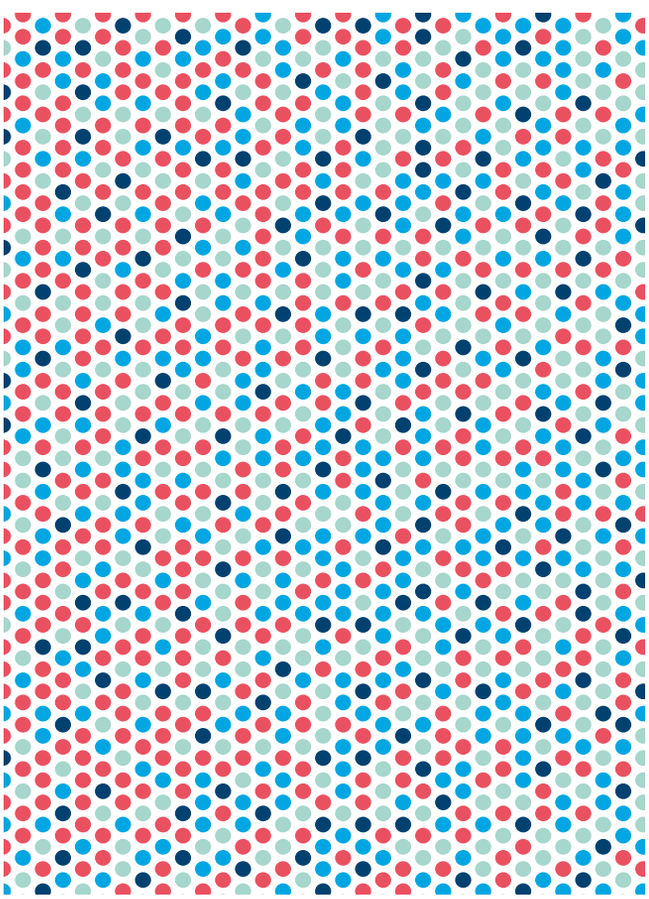
Director Clinical Research

Norbert Spirig

Director of Operations

Five years of visionary science

IOB celebrated its fifth year of operations in 2022 and the three directors reflect here on milestones reached so far and share their vision of the Institute's future.



Where does the IOB stand five years on?

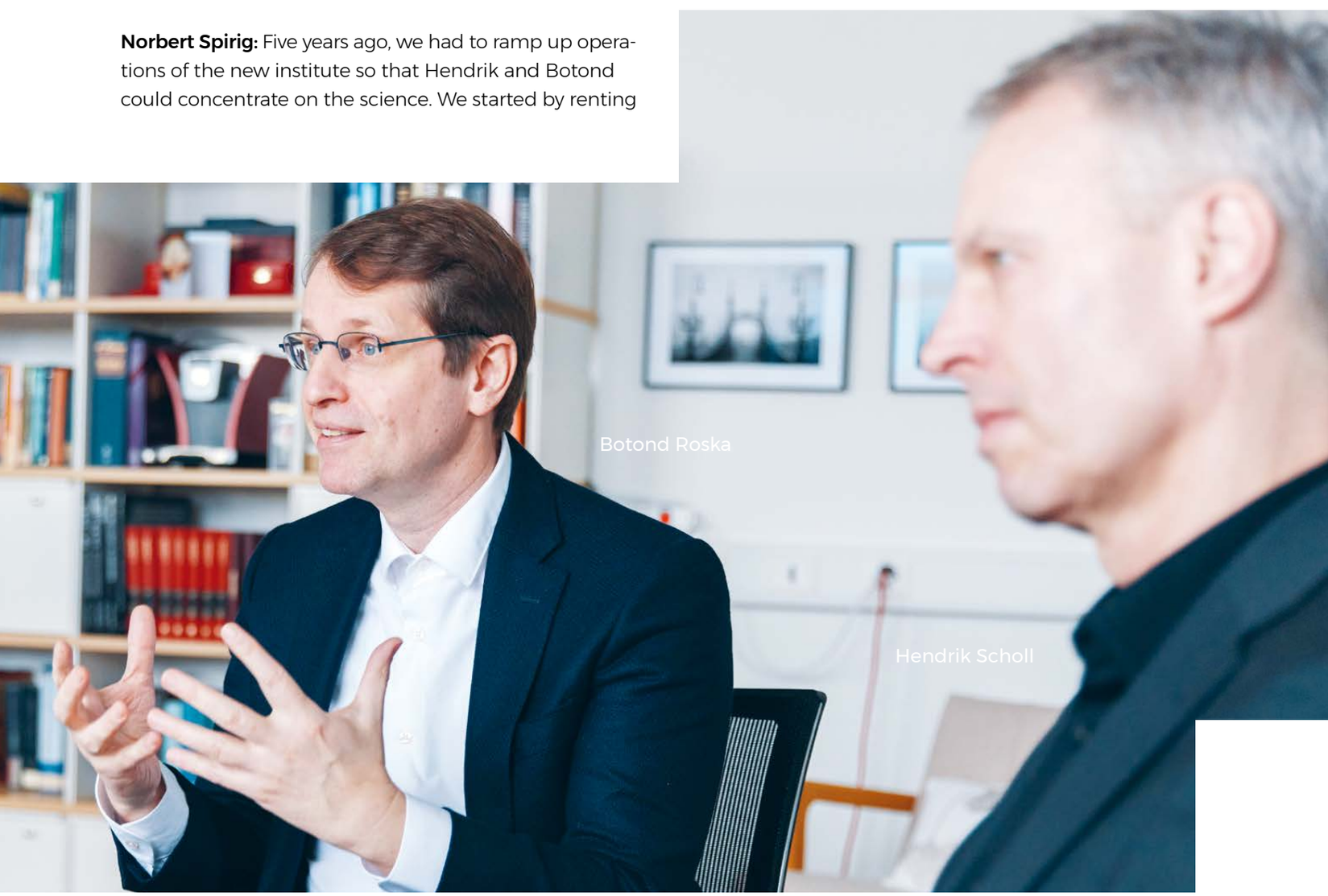
Hendrik Scholl: Five years ago, there was nothing. And now, there is a real institute, an established one and, at least for ophthalmology, one of the biggest in the world.

Botond Roska: I remember that, at the beginning, we were sitting in a small room with Hendrik, thinking about what could possibly be accomplished in just a few years. We agreed on two signature projects: one is cone-targeted optogenetic therapy to restore vision and the second is to develop a gene editing approach to correct mutations in Stargardt disease. As of now, we are handing the cone-optogenetics project over to people who will bring it to clinical application, and we are close to completing the second project. But at that time, it was a dream in a small room.

Norbert Spirig: Five years ago, we had to ramp up operations of the new institute so that Hendrik and Botond could concentrate on the science. We started by renting a small lab and now we have about 140 people developing projects and treatments. We are also continuing to work towards bringing researchers and clinicians together in a new, integrated building.

What were IOB's main achievements in the last five years?

Hendrik: We made significant progress in developing new therapies and we are now entering into collaborations with industrial partners to bring these therapies to clinical application. Also, we are at the leading edge in various disciplines; if people would like to learn about single-cell genomics, or retinal organoid development, or what leads to myopia, then IOB is the go-to place.



Botond: In the first five years, we concentrated on moderately rare diseases and started new projects on very common diseases such as macular degeneration, myopia and glaucoma. We created an atlas of cell type transcriptomes of the human retina, which is now widely used by ophthalmologists around the world to map specific genetic diseases to certain cell types of the retina. We performed, together with Novartis, the first compound screen on human retinal organoids. Finally, we established a translational visual neuroscience PhD program that includes rotations in the clinic, classes taught by IOB clinicians and scientists, and practical training through our platforms. It is an integrated, lively PhD program.

Collaboration between researchers and clinicians is at the core of IOB. How has it changed over the years?

Hendrik: It was a brilliant idea to bring clinicians and scientists together. I am still convinced by the idea five years later. What has emerged over the years is that the interactions between the two groups of colleagues are very concrete. For example, the basic researchers who developed a gene therapy product and the surgeons who do the injections to deliver it underneath the retina are working together to study efficacy and potential side effects.

Botond: Over the years, we have also established a regular clinician-scientist meeting organized by the Head of Ophthalmic Translational Research Group, Bence György. Here clinicians and scientists present their work and then discuss how to move forward and employ the technologies that are available. This meeting is now a central part of our activities.

Norbert: Today there is more mutual awareness among both the clinicians and the researchers, but the interaction is half of what it could be. Clinicians and researchers could get even closer, and a joint building would really help.

What challenges did IOB face in the past years?

Botond: During the COVID pandemic, IOB never stopped. We continued to work as we had a relatively large building and just a few people. But I noticed that young people got isolated and the forceful energy that moves IOB forward kind of slowed down. I was happy to see this year that a lot of that energy has come back.

Hendrik: Science follows a competitive logic and we could have done more had we had more resources,

be it in funding or the number of people working on the projects. These challenges have existed from the beginning and will continue to exist. Developing therapies needs more resources than standard basic or clinical science projects. This means that we, as Directors, are always watching out for new opportunities to acquire more funding and to appoint the best people at IOB.

You have managed to recruit a lot of talent. What attracts people to IOB?

Botond: Our goals! A lot of young people are extremely interested in combining basic science and medicine for translation. IOB is a magnet for them.

Hendrik: We have a tangible purpose, and we convey it. Every day, patients suffering from untreatable diseases walk into our eye hospital and, when we develop something, these people can be treated. For us this purpose is kind of normal because we dedicate our career to it. But it is not trivial at all and it helps recruitment.

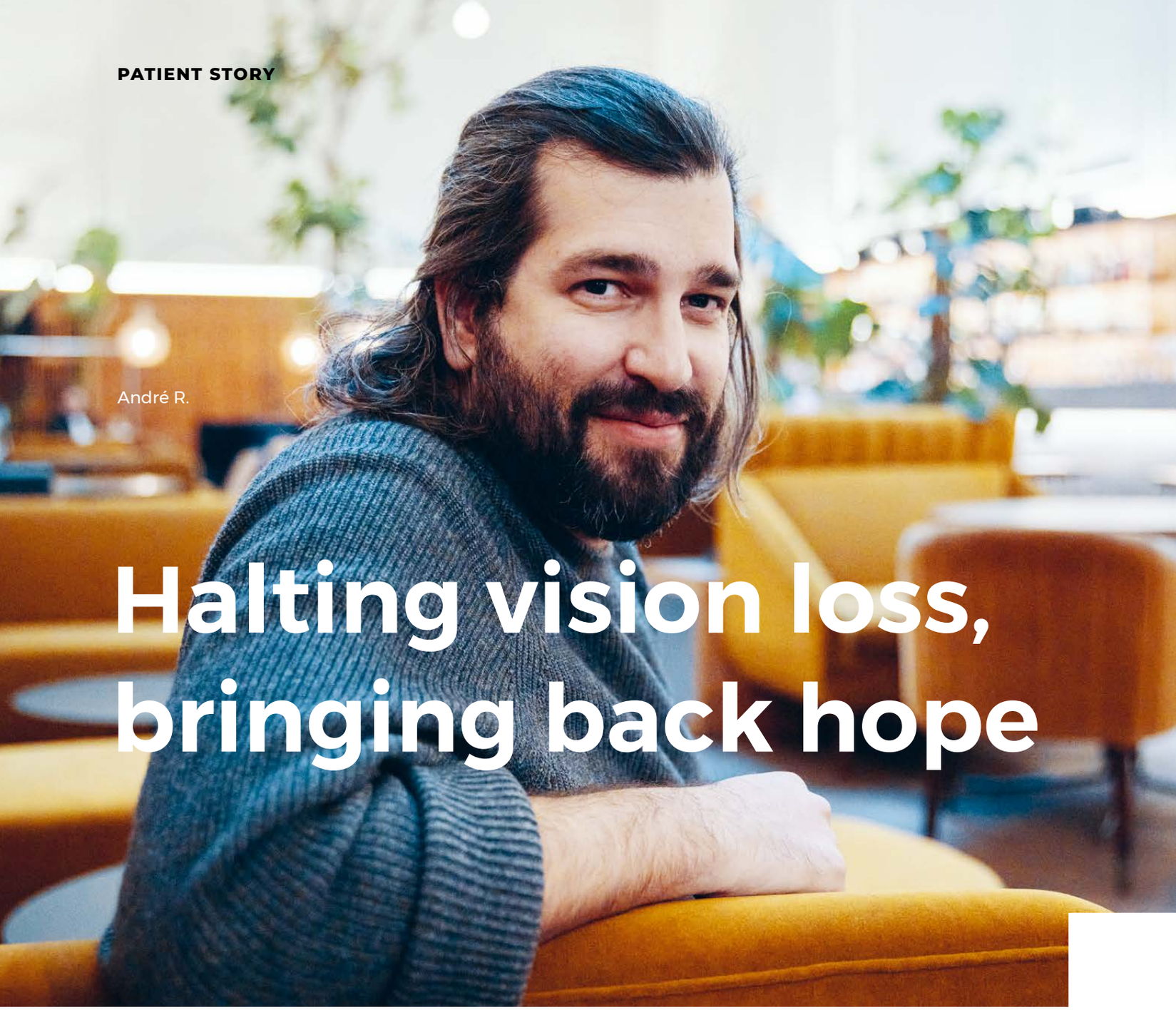
Norbert: We founded the Institute with the goal of learning enough about the eye to develop new therapies and change the current practice of medicine for the benefit of patients affected by blinding eye diseases. In the last five years, we have gone from an idea to concrete projects; this is something that attracts people and also donors.

What are the key goals that will shape IOB in the next five years?

Botond: The first five years have proven that our idea of moving away from developing therapies only in animal models to developing therapies in human tissues can work. In the next five years, we would like to concentrate on diseases that affect hundreds of millions of people.

Hendrik: One of the major decisions in the last few years was to move into diseases such as macular degeneration, myopia and glaucoma, because we know that the technologies we have developed can contribute to treating those conditions.

Norbert: The role of our operations is to enable people to follow through on their ideas, so we will make sure that scientists have enough resources to realize even the most ambitious ideas. I am close to retirement, but we have agreed that I will continue participating in IOB activities, because for me IOB is pure excitement! ■



André R.

Halting vision loss, bringing back hope

A debilitating condition is robbing André R. of his sight, but IOB is testing a groundbreaking treatment for this disease that may prevent André and others from going blind.

Last September, André R. packed his bags for a bucket-list trip: a safari tour through South Africa, Botswana and Zimbabwe that would get him close to some of the world's most impressive wildlife. "It may have been my last chance to see elephants and other big animals," says André, who is gradually losing his sight due to a disease called retinitis pigmentosa.

Retinitis pigmentosa is actually a group of diseases caused by mutations in roughly 100 known genes that trigger deterioration of cells of the retina and eventually blindness. There is no cure, but for André there may be some hope. He suffers from a type of retinitis pigmentosa for which a tentative therapy has shown promise in early trials. IOB is taking part in a clinical study to examine whether that therapy can halt progression of the disease, and André may soon receive the treatment.

"It's the only chance I have," he says, "and if this therapy can stop my condition, I may be able to do another safari in six years."

Going blind

When André was a child, his parents noticed that he often relied on tactile clues for orientation and movement in his surroundings. But it was not until André turned 14 that he was diagnosed with retinitis pigmentosa.

Rod photoreceptors are a type of cell in the retina that allow us to see in dark conditions, and in people with retinitis pigmentosa these start to die off. The earliest symptom is night blindness, followed by a narrowing of the visual field known as 'tunnel vision'.

As the disease progresses, dying rod photoreceptors compromise another type of photoreceptor – the cones, which are most abundant in the center of the eye and allow us to see in light conditions. This leads to loss of central vision and eventually blindness.

André began seeing poorly at night in his late teens, but as long as he was careful and got help to move about in the dark, everything was fine. After finishing school, he started work in a travel agency and a few years later moved to a bank. However, as he approached his 30th birthday his condition worsened. “Even simple tasks started to get difficult and I could no longer read well,” he says.

André eventually went back to the travel agency, but his sight continued to decline and he had to look for a new position within the company. He is now employed as a customer service agent and has had to learn an entirely new way of working. He uses a software application that reads aloud the contents of his inbox one email at a time, and he has mastered a program that allows him to zoom in on images or text on the computer.

In recent years, André’s sight has further declined and six years ago he started to use a white cane to navigate the outside world. Since mid-2022, his guide dog Mysak helps him travel to work, but tasks such as grocery shopping have become extremely complicated. “I can’t read product packages to learn what they contain,” he explains.

Gene therapy

André has a type of condition known specifically as X-linked retinitis pigmentosa that is caused by a faulty gene called RPGR sitting on the X chromosome. Currently, there is no approved treatment for X-linked retinitis pigmentosa, but biotech company MeiraGTx and pharma giant Janssen have developed a therapy that delivers functional copies of the RPGR gene to counteract the loss of photoreceptors in the retina.

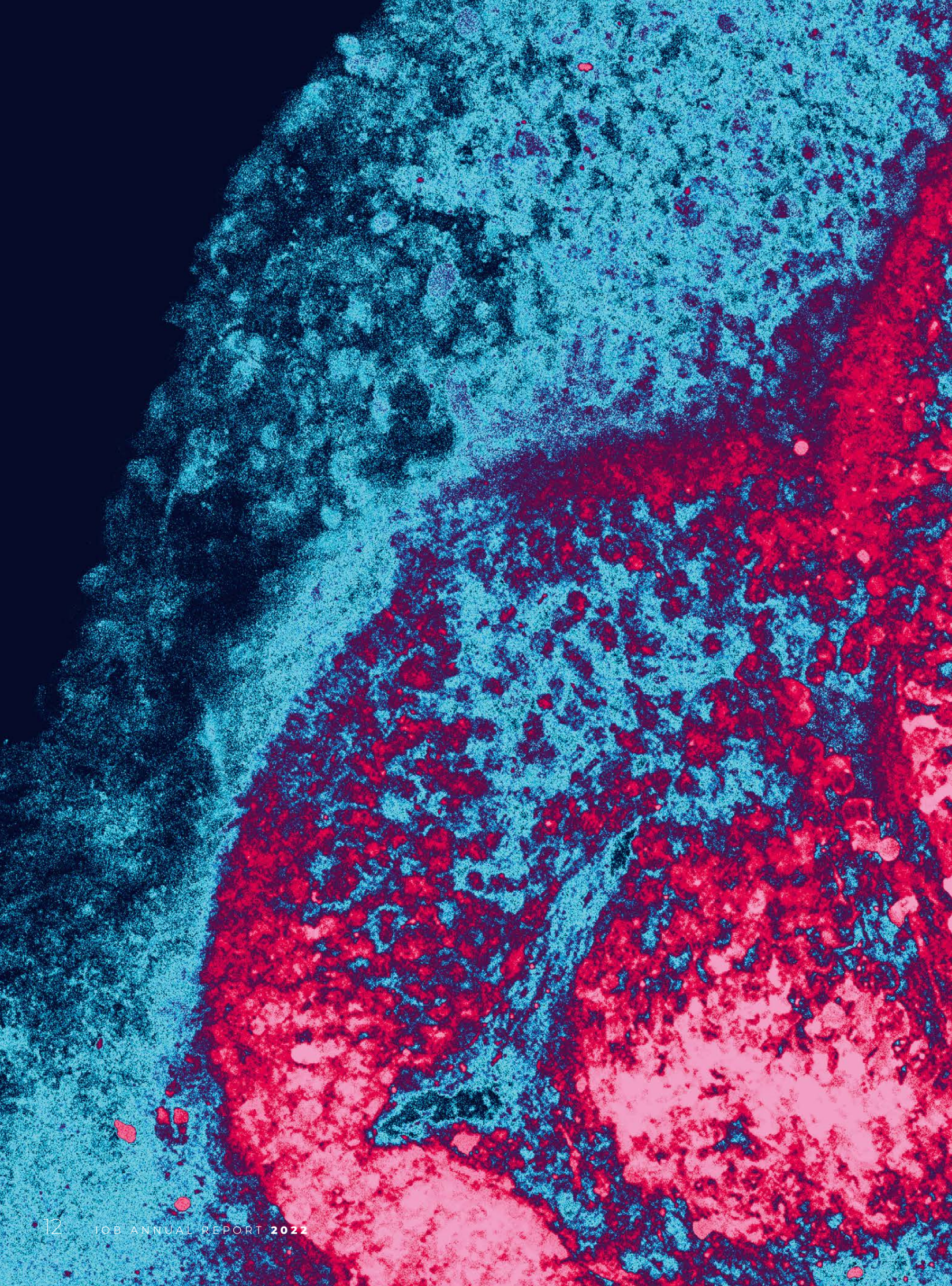
To insert the RPGR gene directly into photoreceptors, scientists use a vehicle called a vector – an innocuous virus that is genetically engineered to deliver the RPGR gene. A tiny amount of solution containing billions of vectors is injected underneath the retina, where the vectors have access to the photoreceptors and deliver the gene. "The healthy gene remains in the target cells forever and, therefore, a one-time injection should be effective for the patient's lifetime," says IOB co-Director Hendrik Scholl.

In early trials, this gene therapy was found to be generally safe and well-tolerated, and it led to significant improvements in retinal and visual function in treated participants compared to untreated controls. IOB and the Eye Clinic of the University Hospital Basel are conducting a late-stage trial to confirm and expand these findings.

"One and a half years ago, we ran a pilot study to find eligible patients based on genetic and visual tests," says study coordinator Nils Schärer at the IOB Clinical Trial Center. The team is now doing a second screening that involves vision assessment using a mobility maze. The maze tests a patient's ability to navigate obstacles across a broad range of light conditions. If André is eligible for the study, he will receive the therapy within one year and then undergo several vision tests to assess whether his vision loss has halted.

"There are few sites around the world that can do these complex trials," Scholl explains, "but we have an outstanding Clinical Trial Center at IOB that can conduct such studies. What is more, both IOB and the University Hospital Basel Eye Clinic have experience with gene therapy as well as unparalleled tools and expertise to examine the retina. Basel is also the only clinical trial site in German-speaking countries that has a mobility maze."

"We all hope that this therapy will stop the vision loss associated with X-linked retinitis pigmentosa," says study coordinator Daniela Hauenstein at the University Hospital Basel and at the IOB Clinical Trial Center. "This trial is the only hope for these patients." ■



SCIENTIFIC ACHIEVEMENTS 2022

Single-Cell Genomics Platform

FLASH-seq: a novel single-cell sequencing protocol for detecting genes at ultra-high resolution

PLATFORM LEADER: Simone Picelli

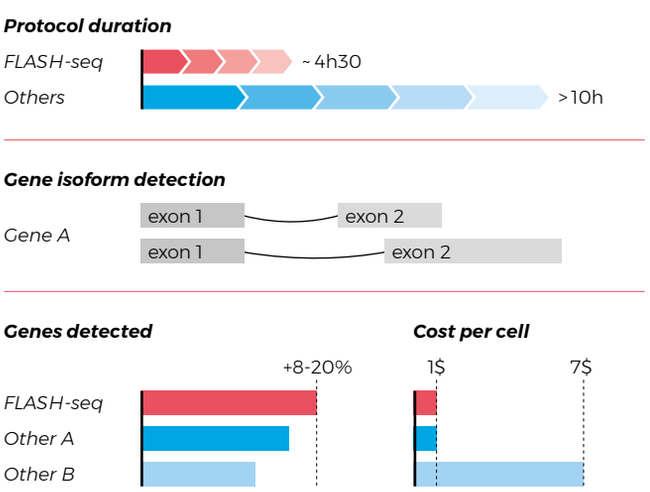
» FLASH-seq enables researchers to obtain a picture of the cell transcriptome at an unprecedented resolution.«

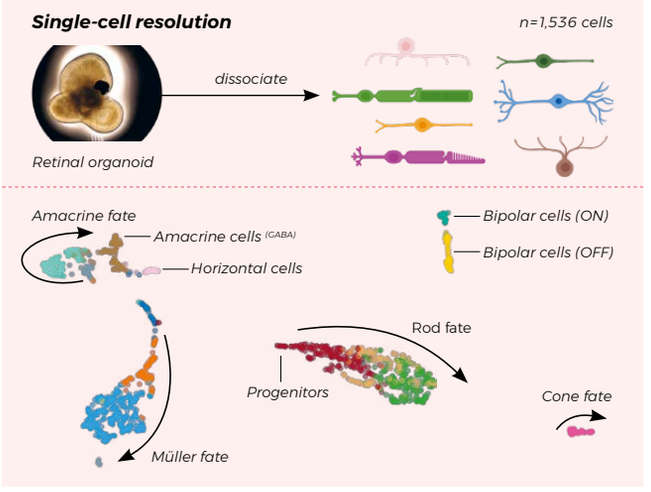
Existing single-cell full-length RNA-sequencing methods are laborious, expensive and often do not guarantee high performance.

To address these limitations, we developed FLASH-seq as a novel and inexpensive protocol that does not require the purchase of any commercial kit. Sequencing-ready single-cell libraries are generated in half a day with limited manual intervention. Reagent consumption is kept to a minimum by reducing reaction volumes to the nanoliter scale, leveraging the laboratory automation capabilities available at IOB. Thanks to its robustness, flexibility, and room for customization, FLASH-seq brings single-cell RNA sequencing within every scientist's reach, enabling the discovery of an unprecedented number of genes in each cell and shedding light on complex molecular mechanisms with unprecedented resolution.

We have used FLASH-seq successfully in human retinal organoids to investigate how key developmental gene isoforms are expressed in different cell types upon fate commitment. The choice of one gene variant over another has significant implications for protein function and offers a more nuanced interpretation of the differential expression results at the gene level. ■

FLASH-seq
A highly sensitive full-length single-cell RNA-sequencing protocol





Human Organoid Platform

High-throughput iPSC-derived retinal pigment epithelium for gene therapy screening

PLATFORM LEADER: Magdalena Renner

» I like to find easy solutions to difficult problems and I am very proud that we can now easily produce thousands of high-quality retinal organoids for screening applications.«

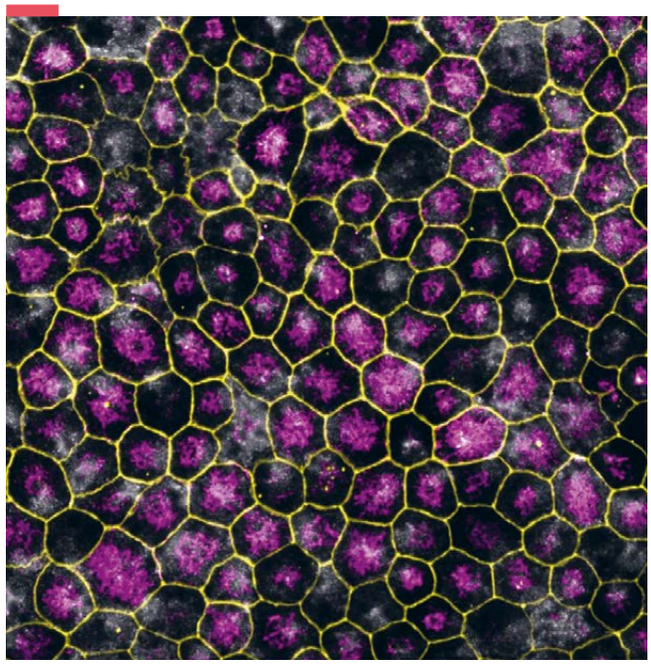
The retinal pigment epithelium (RPE) is crucial for vision and often degenerated in blinding diseases. We mass-produce RPE from human stem cells for gene-therapy screening.

A convenient method to study human RPE is to differentiate RPE cells from induced pluripotent stem cells (iPSC). Many different methods have been used to this end, but most published protocols require enriching RPE cells by time-consuming manual microdissection or cell-sorting procedures. We have developed an optimized protocol that allows the generation of pure RPE for high-throughput screening applications without the need for laborious enrichment steps. We validated our iPSC-derived RPE (iRPE) by thoroughly comparing it to human adult RPE. Furthermore, we analyzed which signaling pathways are important in the differentiation process and modulated those pathways with small molecules to optimize the differentiation outcome.

Finally, we tested whether our iRPE can be used as a gene-therapy pre-screening tool to select only the best candidates for validation in human explant cultures, which are of limited availability. We infected iRPE cells with adeno-associated viral vectors (AAVs) bearing different genetic elements driving the expression of a green fluorescent protein (GFP). We found similar levels of GFP expression in iRPE and human RPE explants, thus validating our in vitro model as a suitable gene-therapy pre-screening tool. ■

Image of iPSC-derived retinal pigment epithelium (RPE)

■ *Brightfield*
■ *ZO-1 (cell junction marker)*
■ *RPE65 (RPE marker)*



Complex Viruses Platform

AAV-screening platform for finding new promoters for targeted gene therapy

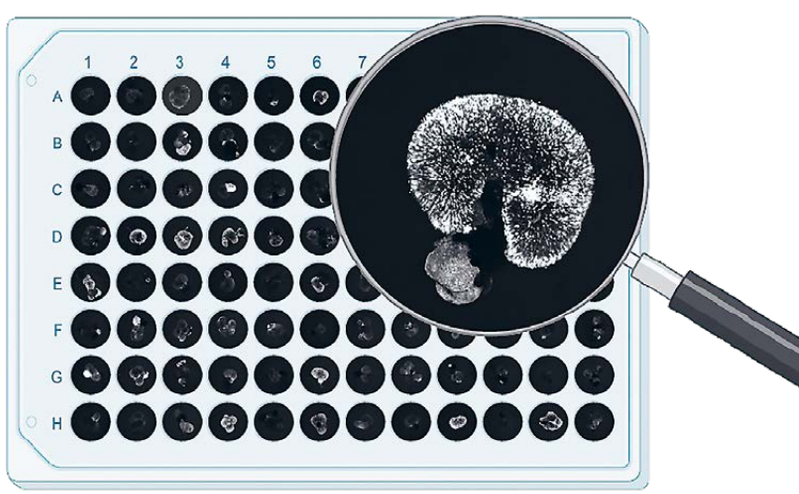
PLATFORM LEADER: Josephine Jüttner

» I am proud to know that automating our processes will benefit many future projects at IOB.«

Gene delivery targeted only to disease-critical cell types greatly enhances the therapeutic potential of adeno-associated virus (AAV)-mediated gene therapy and reduces undesirable side effects.

This is achieved by placing a specific on-off switch for gene expression – a promoter – in the viral genome. Since the precise mechanism of cell type-specific expression is not yet understood, many promoter variants need to be tested to find the ideal expression profile for treatments. Currently, human retina explants from post mortem donations are used to test individual AAV promoters, but limited donations curb the number of variants tested.

Human retinal organoids closely resemble most cell types of the human retina and can be generated in large numbers. Our approach uses the more available model system of retinal organoids to pre-screen promoter variants on human-derived tissue. The semi-automated pipeline starts with the cloning of AAV plasmids harboring promoter variants driving GFP in 96-well plate format, followed by high-throughput production of AAVs on a scale sufficient to infect retinal organoids. AAV promoter variants are evaluated by fluorescent imaging of GFP expression in therapeutically relevant cell types and ranked for further evaluation on human retina explants. Promoters already reported for cell type-specific expression in the human retina could be confirmed (see figure). Besides speeding up discovery of new cell-type targeting promoter sequences, the organoid model provides new tools for understanding retinal diseases. ■



96-well plate with confocal images of organoids infected with promoter AAVs identified in previous studies targeting GFP expression to therapeutically relevant cell types.

Scientific Computing Platform

Analyzing cell types and circuits in the healthy and diseased human eye

PLATFORM LEADER: Cameron Cowan

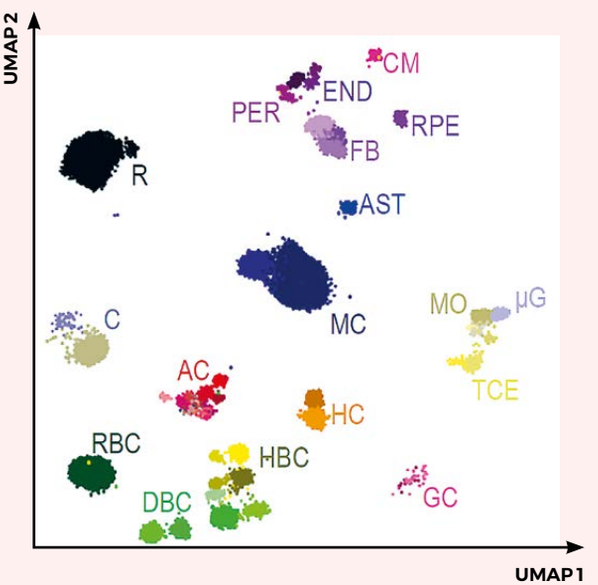
» We are pushing the boundaries of human retinal research by improving standards for tissue, data, and analysis quality.«

We bring quantitative methods to bear on large scientific data sets to generate insights into the genetics and circuitry of the human retina.

On the inner surface at the back of the human eye is a thin tissue layer called the retina. When light from the world around reaches your retina, photons are detected by specialized photoreceptor cells. These visual signals are converted into electrochemical signals as the language of neurons and sent through a series of retinal neural circuits. These circuits compress the high-resolution information into a more useful and easily transported form before it is sent to the brain. While other vertebrates also have retinas, they have different circuits that compress the information. So, in order to understand how human eyes work, we need to study human eyes.

To this end, we have developed methods to grow artificial human retinas in a dish and to maintain functional retinal tissue from organ donors. This allows us to map cell types, observe retinal circuits in action, and compare results between artificial retinal organoids and adult eyes, demonstrating the degree to which the in vitro model recapitulates the ex vivo organ. The result is an atlas of cell types in the human retina and its organoids that sets a new quality standard for these model systems. ■

Map of cell types from the human retina,
markers are individual cells and colors represent one cell type. Cells placed nearby express similar genes.



n=74,558 cells
n=6 eyes
n=3 donors

Quantitative Visual Physiology Group

From light to electrical activity in neurons and to eye-motion control

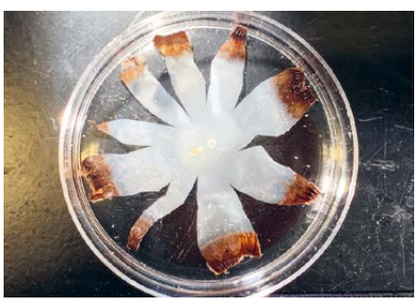
GROUP LEADER: Felix Franke

» We found out how neurons in the human retina keep visual information synchronized over large areas before it is sent to the brain, a necessity for successful vision.«

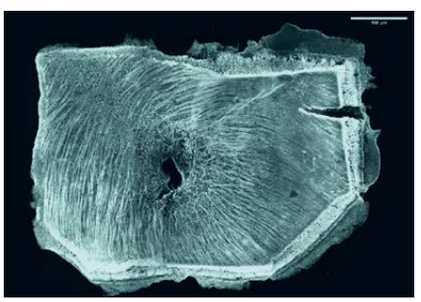
My group studies how the retina encodes incoming light into electrical activity and sends this information to the brain.

The eye is a remarkable sensory organ that converts light into electrical activity of neurons. This activity carries all the information about our visual world that our brain can access. The quantitative visual physiology group asks two central questions: How do neurons in our eyes encode the information about what we see, and what do the downstream neurons in the brain do with this information? We use methods from neurophysiology, ranging from microelectrode arrays to functional ultrasound imaging, to measure the activity of retinal and midbrain neurons when we stimulate the retina with specific light stimuli. Neurons in the retina and central nervous system come in a variety of different types, which can be identified using genetic, morphological, and functional characteristics. In the retina, different cell types encode different information about the visual world and send this information to different projection targets in the brain. Vision is active and we constantly move our eyes to scan the world. Specific cell types encode movement-related information from the light stimulus. One central question is the role these cell types play in coordinating or even eliciting eye movements and thus their role in eye movement disorders. ■

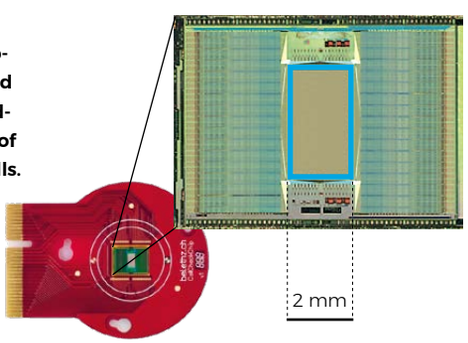
A
Entire dissected human retina.
Yellow spot in the middle: *Macula*
White spot: *Optic disc*
Brown rim: *Ora serrata and connecting tissue*



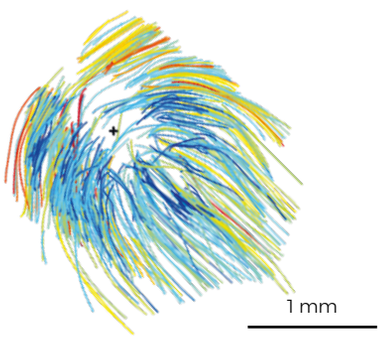
B
Piece of human retina including the fovea (whole in the center) after electrical recording.
Scale bar 500 µm.
Axons of retinal ganglion cells are stained with beta-III tubulin.



C
High-density microelectrode array used for electrical recordings of the activity of retinal ganglion cells.
Active area marked in blue.



D
Trajectories and conduction speeds of human retinal ganglion cell axons around the fovea centralis measured in the piece shown in B.
Blue: *slow*
Red: *fast*



Human Retinal Circuits Group

Cell types and molecules that lead to myopia formation

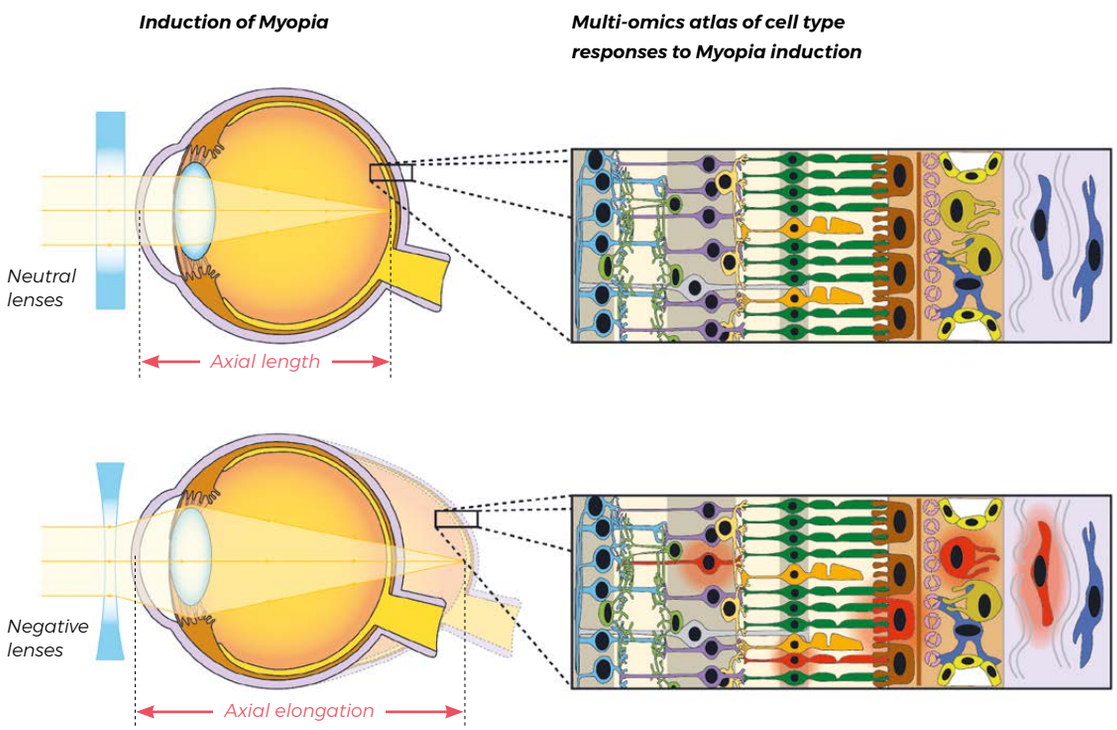
GROUP LEADER: Botond Roska

» We aim to understand the molecular mechanism of myopia and find ways to stop its progression.«

There is an ongoing myopia epidemic. By 2050, myopia will have become the most frequent cause of blindness due to the eye pathologies it induces.

Together with our collaborators, we have started a comprehensive investigation into the cell types and molecules in the retina-choroid-sclera tissues of the eye that control eye growth and are involved in the development of myopia. We perform single-cell RNA sequencing, proteomics, immunohistochemistry, and further quantification in three mammalian species during the induction of myopia by lenses. We then use viral and molecular tools to modulate in vivo the common cell types and pathways identified in the three species. In addition, we develop human organoids comprising retina, choroid and sclera and both activate and inhibit the identified pathways using small molecules and biologics. The goal of these experiments is to describe the molecular biology of eye growth and to find targets that we can modulate to interfere with the excessive eye growth that characterizes myopia. ■

Experimental approach to study cell types and molecules involved in the regulation of eye growth and myopia formation.



Central Visual Circuits Group

The visual thalamus is more than a relay station

GROUP LEADER: Botond Roska

» Understanding the function of the visual thalamus, which connects the retina to the visual cortex, is an exciting field of vision research.«

While we know a lot about the function of the retina and of the visual cortex, the functional role of the visual thalamus is far less understood.

Here we study how information traveling from the retina towards the cortex is modified in the visual thalamus, also called the lateral geniculate nucleus (LGN). We have developed methods to record separately the activity of excitatory and inhibitory neurons of the mouse LGN in vivo while stimulating mice with visual images. Moreover, we have used viral tracing from single inhibitory or excitatory LGN neurons to highlight the retinal ganglion cells that provide input to the targeted neuron in the LGN. We learned that inhibitory neurons are not randomly wired to the retina but are specialized in that they receive input from specific retinal channels formed by distinct types of retinal ganglion cells. Our functional recordings revealed that dLGN inhibitory neurons are also functionally specialized and we could provide a causal link between their anatomical input and functional specialization. Altogether, we found that each inhibitory interneuron globally encodes one visual feature originating mostly in the retina and is ideally suited to perform visual feature-selective attention. ■

Retinal ganglion cells connecting to a single inhibitory neuron of the LGN were labeled by a viral tracer.
The color of the labeled retinal ganglion cells encodes the laminar position within the retina.

Visual Cortex Plasticity Group

Cortical processing requires visual experience

GROUP LEADER: Andreas Keller

» Without previous visual experience, half of our visual system cannot process information correctly.«

Retinal diseases affect the brain beyond malfunction of the retina. The correct development of cortical processing requires visual experience.

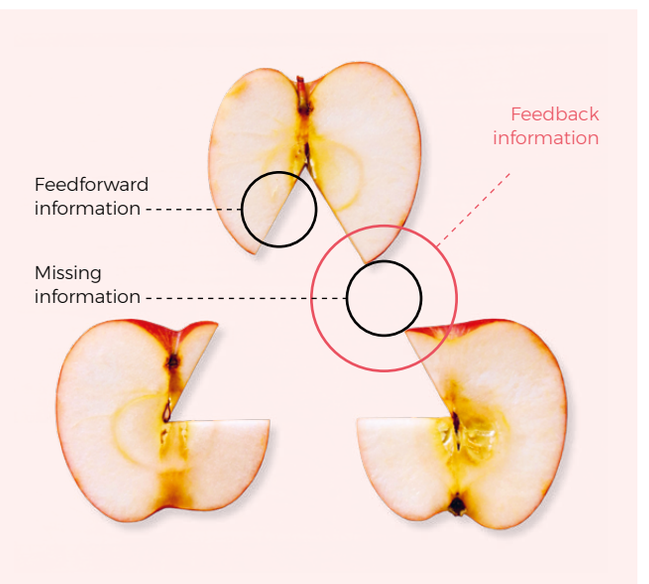
How does visual processing depend on experience? In the visual system, information passes forward from the retina to the primary visual cortex and then to higher visual areas. This feedforward pathway allows extraction of basic features from visual scenes by neurons, such as lines or edges. In addition to this feedforward pathway, the opposite flow of information also plays a crucial role in normal vision – the feedback pathway linking higher cortical areas to the primary visual cortex. When information is missing, for example due to obstruction, information is inferred from the surround through the feedback pathway. Therefore, both pathways are necessary for normal visual processing.

To investigate the experience dependence of visual processing, we raise mice in complete darkness and test whether neurons in the visual cortex can extract visual features based on feedforward and feedback pathways. Preliminary results show that visual experience matures feedforward pathways but is actually required for the development of feedback pathways.

Taken together, this work helps us understand how to support the visual cortex as it learns to process visual information after visual deprivation. ■

Feedforward pathways extract basic features from this image, such as lines (feedforward information, *left black circle).* To create the percept of a triangle, your sensory cortex fills in the missing information *(right black circle)* based on feedback information from higher visual areas *(red circle).*

The reason why you see this illusory triangle is because you have seen many triangles throughout your life. Circuits in the visual cortex are therefore shaped by experience and learning.



Theoretical & Computational Neuroscience Group

Neural coding as an internal simulation of the world

GROUP LEADER: Rava Azeredo da Silveira

» This project departs from classical approaches as it views perception jointly as encoding of the world and simulation of the world by the brain.«

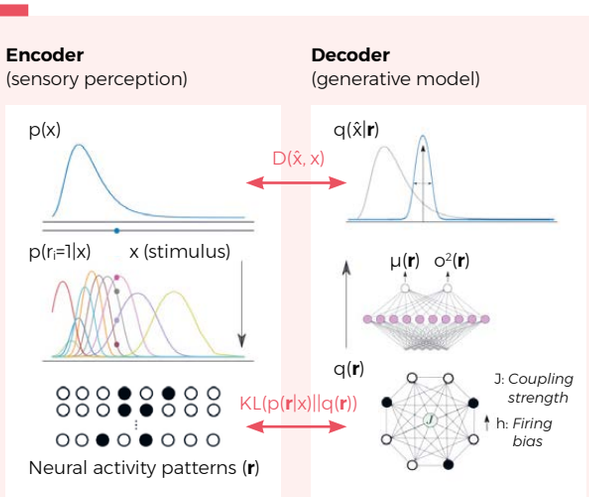
The retina and brain encode the visual world into electrical signals, but the brain can also visualize entities. How are these faculties related?

Classical theoretical approaches to vision and perception assume that the nervous system encodes visual and other sensory information with optimal efficiency. Properties of sensory neurons can be derived from this optimality principle. At the same time, the brain can generate percepts internally, which is what happens when we imagine an object or dream.

In a new approach, we propose that both processes – encoding sensory stimuli and generating internal simulations of sensory stimuli – are optimized jointly by the nervous system. This approach leads to new predictions of sensory neuron properties and of the nature of the internal neural representation of the sensory world. In particular, it attempts to explain why many sensory neurons are 'imprecise': this property leads to greater flexibility of the brain when generating internal simulations of the sensory world. Furthermore, our approach elucidates how the perceptual accuracy of the brain is related to the statistical properties of the sensory world. ■

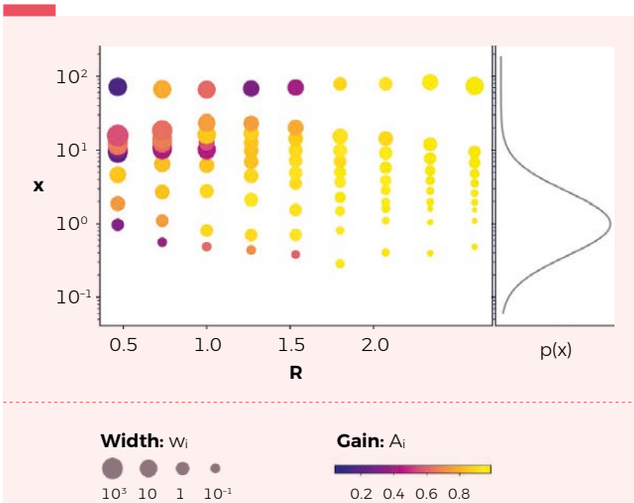
A

The visual system can be modeled as a sequence of an *encoder* and a *decoder*. The encoder is made up of an ensemble of neurons, each responding according to a tuning curve in a noisy manner. The decoder is modeled as a deep network which reconstructs stimuli given the neural population activity.



B

By optimizing jointly the encoder and the decoder subject to a resource constraint *(R)*, given a prior distribution over the stimuli *(p(x), solid curve)*, we predict the response properties of the neural population; each neuron is represented by a dot whose size denotes the width of the tuning curve and whose color represents the amplitude of the tuning curve.



Ophthalmic Genetics Group

Better and more precise diagnosis of genetic diseases

GROUP LEADER: Carlo Rivolta

» By using artificial intelligence, we help patients suffering from inherited visual loss to obtain a genetic diagnosis.«

DNA sequencing often uncovers genetic variants that are neither clearly pathogenic nor clearly benign. They represent a major hurdle for genetic diagnosis.

Some DNA variants of the human genome have no consequences for human health, while others – also known as 'mutations' – can cause disease. Surprisingly, however, despite being associated with very different outcomes, benign variants and mutations may look very similar at the molecular level and, therefore, it may be difficult to recognize them for what they are.

To gain insights into the features that make a DNA alteration innocuous or pathogenic, we studied the geographical distribution of all known variants of the human genome. We discovered that mutations tend to cluster in specific areas, while benign variants cluster in different regions, or not at all. In other words, certain regions within a gene are more susceptible to association with disease, while others are not.

We have taken advantage of these new findings to improve the prediction of pathogenicity for the many DNA changes that are routinely identified during genetic testing of patients. Specifically, we have created a new software, MutScore, that can recognize the deleterious potential of DNA variants as a function of their position within a gene.

MutScore, built with algorithms based on artificial intelligence, is freely available for non-commercial uses. We hope therefore that it will concretely help many physicians and scientists to understand the pathologic anatomy of the human genome and ultimately to provide patients with accurate genetic diagnoses. ■

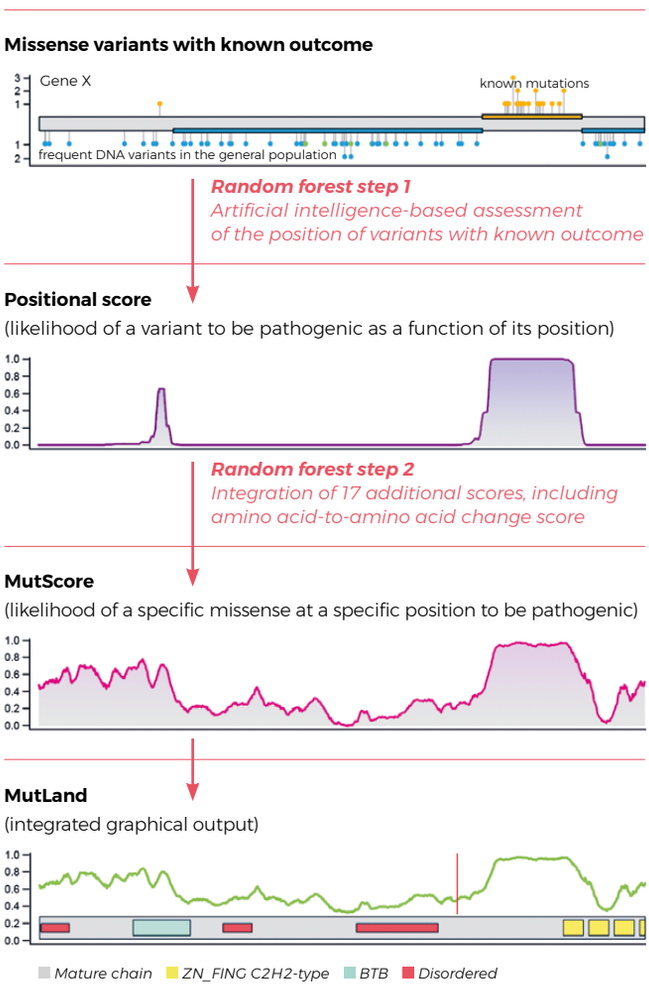


Figure first published in The American Journal of Human Genetics, March 3, 2022.

Genetic Epidemiology of Ophthalmic Diseases Group

ARMS2/HTRA1, the genetic manager of age-related macular degeneration

GROUP LEADER: Caroline Klaver

»Arresting the ARMS2/HTRA1 gene will avert blindness in many people.«

ARMS2/HTRA1 on chromosome 10 has long been a significant genetic puzzle in the AMD field. Solving the course of the disease will likely involve demystifying the science behind this gene.

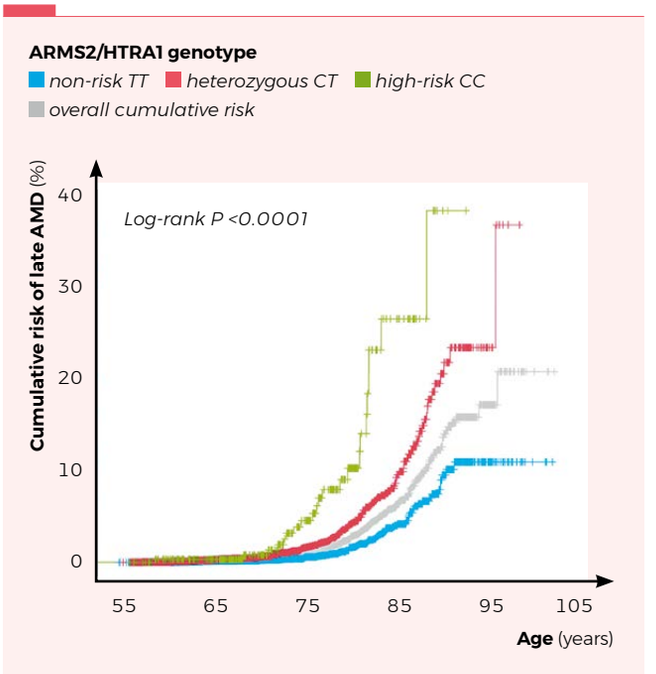
The research field of age-related macular degeneration (AMD) has been grappling with the role of ARMS2/HTRA1 on chromosome 10, a gene locus that is significantly involved in this disease. There is evidence that suggests it differs widely from that of another gene set also known to be strongly related to the development of AMD and encoding complement factors of the immune system. Identifying the function of the genes the variants of which are primarily responsible for the pathogenesis of a disease is key to future therapy development.

We used the currently largest European AMD study (N=17,204) to define AMD disease characteristics in the retina of human subjects carrying risk variants of ARMS2/HTRA1 and compared them to those carrying risk variants of complement factor encoding genes.

We could show that 65% of the subjects with end-stage AMD carried risk variants in ARMS2/HTRA1, whereas 77% carried risk variants in complement genes; in about half of the subjects risk variants could be detected at both sites. Disease characteristics were very similar for all risk variants and risk variants of the analyzed genes were more likely to be identified in late than in early disease stages. Compared to high-risk variants of individual complement genes, ARMS2/HTRA1 high risk variants were stronger related to wet (neovascular) AMD, to end-stage AMD 9 years earlier, and to a higher incidence of blindness.

Our study shows that ARMS2/HTRA1 risk variants are stronger associated with AMD development than individual complement genes. ARMS2/HTRA1 variants are therefore an important target for the development of future AMD therapies. ■

Late AMD
Lifetime risk of end stage AMD for double risk carriers *(green line)*, single risk carriers *(red line)*, and no risk carriers *(blue line)* in ARMS2/HTRA1. The *grey line* represents the population risk of end stage AMD.



Ophthalmic Epidemiology & International Ophthalmology Group

International collaborative ophthalmology

GROUP LEADER: Jost B. Jonas

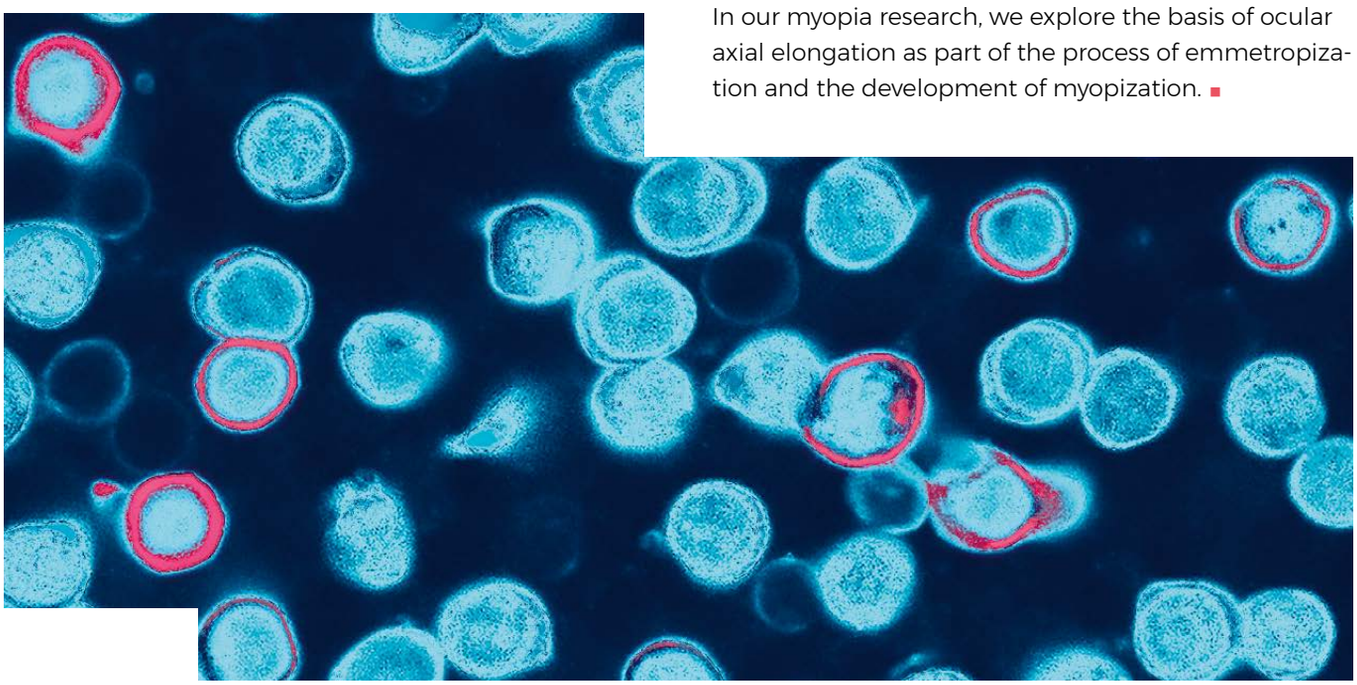
» We advance the frontiers of common scientific knowledge in various fields of ophthalmology.«

The group is involved in international epidemiology with respect to eyes and general medicine in countries such as India and China.

We have strong collaborative ties with institutions such as the Singapore Eye Research Institute; Beijing Institute of Ophthalmology at Beijing Tongren Hospital; Tsinghua University Beijing; the Department of Ophthalmology of the Fudan University Shanghai; the Zhongshan Ophthalmic Center of the Sun-Yat-sen University in Guangzhou; the Department of Ophthalmology of Hohhot, Inner Mongolia; the Ufa Eye Research Institute in Bashkortostan / Russia; the Shankara Nethralaya in Chennai / South India; the Suraj Eye Hospital in Nagpur / Central India; and the Shiley Eye Center, University of Southern California at San Diego, USA.

Our research topics include epidemiology, the diagnosis of optic nerve diseases including the glaucomas, intravitreal cell-encoated drug therapy, the intravitreal application of medications for the treatment of intraocular edematous, proliferative and neovascular diseases such as exudative age-related macular degeneration and diabetic retinopathy, contact lens-associated ophthalmodynamometry, clinical aspects of cornea, cataract, glaucoma, retinal and vitreoretinal surgery, the prevalence, anatomy, development, prevention and therapy of myopia, ocular biomechanics in the eye, and the retinal microglial system.

In our myopia research, we explore the basis of ocular axial elongation as part of the process of emmetropization and the development of myopization. ■



Ophthalmic Translational Research Group

Base editing for Stargardt disease

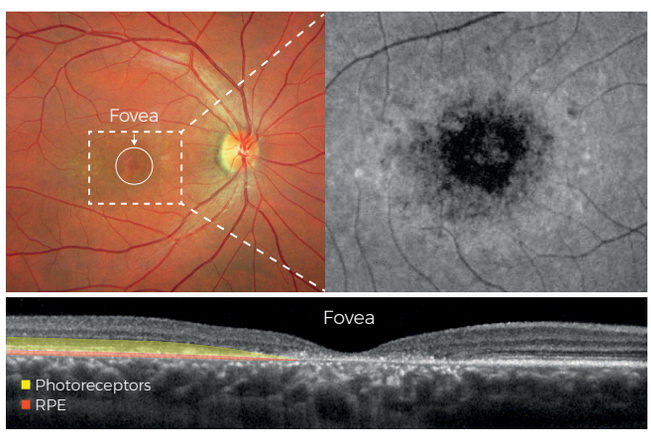
GROUP LEADER: Bence György

» Base editing allows correction of a single typo out of 6.3 billion characters.«

IOB researchers together with BEAM Therapeutics, Inc. (Cambridge, MA) have developed a technology to allow correction of the most common mutation in Stargardt disease.

Stargardt disease is caused by mutations in the *ABCA4* gene and is the most common form of inherited macular degeneration. Affected patients progressively lose their ability to read, drive, and recognize faces, ultimately leaving them blind. In this project, we developed an adenine base-editing strategy to correct the most common point mutation in Stargardt disease. The strategy was developed in human retinal organoids, human retinal explants, and humanized mouse models carrying the target mutation. Gene correction was observed up to ~70% of photoreceptors and 95% of retinal pigment epithelial cells in mutation-carrying mice in vivo. Direct genetic correction of the underlying genetic problem holds promise for patients with Stargardt disease. ■

A – Stargardt disease retina *ABCA4:* [c.5882G>A, p.Gly1961Glu]



B *ABCA4:* [c.5882G>A,c.5883A, p.Gly1961Glu]

5′– CTGTGTGTCGAAGTTCGCCCTGGAGAGGTG –3′
3′– GACACACAGCTTCAAGCGGGACCTCTCCAC –5′
Leu Cys Val Glu[1961] Val Arg Pro Gly Glu
Intron 42

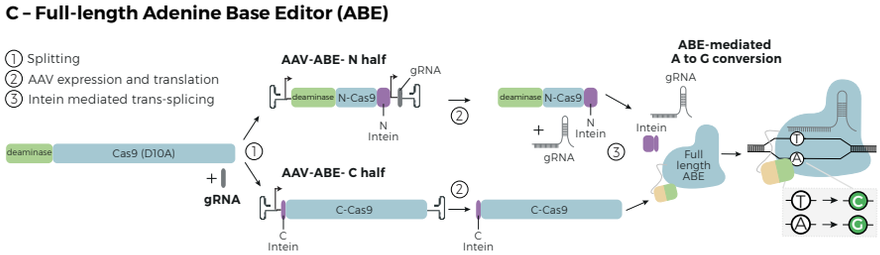
adenine base editing

ABCA4: [c.5882G,c.5883A>G, p.Gly1961=]

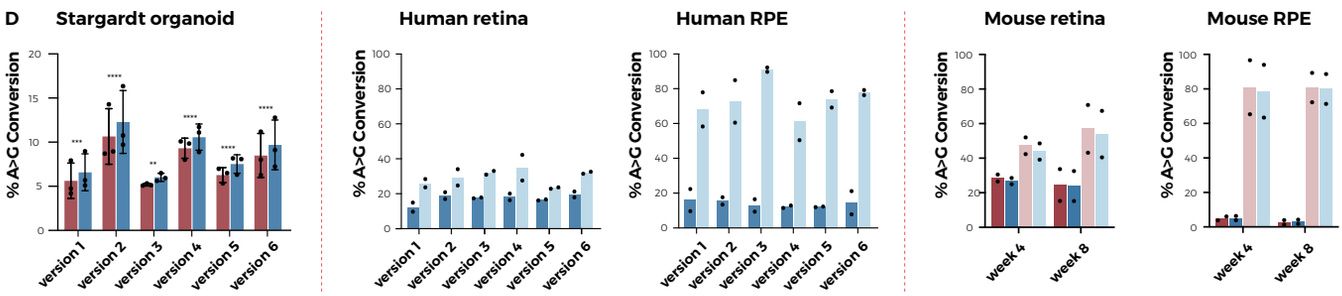
5′– CTGTGTGTCGGGGTTCGCCCTGGAGAGGTG –3′
3′– GACACACAGCCCCAAGCGGGACCTCTCCAC –5′
Leu Cys Val Gly[1961] Val Arg Pro Gly Glu
Intron 42

PAM site ABE window
A7 target base A8 wobble base G7, G8 base editing outcomes

C – Full-length Adenine Base Editor (ABE)



D



genomic DNA target base genomic DNA wobble base
ABCA4 mRNA target base *ABCA4* mRNA wobble base

Myopia Research Group

The retina in myopic eyes stops inhibiting eye growth

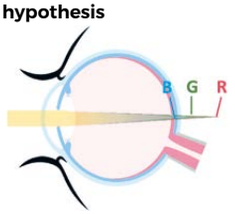
GROUP LEADER: Frank Schaeffel

» The inhibitory pathway of emmetropization, involving signals derived from longitudinal chromatic aberration (color fringes), was found to be compromised in myopic eyes.«

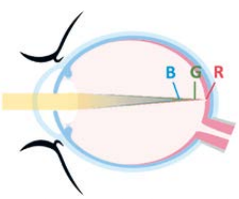
In myopia, the eye grows too long and the retinal image of distant objects is poorly focused.

During development, eye growth is perfectly controlled so that people can see sharply at a distance. An unresolved question is why near-sightedness (myopia) develops and why it is not stopped by inhibiting further eye growth. To be able to do this, the retina needs to detect that the image is focused in front. We found that this is done by comparing focus in the red and the blue. Because red light is refracted less than blue, the eye is less myopic in the red. The difference in focus is called longitudinal chromatic aberration (LCA) and is known to most myopes as they can read red neon signs at night better than blue. We found that the retina uses this information to determine which way the eye should grow. Young subjects watched movies that were digitally filtered to present either the blue or the red channel with a calculated defocus. Already after 30 minutes, eyes became slightly shorter when blue was blurred but slightly longer when red was blurred (effect sizes 10–20 µm), even though the movies looked similar to the subjects. In myopes, such changes in eye length could not be elicited. Apparently, the myopic retina no longer generates a signal for eye growth inhibition. ■

Key hypothesis

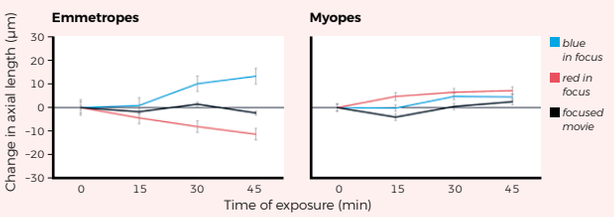


When blue is presented in better focus than red and green, the retina should detect that the eye is too short and induce *axial elongation.*



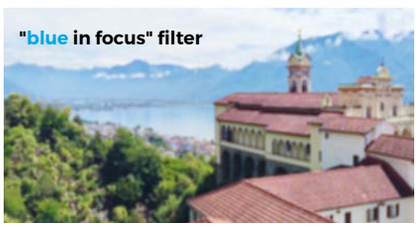
On the other hand, when red is in better focus than blue and green, the retina should inhibit *further eye growth.*

Results



In *emmetropic eyes*, "red in focus" caused significant eye shortening and "blue in focus" caused eye elongation which is in agreement with our hypothesis.

Strikingly, *myopic eyes* did not respond to these stimuli, indicating that they no longer detected chromatic cues to inhibit eye growth.



Example of images that were digitally filtered to present the blue ("blue in focus") or red ("red in focus") image plane in best focus.

Ophthalmic Imaging & OCT Group

Retinal vasculature dynamics

GROUP LEADER: Peter Maloca

» We succeeded in characterizing the dynamics of retinal vessels using time-resolved structural optical coherence tomography (OCT).«

Retinal vessels can be statically imaged with optical coherence tomography. This is also possible with OCT angiography but without features for the dynamics.

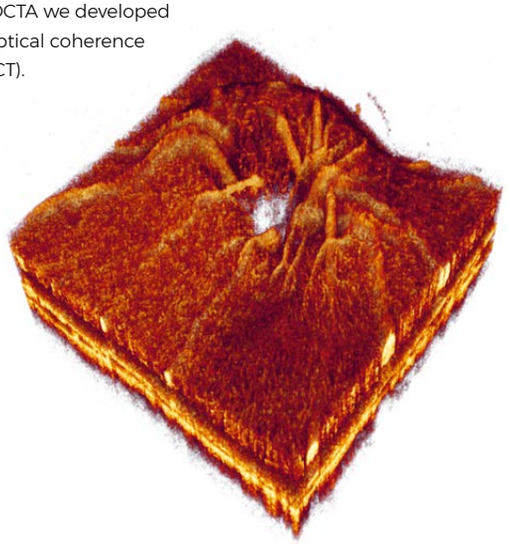
A healthy retinal blood flow is central to maintaining vision. Currently, it is only possible to visualize this blood flow by injecting dyes, although side effects such as nausea or vomiting may occur. Therefore, an imaging method has been developed with optical coherence tomography (OCT), which uses a harmless laser to image retinal tissue with micrometer resolution without even touching the patient.

Retinal images were taken with a special pattern developed by our laboratory that allows visualization of blood flow at four different sensor integration times (7.24 ms, 11.2 ms, 22.4 ms, 44.8 ms). Time-resolved structural OCT revealed pulsatile intensity changes in the analyzed vessels. Fringe washout analysis enabled calculation of the axial components of the blood flow velocity. Time-resolved structural OCT with its high spatial and temporal resolution provides promising information about retinal perfusion. ■

OCTA & time-resolved OCT at the optic nerve head

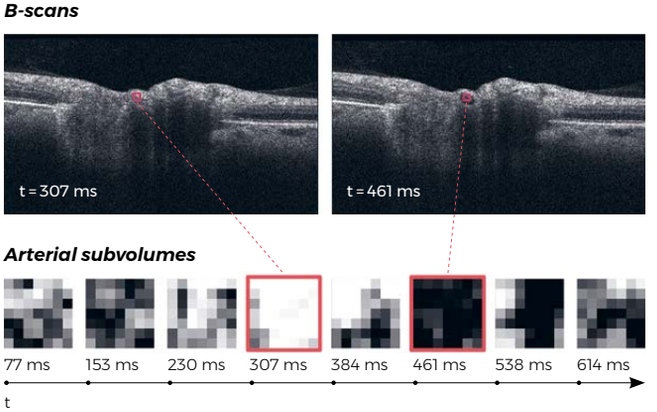
A

Volume-rendered, three-dimensional optical coherence tomography angiography (OCTA) of a healthy optic nerve head. OCTA enables the static visualization of the retinal vasculature at a depth-resolved micrometer-scale. To address the lack of dynamic flow information in OCTA we developed time-resolved optical coherence tomography (OCT).



B

Time-resolved OCT B-scans of optic nerve head vessels. Imaging was performed at the same location. Two B-scans and eight extracted arterial subvolumes are shown with timestamps (corresponding subvolumes framed in red). The intensity changes in the subvolume occur due to varying fringe washout of the OCT signal in the artery over time.



Clinical Trial Center Platform

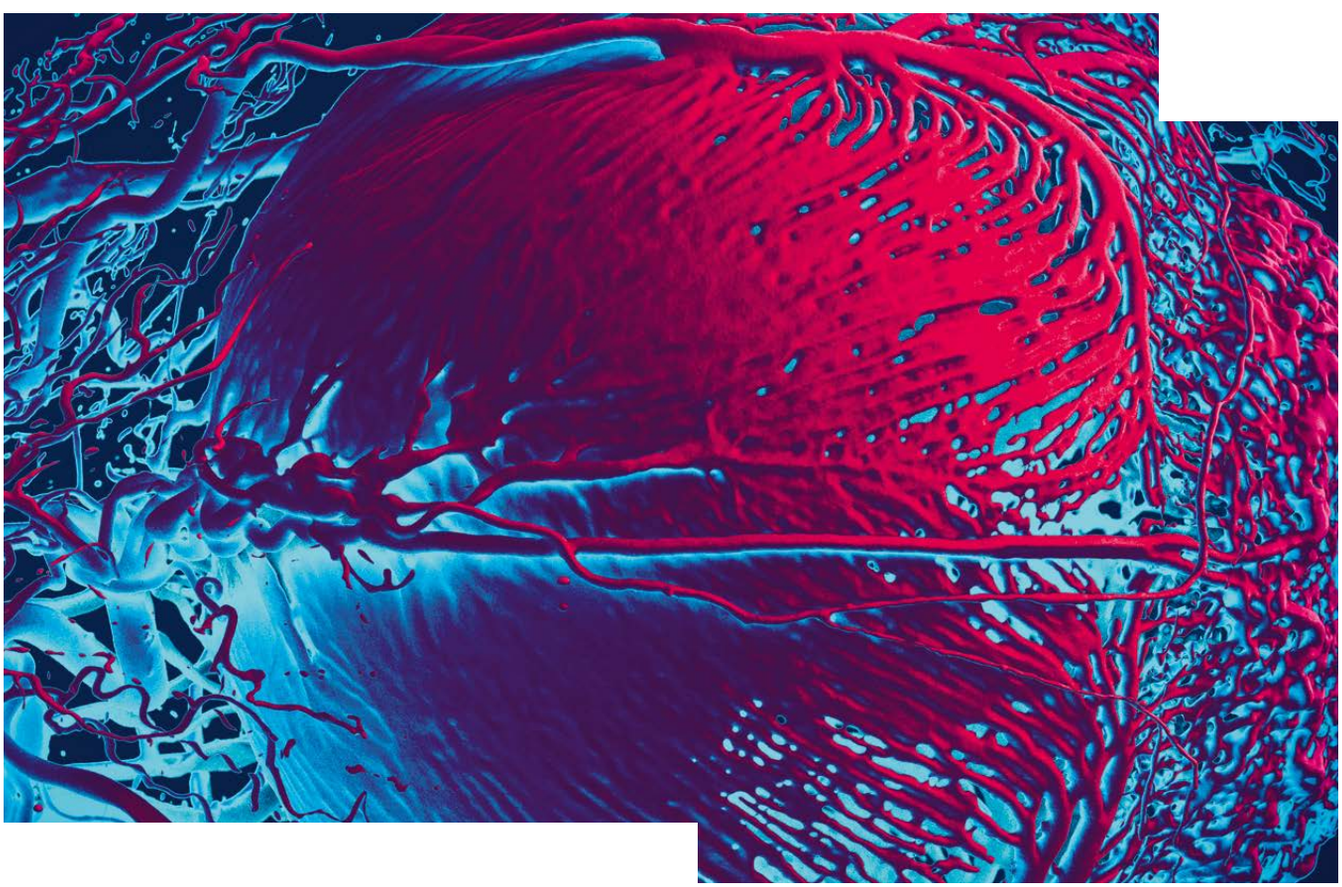
The Clinical Trial Center – service and support of clinical research

PLATFORM LEADER: Christian Prünte

» We design, plan and conduct clinical studies and guarantee their quality with respect to Good Clinical Practice (GCP).«

Presently, the Clinical Trial Center is coaching and supervising 28 trials in the IOB and the University Eye Clinic.

Solving scientific problems and questions in human clinical and translational research often requires a clinical trial with patients and/or healthy volunteers. However, there are numerous regulations and comprehensive standards that take into account the safety and rights of participants. The highly professional staff of the Clinical Trial Center helps investigators to translate a research idea into a realistic study design and then plan and conduct the study. There are many hurdles to overcome, such as certifying investigators and nurses, writing applications, patient information and case report forms (CRFs), and finally convincing local and national ethics committees. Clinical trials remain the ultimate proof of testable hypotheses of clinical relevance and the vehicle for introducing new therapies for clinical use. ■



Visual Neurophysiology Platform

Determining the progression rate of G1961E-associated Stargardt disease

PLATFORM LEADERS: Maximilian Pfau & Hendrik Scholl

»As the next step toward precision medicine, we are investigating how specific ABCA4 gene variants – besides causing Stargardt disease – influence the age of onset and subsequent progression rate of Stargardt disease.«

The 'First Orbit' study investigates the progression of retinal degeneration and its functional consequences in patients with G1961E-associated Stargardt disease.

Stargardt disease (STGD1) is the most common inherited retinal disease leading to legal blindness in the working population. Two decades after identifying the causative gene, it is becoming increasingly clear that the specific *ABCA4* variants – besides causing the disease – markedly influence the disease trajectory.

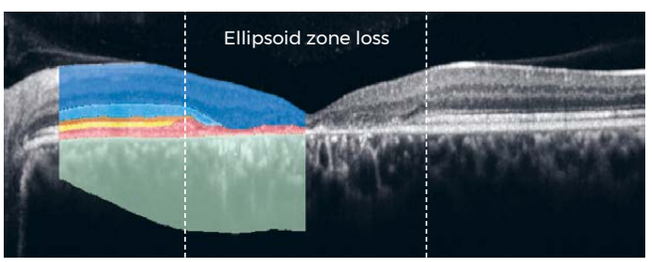
Paralleling the development of a gene-editing therapy for the common *ABCA4* p.G1961E variant at IOB (PI: Bence György, Head of the Clinical Translation Group), we have now initiated a natural history study for this distinct subgroup of patients.

The 'First Orbit' study (a reference to the first space flight in 1961) will follow patients with G1961E-associated Stargardt disease for two years to assess their visual function and retinal structure over time.

We will systematically score the re-test reliability and the ability to detect a change for a panel of visual function assessments. This includes refined visual acuity, contrast sensitivity as well as light- and dark-adapted visual field testing. Through genotype-phenotype correlation, we will assess the influence of the second *ABCA4* variant on the disease progression.

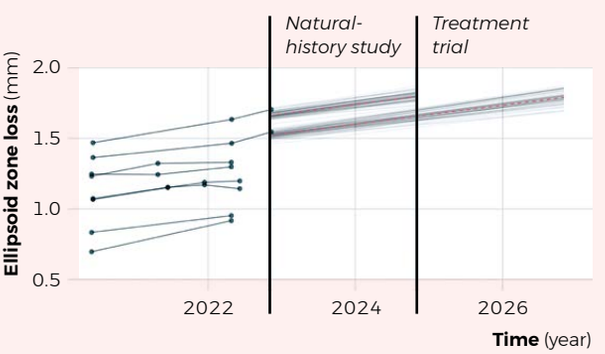
Combining these data will allow us to identify patients who could benefit the most from therapy, select the optimal visual function assessment to follow patients, and define the follow-up intervals required to prove treatment effects. ■

A.I.-based segmentation



Inner retina
Outer nuclear layer
Photoreceptor inner segments
Photoreceptor outer segments
Retinal pigment epithelium
Choroid

Progression of photoreceptor loss



Training the leaders of tomorrow

In its first five years, IOB has established itself as one of the world's flagship centers for vision research. Now, the Institute is working towards a further ambitious goal, that of training talented young scientists to become future leaders in academia, industry, and other sectors.

To achieve this goal, in 2022 IOB launched a PhD and MD-PhD program in Translational Visual Neurosciences. This is open to students with a Master degree or equivalent in natural sciences, computer science, medicine, or engineering. The program provides a one-of-a-kind opportunity to make breakthrough discoveries in vision research and develop new therapies for eye diseases. In addition to excellent scientific training, the program offers core courses and transferable-skill workshops to help students realize their full potential.

Program coordinator **Anita Soltermann** talks about the mission and content of the program and what makes it unique.

What is the mission of the IOB PhD and MD-PhD program?

IOB is establishing a spirit of education and training on top of great research. With this new program, we aim to train future innovative, interdisciplinary researchers and clinicians in the field of vision science. The goal is to develop a curriculum that spans basic, translational, and clinical research, so that PhD candidates in basic science can make contact with clinicians and possibly see a direct application of their findings in the clinic.

How many students per year will IOB accept?

We are planning to hire five to seven new students in each call, and there will be a call every year.

What makes this program unparalleled?

Its strong commitment to translational research. IOB covers the entire spectrum of vision research from basic research to patient-oriented clinical research, and we aim to expose our students to different fields, approaches, and technologies. Since IOB is a relatively small institute, we have the flexibility to tailor the curriculum to meet the needs and interests of individual students.

How will the program bridge basic and clinical research?

There will be a lecture series on Translational Visual Neurosciences where IOB group leaders present their research, and students pursuing a PhD in basic science will spend time in the clinic. In addition, scientists in the Technology Platforms will teach students different methods and technologies. Students will also have the opportunity to help develop the program and build on their own ideas.

What does the curriculum include?

When students start, they receive training in skills that they will need during their PhD, including data analytics, statistics and science visualization. But we also want to equip young researchers with skills they will need in their future careers, whether in academia or industry. So, we will offer management and leadership courses, training in communication and scientific writing, career development workshops, and more. We are also planning an Industry Day when students can come into contact with industry representatives. The strong core and complementary training, in addition to the opportunity to take part in cutting-edge vision research, will boost our students' overall employability.

What do you enjoy most about your role as program coordinator?

I like meeting young researchers from all over the world, and it is great to see how everybody works towards the same goal. The PhD and MD-PhD program is supported by a foundation and this allows us to mentor a larger group of students at IOB on the one hand, and on the other hand to develop our own tailored training in addition to the excellent courses offered by the University of Basel. I am really enjoying building such a unique program. ■

Awards 2022

Awardee	Award	Institution
Alex Fratzl	EMBO Postdoctoral Fellowship	*European Molecular Biology Organization*
Jost Jonas	José Rizal Medal	*Asia-Pacific Academy of Ophthalmology*
Martin Munz	Bridge to Independence Award	*Simons Foundation Autism Research Initiative (SFARI)*
Dasha Nelidova & Botond Roska	Point of View Award	*ARVO Foundation for Eye Research*
Dasha Nelidova	Dieter W. Bäuerle Prize 2022 for Fundamentals and Applications of Laser-Matter-Interaction	*Dieter W. Bäuerle Foundation*
	ZEISS Research Award	*ZEISS*
Alvaro Herrero Navarro	EMBO Postdoctoral Fellowship	*European Molecular Biology Organization*
Maximilian Pfau	David R. Hinton MD Award	*Stephen J. Ryan Initiative for Macular Research*
Mathieu Quinodoz	SSMG Young Investigator Award	*Swiss Society of Medical Genetics*
	Grundlagenwissenschaftlicher Forschungspreis 2022	*PRO RETINA Deutschland e.V. und der Retina Suisse*
Magdalena Renner	Bert M. Glaser, MD Award 2022 for Innovative Research in Retina	*ARVO Foundation for Eye Research*
Botond Roska	Member of the Hungarian Academy of Sciences	*Hungarian Academy of Sciences*
Barbara Świątczak	Swiss OphthAward 2022	*Schweizerische Ophthalmologische Gesellschaft SOG & Bayer*
	Sek-Jin Chew Travel Grant	*ARVO Foundation for Eye Research*
Cameron Cowan & Magdalena Renner	Pfizer Research Prize	*Stiftung Pfizer Forschungspreis*

Key publications 2022

View all our papers listed in PubMed:

Title / Authors	Journal
Fast and highly sensitive full-length single-cell RNA sequencing using FLASH-seq *Hahaut V, Pavlinic D, Carbone W, Schuierer S, Balmer P, Quinodoz M, Renner M, Roma G, Cowan CS, Picelli S.*	*Nature Biotechnology*
General anesthesia globally synchronizes activity selectively in layer 5 cortical pyramidal neurons *Bharioke A, Munz M, Brignall A, Kosche G, Eizinger MF, Ledergerber N, Hillier D, Gross-Scherf B, Conzelmann KK, Macé E, Roska B.*	*Neuron*
Analysis of missense variants in the human genome reveals widespread gene-specific clustering and improves prediction of pathogenicity *Quinodoz M, Peter VG, Cisarova K, Royer-Bertrand B, Stenson PD, Cooper DN, Unger S, Superti-Furga A, Rivolta C.*	*The American Journal of Human Genetics*
Myopia – why the retina stops inhibiting eye growth *Świątczak B, Schaeffel F.*	*Scientific Reports*
Longitudinal Changes in Scotopic and Mesopic Macular Function as Assessed with Microperimetry in Patients With Stargardt Disease: SMART Study Report No. 2 *Kong X, Ibrahim-Ahmed M, Bittencourt MG, Strauss RW, Birch DG, Cideciyan AV, Ervin AM, Ho A, Sunness JS, Audo IS, Michaelides M, Zrenner E, Sadda S, Ip MS, West S, Scholl HPN; SMART Study Group.*	*American Journal of Ophthalmology*
Identification of New Vulnerabilities in Conjunctival Melanoma Using Image-Based High Content Drug Screening *Nardou K, Nicolas M, Kuttler F, Cisarova K, Celik E, Quinodoz M, Riggi N, Michielin O, Rivolta C, Turcatti G, Moulin AP.*	*Cancers (Basel)*
Iris Color Matters-A Contractility Analysis With Dynamic Volume-Rendered Optical Coherence Tomography Pupillometry *Valmaggia P, Inglin N, Kaiser P, Scholl HPN, Maloca PM.*	*Translational Vision Science & Technology*
Mutations in the ribosome biogenesis factor gene LTV1 are linked to LIPHAK syndrome, a novel poikiloderma-like disorder *Han JH, Ryan G, Guy A, Liu L, Quinodoz M, Helbling I, Lai-Cheong JE; Genomics England Research Consortium; Barwell J, Folcher M, McGrath JA, Moss C, Rivolta C.*	*Human Molecular Genetics*
Longitudinal Changes of Fixation Stability and Location Within 24 Months in Stargardt Disease: ProgStar Report No. 16 *Schönbach EM, Strauss RW, Cattaneo MEGV, Fujinami K, Birch DG, Cideciyan AV, Sunness JS, Zrenner E, Sadda SR, Scholl HPN; ProgStar Study Group.*	*American Journal of Ophthalmology*
Reference database of total retinal vessel surface area derived from volume-rendered optical coherence tomography angiography *Maloca PM, Feu-Basilio S, Schottenhamml J, Valmaggia P, Scholl HPN, Rosinés-Fonoll J, Marin-Martinez S, Inglin N, Reich M, Lange C, Egan C, Zweifel S, Adnan Tufail, Spaide RF, Zarranz-Ventura J.*	*Scientific Reports*

SCIENTIFIC ADVISORY BOARD

Translating science, advancing medicine

Professor Tien Wong, an internationally renowned physician-scientist, joined the Scientific Advisory Board (SAB) of IOB last year. Wong talked about what his expertise will bring to the table and shared his perspective on the Institute's strengths and the main challenges and opportunities for vision research.

What motivated you to join IOB's SAB?

I've known [IOB co-director] Hendrik Scholl for a long time, and I see that he's really pushing translational research, which I've also been very passionate about. Our visions match. Also, IOB is a new, ambitious organization: it is fairly independent and is more flexible and agile than traditional university-based institutes in Europe.

How will your expertise complement the skills and experience of IOB's directors and researchers?

I've developed at least two or three major institutes like IOB – in Australia and Singapore. So, I've seen some of the common challenges of building research centers and I may be able to help IOB not to make painful mistakes. Another thing that I bring to the table is an Asia-Pacific perspective. Hopefully, that perspective will also add to the diversity of the SAB.

What are IOB's main strengths?

Its interdisciplinary nature and the balance between basic science and clinical research are quite important. Major scientific achievements are collaborative and we need to make sure that IOB has that kind of perspective.

What is your view on the value of collaboration between researchers and clinicians that is at the core of IOB?

The concept is very easy: you don't want to only have scientific discoveries and you don't want just clinical strength. You need to have them combined together. Translational research means knowing two languages, so IOB must foster a culture where the scientists' language can be transferred to the clinical language, and the clinical needs and understanding of disease can be translated back to the scientific language. It's important that translators in any organization are those who know all the languages: the clinician-scientists.

What are the main challenges and opportunities for vision research?

One challenge is that governments do not fund vision research very much. The second is that a lot of vision research is relatively behind some other medical fields, so it's important for ophthalmology researchers to connect with researchers in other fields and maybe even attend conferences in other fields. Of course, there are also opportunities. For example, ophthalmology is ahead of the game in artificial intelligence, and the eye is easily accessible, unlike other organs such as the brain. Ophthalmology must take advantage of those opportunities. ■

Professor Tien Wong

Tien Y Wong is a physician-scientist and an internationally renowned retinal specialist with a focus on macular and retinal diseases. He leads an interdisciplinary research program on epidemiological, translational and clinical research on retinal diseases and ocular imaging. In 2022, Wong was appointed the Founding Head and Chair Professor of Tsinghua Medicine, a new academic healthcare system based at Tsinghua University in Beijing, China. From 2014 to 2021, he was the Arthur Lim Professor of Ophthalmology and Medical Director at the Singapore National Eye Centre, one of the world's largest tertiary eye hospitals. Prior to these roles, he held various appointments, including Executive Director of the Singapore Eye Research Institute and Head of the Department of Ophthalmology at the University of Melbourne, Australia.

Wong completed medical school at the National University of Singapore and later obtained an MPH and PhD from the Johns Hopkins University in Baltimore, USA. He received clinical training in ophthalmology at the Singapore National Eye Centre, with fellowships at the University of Wisconsin, Madison, USA, and the University of Sydney, Australia.

Members

José-Alain Sahel
M.D.

Chairman of the IOB Scientific Advisory Board –
Distinguished Professor and Chairman,
Department of Ophthalmology,
University of Pittsburgh School of Medicine –
Professor of Ophthalmology, Sorbonne Université

» Given the stature of the scientific and clinical leaders of IOB, it is not surprising, but quite unprecedented, to observe the trajectory of this brand new institute. Indeed IOB, which was created only a few years ago, is already considered broadly as a leading institution in the field, with landmark contributions in both basic and translational vision research. The depth and breadth of the programs conducted and the achievements in terms of understanding the mechanisms of vision from the retina to the cortex, developing cutting edge technologies for cell-specific targeting, new markers for monitoring disease progression and the impact of therapies, only to name a few, have already had a major impact in the field. One cannot think of a better investment in talent, as confirmed by the caliber of all the recruits over the past few years.«

Constance Cepko
Ph.D.

Professor of Genetics and Ophthalmology, Harvard Medical School, Howard Hughes Medical Institute

» The IOB has very rapidly emerged as the leading institute of ophthalmology in the world. It is extremely impressive how well the leadership has assembled a top team of people developing therapeutics based upon their beautiful basic science work. They have taken several different approaches based upon molecular biology, human genetics, animal physiology, imaging… all performed at the most advanced level. As an example, they have been able to take what was almost a science fiction finding, that is, the control of neurons by an algal protein that senses light, and apply it to two different kinds of retinal neurons in humans. This has allowed a retina that was previously unable to see or process light to be functional.«

Alexander Borst
Ph.D.

Director Max Planck Institute of Neurobiology,
Martinsried

» The advisory board has been extremely impressed by the development of IOB, the number and quality of the groups, and the progression of numerous projects. The ability of both Botond Roska and Hendrik Scholl to not only further their own research at the highest level but also to attract and inspire outstanding scientists and clinicians has built a truly exceptional research environment integrating basic, translational and clinical research: One can only congratulate them on this success!«

Cynthia Grosskreutz
M.D., Ph.D.

Global Head of Ophthalmology,
Novartis Institutes for BioMedical Research

» The IOB continues to grow and to expand its influence. The performance and publication of innovative science in high impact journals by researchers at IOB is impressive and has had a significant impact on the field.«

Paul Sieving
M.D., Ph.D.

Professor, Department of Ophthalmology, School of Medicine – Director, Center for Ocular Regenerative Therapy, CORT, University of California Davis

» Under the leadership of Professors Hendrik Scholl and Botond Roska, the Institute of Molecular and Clinical Ophthalmology Basel has grown and prospered during its first five years. This five-year anniversary marks true progress in elucidating the molecular basis of eye diseases, and the IOB is recognized internationally for leading the way with translational projects that will bring new vision and eye health to those suffering from genetic retinal diseases, including blinding Usher Syndrome and Stargardt macular degeneration.«

Eberhart Zrenner
Prof. Dr. med.
Dr. h.c.mult.

Distinguished Professor of Ophthalmology, Eberhard Karls University of Tübingen, Institute for Ophthalmic Research

» IOB's synergy between outstanding basic research by Botond Roska and his team and Hendrik Scholl's unique international experience in translational clinical trials of the highest quality guarantees breakthroughs for novel therapeutic approaches for so-far untreatable eye diseases. A major, very beneficial impact of IOB' s accomplishments on the curative power of clinical ophthalmology worldwide can be foreseen.«

Thank you!

Prof. Eberhart Zrenner has been a highly valued member of the Scientific Advisory Board since the founding of IOB in 2017, and has now stepped down from this position. The IOB thanks Prof. Zrenner for his outstanding commitment to the Institute, his valued insights, and his support.

Dr. Zrenner is currently Senior Professor of Ophthalmology and founding Director of the Institute for Ophthalmic Research at the Centre for Ophthalmology, University of Tübingen, where he established a special clinic for hereditary retinal degenerations. His research interests range from neuro-ophthalmology and retinal electrophysiology to ophthalmogenetics and gene therapy. He has not only coordinated EU projects and served as Principal Investigator in clinical trials, but has also developed a subretinal electronic microphotodiode array to replace degenerated photoreceptors in blind people.

Dr. Zrenner studied electronic engineering and medicine and received his MD at the Technical University Munich in 1972 and his PhD in 1974. He then began a 16-year-long association with the Max Planck Society, starting as a postdoc at the Max Planck Institute for Physiological and Clinical Research, Bad Nauheim. After a Fogarty International Fellowship (1977/78) at the Laboratory of Vision Research, National Eye Institute (NIH) in Bethesda, he became an associate professor at the University Eye Hospital in Munich. In 1989, he became full professor of Ophthalmology and department chair of the University Eye Hospital in Tübingen. ■

FINANCIAL STATEMENT FOR 2022

General information

The Institute of Molecular and Clinical Ophthalmology Basel exists as a foundation in accordance with articles 80 et seq. of the Swiss Civil Code. The purpose of the foundation is to conduct basic and translational research in human health, among others, to improve society's understanding of the function and diseases of the human eye, to counter degeneration, and to treat impaired vision and blindness and thus to foster Basel as a center of life science research. The Board of Trustees can expand the research activities to other fields of research.

Organization and governance

Board of Trustees

- Hans Jörg Reinhardt – *President of the Board of Trustees*
- Werner Friedrich Kübler – *Member of the Board of Trustees*
- Andrea Schenker-Wicki – *Member of the Board of Trustees*

The Board of Trustees works on a voluntary basis.

Supervisory Authority

BVG- and Stiftungsaufsicht beider Basel (BSABB)

Auditors

PricewaterhouseCoopers AG, Basel

Basis of preparation and accounting policies

Accounting standard

The financial statements of the Institute of Molecular and Clinical Ophthalmology Basel, with registered office in Basel, comply with the requirements of Swiss accounting legislation within the Swiss Code of Obligation (SCO).

Currency

The IOB presentation currency is CHF (Swiss francs).

Foreign currency positions

The items in foreign currencies were converted into CHF at the following exchange rates:

31.12.2022	*Foreign currency*	*Balance*
	EUR	0.9859

Trade account receivables

Trade account receivables and other short-term receivables are initially recognized at their invoiced amounts including any related VAT. Provisions for doubtful trade receivables are established once there is an indication that a loss will be incurred.

Non-current assets and leasing

Property, plant and equipment and intangible assets are carried at cost less accumulated depreciation/amortization. Assets financed by longterm operating leasing contracts are not recognized in the balance sheet. The following useful lives and depreciation/amortization methods are used to calculate the depreciation/amortization amounts:

Non-current assets	*Durability*	*Method*
Research & medical equipment	8 years	25% degressively
IT equipment	4 years	50% degressively
Other property	5 years	40% degressively
Software	8 years	25% degressively
IP rights	8 years	25% degressively

Notes to the financial statements

1 Unrestricted and restricted funds

In 2022, the income from fund raising amounted to CHF 9 055 395, thereof CHF 4 655 986 have already been used for projects. This results in net funds available as per 31.12.2022 in the amount of CHF 4 399 410, whereof CHF 2 137 362 are restricted (unrestricted: CHF 2 262 047).

	31.12.2022	31.12.2021
Net amount of funds received from	CHF	CHF
Private entity	473 173	902 003
Legal entities	1 788 874	1 380 551
Total unrestricted funds	**2 262 047**	**2 282 554**
Private entity	171 498	104 691
Legal entities	1 965 864	1 122 583
Total restricted funds	**2 137 362**	**1 227 274**
Total funds	**4 399 410**	**3 509 828**

2 Income from contributions

Income from contributions	**18 510 000**	**15 600 000**
Novartis	9 250 000	7 800 000
Canton of Basel-Stadt	4 630 000	3 900 000
University Hospital Basel	2 780 000	2 340 000
University of Basel	1 850 000	1 560 000

3 Research expenses

Research expenses	**5 465 592**	**5 553 445**
Consumables	3 671 166	3 745 329
Non-capital equipment	1 032 166	809 873
External services	658 146	877 551
Rent medical equipment	104 115	120 692

4 Administrative expenses

Administrative expenses	**3 718 667**	**2 962 725**
Legal and consulting expenses	1 514 406	1 230 861
Transport and travel expenses	213 686	58 715
Board and lodging expenses	335 224	74 856
IT expenses	1 235 729	1 207 773
Other expenses	419 622	390 520

Balance sheet

Assets	*Notes*	***31.12.2022*** CHF	*31.12.2021* CHF
Cash and cash equivalents		1 416 390	525 084
Accounts receivable		1 306 821	900 012
from third parties		822 075	738 888
from affiliated parties		484 746	161 124
Other short-term receivables		29 163	243 807
from third parties		29 163	243 807
Prepaid expenses		353 158	529 851
Total current assets		**3 105 532**	**2 198 753**
Property, plant and equipment		8 530 229	8 963 309
Intangible assets		352 442	393 424
Total non-current assets		**8 882 671**	**9 356 734**
Total assets		**11 988 202**	**11 555 487**
Liabilities and equity			
Accounts payable		1 308 645	1 189 849
from third parties		1 118 712	979 826
from affiliated parties		189 933	210 022
Other short-term payables		310 013	455 723
from third parties		310 013	455 723
Short-term interest-bearing liabilities		1 000 000	1 000 000
from third parties		1 000 000	1 000 000
Accrued expenses and deferred income		789 959	633 786
Restricted funds		2 137 362	1 227 274
Total short-term liabilities		**5 545 979**	**4 506 632**
Long-term interest-bearing liabilities		5 000 000	7 000 000
from third parties		1 000 000	2 000 000
from affiliated parties		4 000 000	5 000 000
Other long-term liabilities		417 503	0
from third parties		417 503	0
Total long-term liabilities		**5 417 503**	**7 000 000**
Total liabilities		**10 963 482**	**11 506 632**
Foundation capital		500 000	500 000
Profit brought forward		–2 733 699	–1 430 480
Unrestricted funds	1	2 262 047	2 282 554
Net result for the year		996 372	–1 303 220
Total equity		**1 024 720**	**48 855**
Total liabilities and equity		**11 988 202**	**11 555 487**

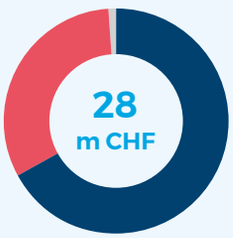
Income statement

	Notes	01.01.2022 – 31.12.2022	01.01.2021 – 31.12.2021
		CHF	CHF
Income from contributions	2	-18 692 631	-15 838 713
Income from fundraising		-9 055 395	-6 824 186
Other income		-213 286	-126 332
Total operating income		**-27 961 312**	**-22 789 231**
Personnel expenses		12 592 953	11 532 149
Research expenses	3	5 465 592	5 553 445
Maintenance, repair, replacement		276 313	209 833
Rent and utility expenses		1 612 708	1 644 937
Energy, gas, water, disposal		432 611	246 797
Administrative expenses	4	3 718 667	2 962 725
Other expenses		42 416	49 662
Depreciation on property, plant and equipment		1 741 458	1 545 391
Amortization of intangible assets		40 982	0
Total operating expenses		**25 923 701**	**23 744 939**
Operating result		**-2 037 610**	**955 708**
Financial income		-96 664	-83 197
Financial expenses		181 263	179 737
Ordinary result for the period		**-1 953 011**	**1 052 247**
Extraordinary, non-recurring or prior period income		0	-831 658
Extraordinary, non-recurring or prior period expenses		0	521 765
Net result for the period		**-1 953 011**	**742 354**
Net allocation to restricted funds	1	977 145	127 276
Net result for the period before net allocation to restricted funds		**-975 866**	**869 630**
Net allocation to unrestricted funds	1	-20 507	433 589
Net result for the period after net allocation to unrestricted funds		**-996 372**	**1 303 220**

Cash flow statement

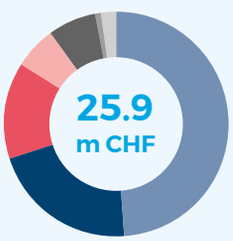
	01.01.2022 – 31.12.2022	01.01.2021 – 31.12.2021
	CHF	CHF
Net result for the period before allocation to unrestricted funds	975 866	-869 630
Depreciation on property, plant and equipment	1 741 458	1 545 391
Amortization of intangible assets	40 982	0
Changes in accounts receivable and other short-term receivables	-192 166	-378 363
Changes in prepaid expenses	176 693	104 388
Changes in accounts payable and other short-term payables	-26 913	-58 133
Changes in accrued expenses and deferred income	156 172	64 942
Changes in restricted funds	910 088	-75 288
Changes in other long-term liabilities	417 503	0
Post capitalization of property, plant and equipment	0	-831 658
Cash flow from operating activities	**4 199 684**	**-498 353**
Capital expenditure on property, plant and equipment	-1 308 378	-2 147 869
Cash flow from investing activities	**-1 308 378**	**-2 147 869**
Proceeds from interest-bearing liabilities	0	2 000 000
Repayment of interest-bearing liabilities	-2 000 000	-1 000 000
Cash flow from financing activities	**-2 000 000**	**1 000 000**
Changes in cash and cash equivalents	**891 306**	**-1 646 223**
Verification of changes in cash and cash equivalents		
Beginning of period	525 084	1 671 307
End of period	1 416 390	525 084
Changes in cash and cash equivalents	**891 306**	**-1 146 223**

Funding 2022



- Income from contributions: **67%**
- Income from third parties: **32%**
- Other income: **1%**

Expenses 2022



- Personnel expenses: **49%**
- Research expenses: **21%**
- Administrative expenses: **14%**
- Rent and utility expenses: **6%**
- Depreciation on non-current assets: **7%**
- Maintenance, repair: **1%**
- Other expenses: **2%**

Partner institutions

A network
around the world

Switzerland	**1**	Alfred Vogt-Foundation for Research in Ophthalmology	*Zurich*	Switzerland
	2	Apellis Switzerland GmbH	*Zug*	Switzerland
	3	Biozentrum, University of Basel	*Basel*	Switzerland
	4	Brain Mind Institute, Swiss Federal Institute of Technology Lausanne	*Lausanne*	Switzerland
	5	Department of Biomedical Engineering, University of Basel	*Basel*	Switzerland
	6	Department of Biomedicine, University of Basel	*Basel*	Switzerland
	7	Department of Clinical Research, University of Basel	*Basel*	Switzerland
	8	Ecole Polytechnique Fédérale de Lausanne	*Lausanne*	Switzerland
	9	F. Hoffmann-La Roche Ltd, Pharmaceutical Research and Early Development (pRED)	*Basel*	Switzerland
	10	Fondation Leenaards	*Lausanne*	Switzerland
	11	Fondation Louis-Jeantet	*Geneva*	Switzerland
	12	Friedrich Miescher Institute for Biomedical Research	*Basel*	Switzerland
	13	Hedy Glor-Meyer Foundation	*Lucerne*	Switzerland
	14	Helbling Technik Bern AG	*Liebefeld-Bern*	Switzerland
	15	Hôpital Ophtalmique Jules Gonin	*Lausanne*	Switzerland
	16	Universitätsklinik für Augenheilkunde – Inselspital	*Bern*	Switzerland
	17	MaxWell Biosystems AG	*Zurich*	Switzerland
	18	National Centre of Competence in Research (NCCR) of Molecular Systems Engineering	*Basel*	Switzerland
	19	Neuroscience Network Basel	*Basel*	Switzerland
	20	Novartis Pharma AG	*Basel*	Switzerland
	21	Palatin Foundation	*Basel*	Switzerland
	22	Professor Dr. Max Cloëtta Foundation	*Zurich*	Switzerland
	23	ProgStar study group	*Basel*	Switzerland
	24	Retina International	*Zurich*	Switzerland
	25	Retina Suisse	*Zurich*	Switzerland
	26	Swiss Tropical and Public Health Institute	*Basel*	Switzerland
	27	University Hospital Basel	*Basel*	Switzerland
	28	University of Applied Sciences and Arts Northwestern Switzerland	*Windisch*	Switzerland
	29	University of Basel	*Basel*	Switzerland
	30	Spectrum Foundation	*Lucerne*	Switzerland
	31	Fond'Action contre le cancer	*Lausanne*	Switzerland
Middle East	**32**	Hebrew University of Jerusalem	*Jerusalem*	Israel
	33	Hadassah Hebrew University Medical Center	*Jerusalem*	Israel
	34	St John Eye Hospital Group	*Jerusalem*	Palestine
	35	Technion – Israel Institute of Technology	*Haifa*	Israel
Asia	**36**	Nanyang Technological University, Ophthalmology and Biomedical Engineering	*Singapore*	Singapore
	37	Singapore Eye Research Institute	*Singapore*	Singapore
	38	Japan Eye Genetics Consortium	*Tokyo*	Japan
	39	National Institute of Sensory Organs Tokyo	*Tokyo*	Japan
	40	Nagoya University Hospital – Dept. of Ophthalmology	*Nagoya*	Japan
	41	Beijing Institute of Ophthalmology	*Beijing*	China
	42	L.V. Prasad Eye Institute	*Hyderabad*	India
Europe	**43**	Department of Ophthalmology, Kepler University Clinic	*Linz*	Austria
	44	Department of Ophthalmology, Medical University of Graz	*Graz*	Austria
	45	Institute of Molecular Biotechnology of the Austrian Academy of Sciences (IMBA)	*Vienna*	Austria
	46	Medical University of Vienna	*Vienna*	Austria
	47	European Vision Institute	*Brussels*	Belgium
	48	Ghent University Hospital	*Ghent*	Belgium
	49	Novo Nordisk	*Bagsværd*	Denmark
	50	Centre de Recherche des Cordeliers	*Paris*	France
	51	Ecole Normale Supérieure	*Paris*	France
	52	GenSight Biologics	*Paris*	France
	53	Institut de l'Audition, Institut Pasteur	*Paris*	France
	54	Institut de la Vision	*Paris*	France
	55	Institute for Neurosciences of Montpellier	*Montpellier*	France

56	SILABE	*Strasbourg*	France
57	SparingVision	*Paris*	France
58	Boehringer Ingelheim	*Ingelheim*	Germany
59	Forschungsplattform Degenerative Erkrankungen, Deutsches Primatenzentrum	*Göttingen*	Germany
60	Heidelberg University	*Heidelberg*	Germany
61	Institute for Ophthalmic Research, University of Tübingen	*Tübingen*	Germany
62	Körber-Stiftung	*Hamburg*	Germany
63	Max Planck Institute for Biophysics	*Frankfurt a. M.*	Germany
64	Max Planck Institute of Neurobiology	*Martinsried*	Germany
65	Okuvision GmbH	*Reutlingen*	Germany
66	Peter und Traudl Engelhorn-Stiftung	*Weilheim*	Germany
67	PRO RETINA Deutschland e. V.	*Bonn*	Germany
68	STZ eyetrial, Department für Augenheilkunde, University of Tübingen	*Tübingen*	Germany
69	University of Bonn	*Bonn*	Germany
70	University Hospital Freiburg	*Freiburg i. Br.*	Germany
71	Augenzentrum am St. Franziskus-Hospital	*Münster*	Germany
72	Aristotle University of Thessaloniki	*Thessaloniki*	Greece
73	Femtonics	*Budapest*	Hungary
74	Semmelweis University	*Budapest*	Hungary
75	Trinity College Dublin	*Dublin*	Ireland
76	Instituto Neurologico Casimiro Mondino Pavia	*Pavia*	Italy
77	Telethon Institute of Genetics and Medicine Pozzuoli	*Naples*	Italy
78	Erasmus Medical Center, Erasmus University Rotterdam	*Rotterdam*	Netherlands
79	Radboud University Medical Center, Radboud University Nijmegen	*Nijmegen*	Netherlands
80	European Vision Institute Clinical Research Network EVICR.net	*Coimbra*	Portugal
81	Instituto de Investigacion Sanitaria-Fundacion	*Madrid*	Spain
82	University and Polytechnic Hospital La Fe of Valencia	*Valencia*	Spain
83	Imperial College London	*London*	United Kingdom
84	Institute of Ophthalmology, University College London	*London*	United Kingdom
85	King's College London	*London*	United Kingdom
86	Moorfields Eye Hospital	*London*	United Kingdom
87	PINNACLE study group	*Southampton*	United Kingdom
88	ReNeuron Group Plc/Ora Inc.	*Bridgend*	United Kingdom
89	Sainsbury Wellcome Center	*London*	United Kingdom
90	University of Southampton	*Southampton*	United Kingdom
91	University of Leeds	*Leeds*	United Kingdom
92	The University of Manchester	*Manchester*	United Kingdom
93	Wellcome Trust	*London*	United Kingdom
USA			
94	Affinia Therapeutics	*Waltham*	USA
95	Allen Institute for Brain Science	*Seattle*	USA
96	Astellas Pharma Global Development, Inc./Astellas Institute for Regenerative Medicine	*Deerfield/ Marlborough*	USA
97	Bascom Palmer Eye Institute	*Miami*	USA
98	Beam Therapeutics	*Cambridge*	USA
99	Belite Bio	*San Diego*	USA
100	Biogen MA Inc	*Cambridge*	USA
101	Byers Eye Institute, Stanford University	*Palo Alto*	USA
102	Cole Eye Institute, Cleveland Clinic	*Cleveland*	USA
103	Columbia University	*New York*	USA
104	David Geffen School of Medicine, University of California	*Los Angeles*	USA
105	Department of Ophthalmology, Case Western Reserve University	*Cleveland*	USA
106	Doheny Eye Institute, University of California	*Los Angeles*	USA
107	End Blindness 2020	*Washington DC*	USA
108	Greater Baltimore Medical Center	*Towson*	USA
109	Harvard Medical School	*Cambridge*	USA
110	Inscopix, Inc.	*Palo Alto*	USA
111	Janssen Research & Development, LLC (Johnson & Johnson)	*Raritan*	USA
112	Moran Eye Center, University of Utah	*Salt Lake City*	USA
113	National Institutes of Health (NIH), the National Eye Institute	*Bethesda*	USA
114	Novartis Institutes for Biomedical Research	*Cambridge, Basel*	USA, Switzerland
115	Retina Foundation of the Southwest	*Dallas*	USA
116	ReVision Therapeutics, Inc.	*Ridgewood*	USA
117	Scheie Eye Institute, University of Pennsylvania	*Philadelphia*	USA
118	Stargazer Pharmaceuticals, Inc.	*Boston*	USA
119	State University of New York College of Optometry	*New York*	USA
120	University Hospitals Clinical Research Center, Cleveland Medical Center	*Cleveland*	USA
121	University of Houston College of Optometry	*Houston*	USA
122	University of Michigan	*Michigan*	USA
123	University of Pittsburgh	*Pittsburgh*	USA
124	University of California San Francisco	*San Francisco*	USA
125	Wilmer Eye Institute, Johns Hopkins University	*Baltimore*	USA
Canada			
126	McGill University Health Centre	*Montreal*	Canada
127	NanoVation Therapeutics	*Vancouver*	Canada
128	Ophthalmology & Vision Sciences University of Toronto	*Toronto*	Canada

Thank you for supporting us in 2022!

Our work is only possible thanks to the broad support of numerous private and institutional donors. We consider ourselves very fortunate to have received very generous donations and to be able to build on our long-standing partnerships with our supporters.

Swiss:

- Accentus Charitable Foundation
- Bandung Foundation
- Bertarelli Foundation
- Canton of Basel-Stadt
- Christian Ziesolleck
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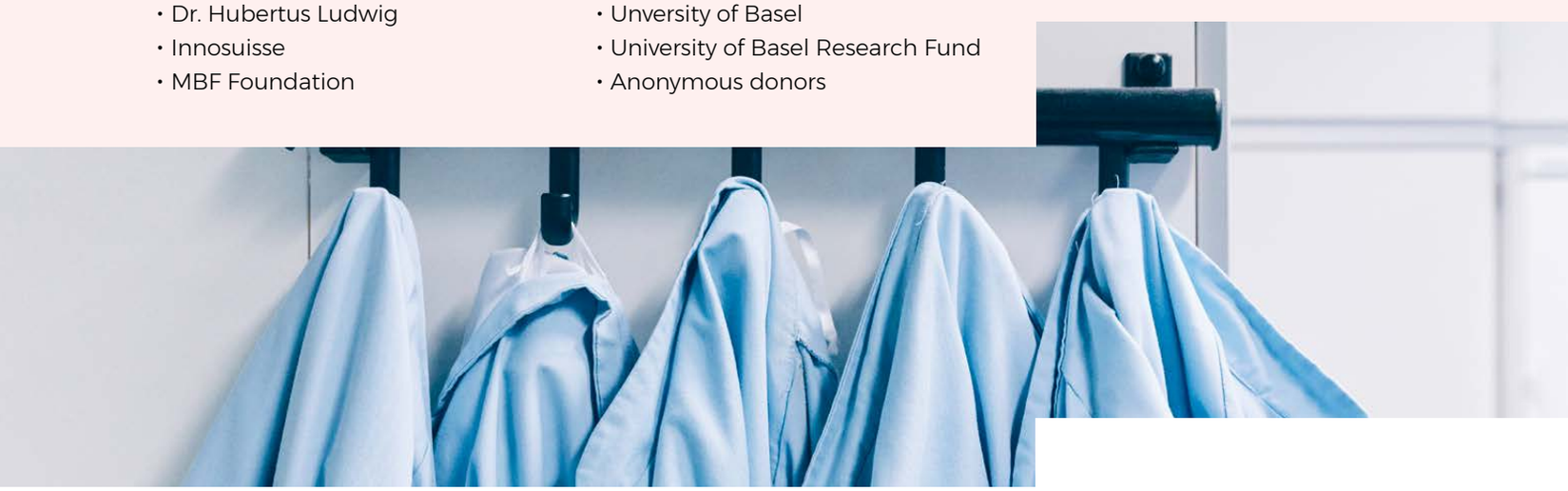

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Researchers and Clinicians united to restore vision.

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