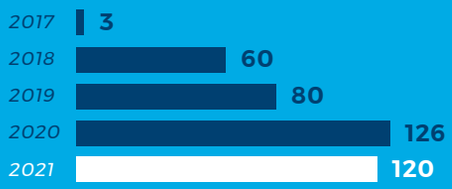
ANNUAL REPORT **2021**

IOB Institute of Molecular and Clinical Ophthalmology Basel

from MOLECULAR to CLINICAL

IOB in numbers

People



Groups

10

Platforms

6

Nationalities

27

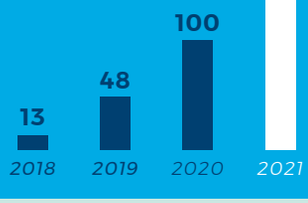
Awards

since 2018

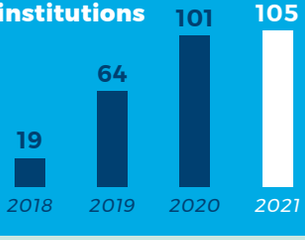
54

Publications

per year

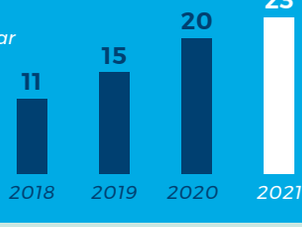


Partner institutions



Funding

m CHF/year



Groups and platforms at IOB

	MOLECULAR +	CLINICAL
10 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
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,

2021 has been a very successful year for IOB: we have continued to produce scientific breakthroughs that may help countless blind people to see again.

In its fourth year of operations, IOB has established itself as one of the leading centers in vision research worldwide. Our work has been recognized through prestigious national and international awards. Our scientists have made significant progress in a series of key translational projects, including our flagship optogenetic therapy. On the clinical side, we have advanced by leaps and bounds towards supplying this and other innovative procedures to patients.

In 2021, we have continued to attract talented researchers and clinicians and to provide them through state-of-the-art platforms with tools and expert advice on organoids, single-cell analyses, bioinformatics, imaging and other cutting-edge technologies.

Working hand in hand, IOB's molecular and clinical teams have championed projects that deepen our understanding of the biology of vision and bring us closer to novel diagnostic tools and treatments for eye diseases.

In 2021, IOB produced 142 peer-reviewed publications – about 40% more than in the previous year. Of these, many were published in top journals and received accolades from the media.

At IOB, we strive every day to turn scientific knowledge into life-changing treatments for patients, and the success of our visionary projects depends on the proximity between research and clinical practice. That is why we are working to strengthen collaboration between scientists and medical doctors by bringing them together under one roof – a new, integrated building that will facilitate scientific exchange and promote interdisciplinary research.

None of what we have achieved so far would have been possible without our founding partners and the many actors who provided generous financial support. Looking ahead, we hope that more people will help us to make our vision reality: uniting researchers and clinicians to cure eye diseases.

Sincerely,

Botond Roska

Director Molecular Research

Hendrik Scholl

Director Clinical Research

Norbert Spirig

Director of Operations

PATIENT STORIES

Patient:
Dario S.

Diagnosis:
Usher syndrome

Identifying diseases, developing therapies, reigniting hope

Cutting-edge technologies and close collaborations between researchers and clinicians allow IOB to solve diagnostic challenges and advance new therapeutic approaches – giving hope to countless people with eye diseases.

Dario S. and his older brother, Matteo, were both born with severe hearing difficulties. Hearing aids improved their ability to distinguish sound and the growing boys took comfort in knowing that those aids would help them through life. But when puberty hit, Dario and Matteo realized that something else was wrong: they couldn't see well in the dark and they sometimes tripped over objects.

In 1995, doctors suspected that the brothers had Usher syndrome, a rare genetic condition that affects both hearing and vision, and they ordered analysis of the boys' DNA. But only in 2021 was the diagnosis of Usher syndrome confirmed at the molecular level, thanks to genetic analyses done at IOB.

Arriving at a correct diagnosis sometimes follows a short and simple journey. At other times, the journey can take years, even decades. At IOB, clinicians and researchers work together to overcome diagnostic challenges. This close collaboration allows them to solve about 6 in 10 'tough' cases – instances where people with eye conditions struggle to have their genetic mutations identified.

With a correct diagnosis, Dario and Matteo will now have access to potential treatments – including some that are being developed at IOB. "It rekindles the hope that vision loss in people with Usher syndrome may be stopped or even reversed during the course of my lifetime," says Dario, who is an advocate for people with the syndrome through his non-profit association NoisyVision.

Genetic detectives

Nearly 30 years after the first signs of vision loss, Dario's sight has significantly worsened: he can no longer drive a car or a bicycle, he has difficulties seeing in dimly lit environments such as bars or churches, and has trouble moving around in crowded places such as airports or train stations. He can't read printed books and he uses phone apps that work like a magnifying glass to get a closer look at menus or small objects. In the evening, he needs a flashlight to locate things like keys in drawers and cupboards.

Usher syndrome is caused by genetic mutations in any one of at least 12 known genes, resulting in a combination of variably severe deafness and an eye disease called retinitis pigmentosa. Some people with Usher syndrome may also experience balance problems. Retinitis pigmentosa causes breakdown and loss of cells in the retina – the light-sensitive tissue at the back of the eye. Common symptoms include difficulty seeing in the dark and loss of side vision. There are four main types of Usher syndrome, each with different symptoms, but everyone with the condition develops retinitis pigmentosa, which worsens over time.

Previous tests on Dario's and Matteo's DNA identified one mutation in a gene called USH2A, which can cause Usher syndrome type 2. To confirm this diagnosis, it was necessary to find a second mutation – but a series of follow-up genetic tests didn't succeed. Then, in 2020, Dario's ophthalmologist, Giacomo Calzetti, suggested that he get tested at IOB. Giacomo had started to work at IOB a few months before and knew that the Institute had expertise in genetic testing and the identification of disease-associated genes.

Karolina Kaminska and her colleagues in the Ophthalmic Genetics Group led by Carlo Rivolta conducted advanced

analyses on Dario's DNA. They confirmed the first genetic mutation in the USH2A gene and discovered a second mutation that affects the same gene in one of its non-coding segments. The same mutation was identified in the DNA of Dario's brother. These so-called intronic mutations are not evaluated in conventional genetic tests, which explains why they were not found before, Giacomo says. "IOB is at the cutting edge of making diagnoses for patients with rare eye conditions that had not been diagnosed by other centers."

New opportunities

A correct diagnosis can pave the way for treatment. Although currently there is no cure for Usher syndrome, Dario and his brother now have the opportunity to enroll in a clinical trial that is currently being conducted to test the efficacy of a therapy to stop vision loss in people with Usher syndrome.

IOB researchers are also working on therapies that could help people with the disease to regain some sight. One is called "optogenetic therapy" and it functions by sensitizing the eyes of a blind person to light, allowing them to see again. The therapy has already succeeded in partially restoring vision in a blind man with retinitis pigmentosa.

Another therapy that is being developed at IOB relies on an efficient and precise gene-editing technique called prime editing, which replaces one DNA base with another without completely breaking the DNA backbone. Using this approach, IOB researchers hope to correct the most common mutations found in people with Usher syndrome. According to Giacomo: "This therapy is in the preclinical stage, but in the future it will be another promising option for Dario."

Patient:
Julia L.

Diagnosis:
Stargardt disease

Lucky coincidences

"Things happen for a reason." That's what 25-year-old Julia L. thought when she learned that her boyfriend had bumped into an ophthalmologist working on Stargardt disease – an eye condition that she had been diagnosed with when she was 8 years old.

That ophthalmologist was Lucas Janeschitz-Kriegl, who is doing his PhD in the lab of Bence György at IOB. Lucas was on a night train from Graz to Basel when he fortuitously met Julia's boyfriend, who told him about her condition. But Stargardt disease is often misdiagnosed, because it's a rare disorder that's difficult to recognize with precision. What's more, because the disease is caused by mutations in a gene called ABCA4, genetic testing is key to confirming the diagnosis. Lucas suggested that Julia undergo thorough eye tests at the Eye Clinic of the University Hospital Basel and an analysis of her DNA at IOB.

The first visit took place on a crisp afternoon in January 2022. "I'm a bit nervous but also excited," Julia said as she prepared to undergo the examination. It will take a few months before she gets the results of the genetic test, but she is hopeful, if the diagnosis of Stargardt disease is confirmed, that there may be more IOB can do for her.

High hopes

Stargardt disease happens when fatty material builds up on the part of the retina needed for sharp, straight-ahead vision. Vision loss usually starts in childhood and can progress to near-complete blindness. Julia's disease has progressed slowly since she was a teenager, and although she can work as a massage therapist, dance, and do sport, her condition makes it impossible to read printed books or drive a car.

At the moment, there is no approved treatment for Stargardt disease, but IOB is working on a base-editing approach to fix the most prevalent mutation in the ABCA4 gene. The therapy is being developed by the team of Bence György in collaboration with US-based biotech company Beam Therapeutics. IOB researchers and clinicians are now progressing towards the first clinical trial of the therapy in patients. "IOB has a combination of methods and skills that no other center in the world has, and we are making leaps forward in developing solutions for patients," Lucas says.

"I look forward to what IOB will do for me and for others with the same disease," says Julia. She feels in good hands, and so does Dario. "I finally have the feeling that something is going to happen," he says. "I have hope again." ■

SCIENTIFIC ACHIEVEMENTS 2021

MOLECULAR RESEARCH CENTER →

SINGLE-CELL GENOMICS PLATFORM

FLASH-seq, a new protocol for detecting genes in single cells at ultrahigh resolution

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

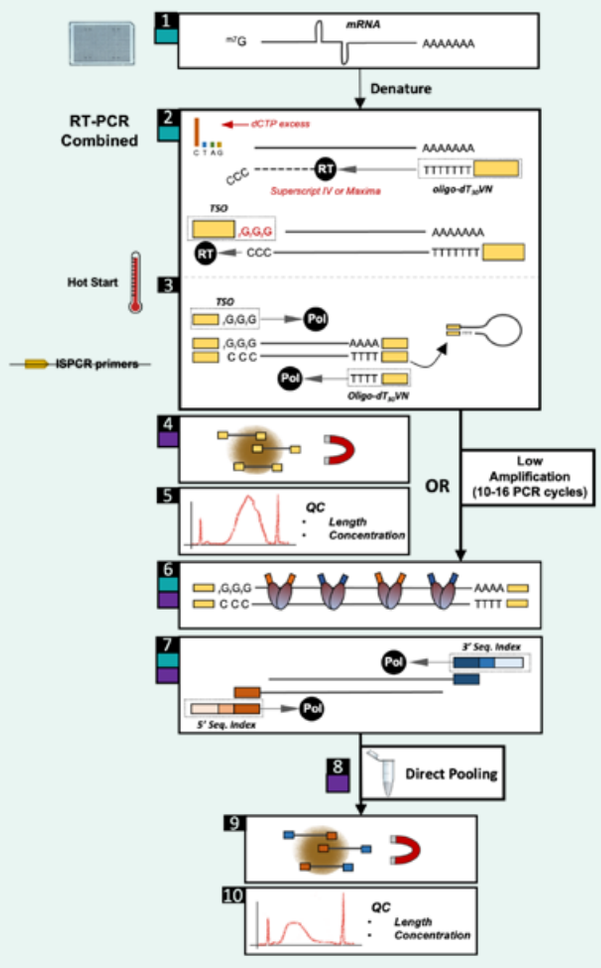
PLATFORM LEADER
Simone Picelli

» With FLASH-seq, we have enabled researchers to get insights into gene expression in single cells with a resolution that was not possible before. «

To address these limitations, we developed FLASH-seq, a new protocol that can be entirely carried out with off-the-shelf reagents and therefore does not require the purchase of any expensive commercial kit. The protocol can be completed in half a day of work with minimal hands-on time, and it lends itself to automation and miniaturization. Thanks to its robustness, flexibility and potential for customization, FLASH-seq brings full-length RNA-sequencing within every researcher´s reach, enabling the discovery of an unprecedented number of genes in each cell and shedding light onto complex molecular mechanisms at an unprecedented resolution.

We have successfully tested FLASH-seq in human retinal organoids, investigating 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 the opportunity to get a more nuanced interpretation of the differential expression results at the gene level. ■

The FLASH-seq workflow



- *Liquid Handling Robot (i.e., Fluent® Automatic Workstation, Tecan)*
- *Nanodispenser (i.e., I.DOT, Cellink)*

HUMAN ORGANOID PLATFORM

Stem-cell models to test gene therapy tools

At the IOB Human Organoid Platform, we generate a variety of cells of the human eye from induced pluripotent stem cells (iPSC). We reprogram iPSC from the blood or skin cells of healthy people or individuals with eye diseases. This way we can study human disease and new therapeutic approaches in cell culture.

We developed a method to generate thousands of miniature retinas called retinal organoids from iPSC. They contain all the major retinal cell types, which are arranged in layers like in the adult human retina and express disease-associated genes.

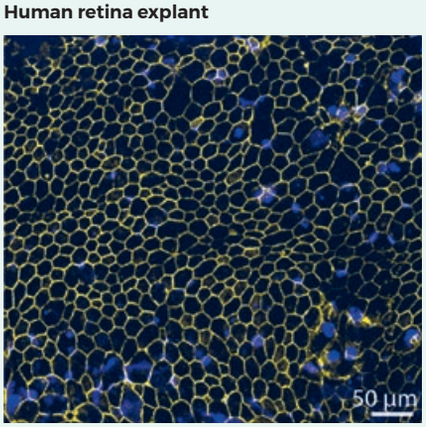
One cell type that is not correctly localized within retinal organoids are retinal pigment epithelial cells (RPE). RPE cells are normally tightly associated with photoreceptors and are crucial to photoreceptor function. We therefore optimized a protocol to generate RPE cells from iPSC in large numbers and with high purity, and we are comparing these cells to human adult RPE cells.

A major goal of the organoid platform is to collaborate with other research labs and platforms at IOB to develop novel treatments for eye diseases. Since mutations in a single gene can lead to visual impairment, repairing the mutations in the cell's DNA or re-introducing a functional copy of the gene into the cell is a very promising approach called gene therapy. We are using retinal organoids and iPSC derived RPE cells to optimize novel gene-therapy tools with the goal of developing new treatment strategies. ■

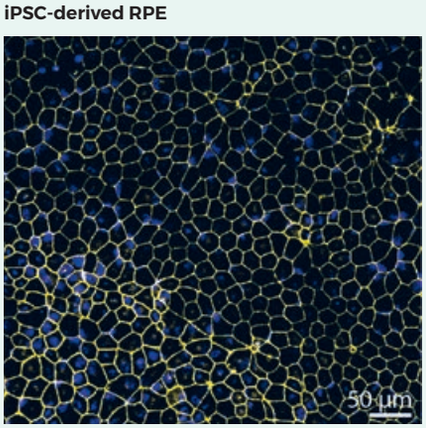
PLATFORM LEADER
Magdalena Renner

» What sounded like science fiction some years ago is now possible in the lab: we can generate thousands of miniature retinas from human stem cells and use them to develop new treatments. «

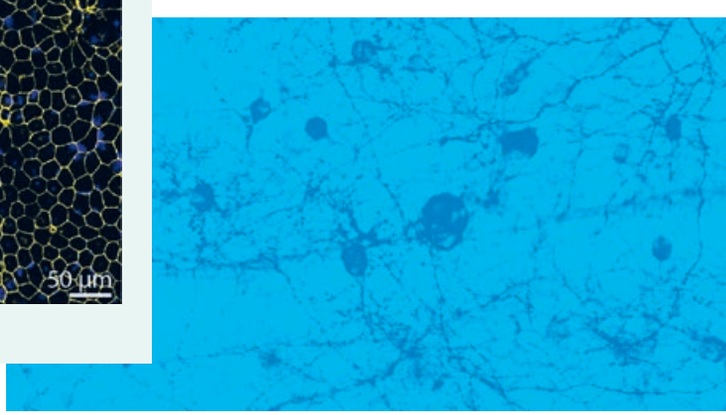
Human retina explant



iPSC-derived RPE



ZO-1 (cell junctions) *Hoechst (nuclei)*



COMPLEX VIRUSES PLATFORM

Generating tools for ocular gene therapy and basic research

The ability to direct the expression of a gene to a specific cell type is useful for understanding and repairing neuronal networks of the retina.

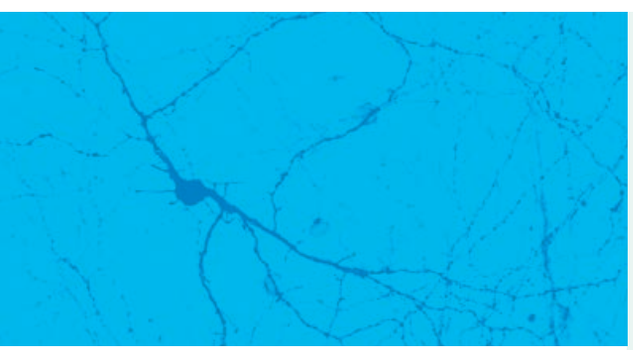
Most current gene-therapy approaches rely on modified viruses such as AAVs, which cannot multiply within the body, to insert copies of potentially therapeutic genes into cells. While these viruses are extremely efficient, they infect many different cell types, making it difficult to direct therapeutic genes to only one cell type. Our strategy places the gene in the viral genome under the control of a synthetic promoter – an on-off switch for gene expression – that drives transgene expression in a cell-type-specific manner.

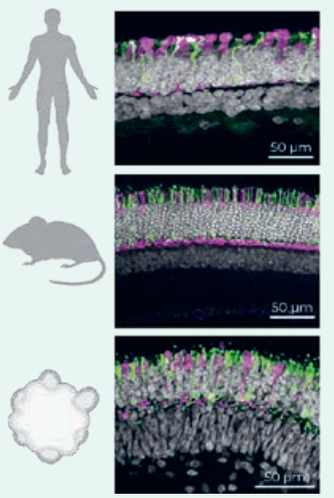
To identify cell-type-specific promoters, we developed a pipeline that starts with the design of promoters using distinct strategies based on the transcriptomic identities of cell types in the human retina. As a proof of concept, we produced viral vectors in which the synthetic promoter drives an optogenetic tool fused to GFP, a fluorescent tag. We previously found that promoter activity and specificity vary unpredictably between species. Since our ultimate goal is to use these vectors for gene therapy in humans, AAVs carrying the synthetic promoters are first tested in human post-mortem retinal explants by evaluating the expression pattern of GFP. Vectors with useful expression profiles are then evaluated in mouse retina and retinal organoids.

AAVs that induce reproducible cell-type-specific expression are shared with IOB researchers and collaborators to accelerate translation of research in model systems, such as mouse and organoids, to gene therapy in humans. ■

PLATFORM LEADER
Josephine Jüttner

» *Our new tools enable efficient targeting of gene expression to specific cell types, which will improve the efficacy and safety of AAV-mediated gene therapies.* «

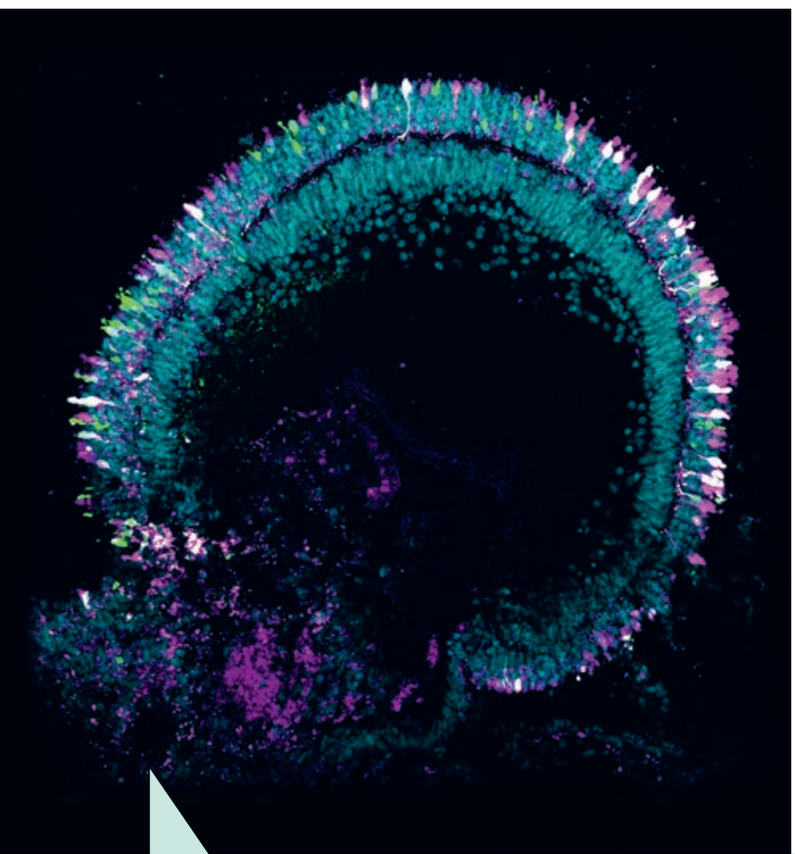




Targeted expression to rod photoreceptors in the retina of humans, mice, and organoids

SCIENTIFIC COMPUTING PLATFORM

Cell types of the human retina and its organoids at single-cell resolution



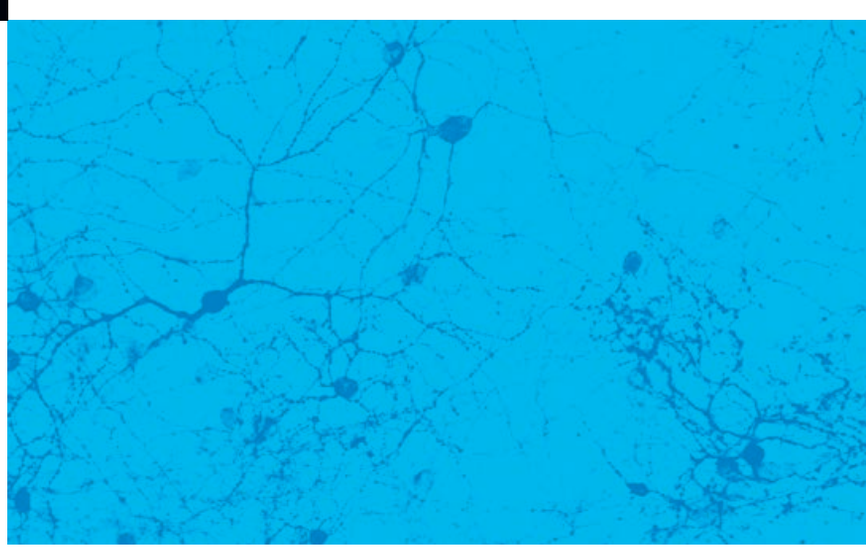
Cross-section of a retinal organoid grown in a dish from human induced pluripotent stem cells

There is a fundamental unmet need to develop model retinas that closely resemble the real human organ.

We are addressing this need by producing retinal organoids – stem-cell-derived artificial organs – at a quality and in quantities that were not previously possible. The necessary benchmark for these organoids is healthy retinal tissue from a human donor, but no functional human retinas had previously been recovered. We therefore developed a method to preserve eye tissue with minimal oxygen deprivation, and demonstrated for the first time a human retina with intact responses to light post mortem. Comparing organoids to organs, we found that organoids reproduce many retinal cell types and the expression of important disease-associated genes. Together with advances from other labs within IOB, these improvements are opening up the possibility of developing treatments in a dish tailored to individual patients. ■

PLATFORM LEADER
Cameron Cowan

» *When you're working with human model systems every day, the translational impact of your work becomes even more clear.* «



QUANTITATIVE VISUAL PHYSIOLOGY GROUP

Action potential speeds compensate for traveling distances in the human retina

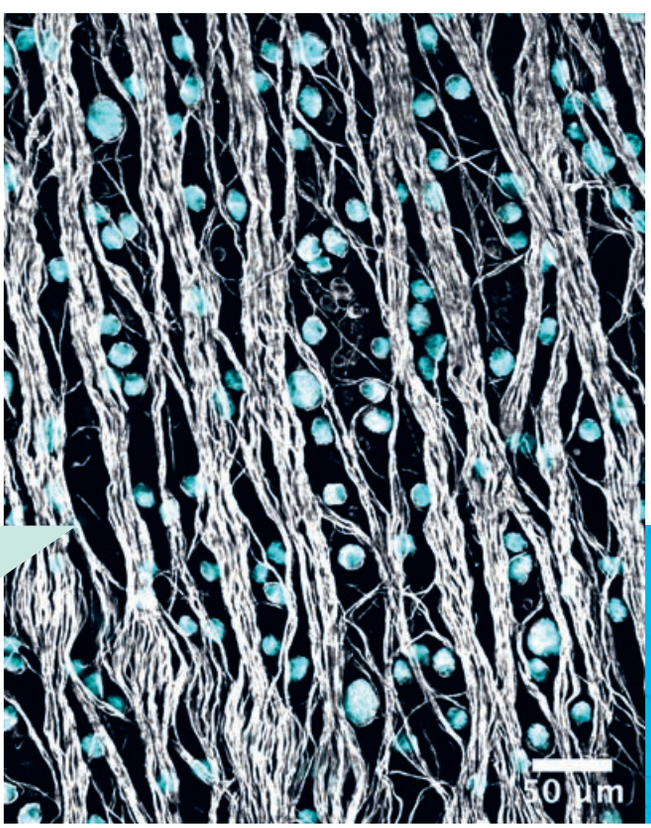
Timing between action potentials is crucial for information processing in real neural networks. In the human retina, signals have to travel dramatically different distances before reaching the optic nerve.

GROUP LEADER
Felix Franke

» *We found that there is a compensatory mechanism in the human retina that makes longer axons faster, so that signals from different parts of the visual world arrive synchronously at the brain.* «

The retina is the part of the eye that detects light and sends information about the visual world to the brain through the optic nerve, which leaves the eye on its back side. The human eye is so large that the signals have to travel dramatically different distances depending on where they are detected. This led us to the question of whether signals need different times to reach the brain depending on where they are detected, for example right in front of us or in our visual periphery.

We measured signal-conduction velocities in the human retina and found that they were spatially heterogeneous and dependent on the location of their origin. Around the fovea centralis, the region of the eye we use for reading, signals traveled up to 50% faster on one side than on the other. Moreover, we observed an up to three times higher speed of signals coming from the visual periphery. Our measurements suggest that a compensatory mechanism in the human retina contributes to synchronizing the arrival times of visual signals in the brain. ■



Axons (white) of neurons in the human retina (cell bodies are in blue) send the visual signals detected by the photoreceptors (not shown) to the brain

HUMAN RETINAL CIRCUITS GROUP

High-throughput, cell-type-specific screen of small molecules in human retinal organoids

Cone photoreceptors enable high-resolution vision. Preventing the degeneration of cones in various diseases is a key target for counteracting vision loss.

The possibility of making a large number of human retinal organoids in vitro, together with the possibility of targeting cell types of the human retina using gene-therapy vectors equipped with synthetic promoters, enable us to perform high-throughput, cell-type-specific screens in retinal organoids.

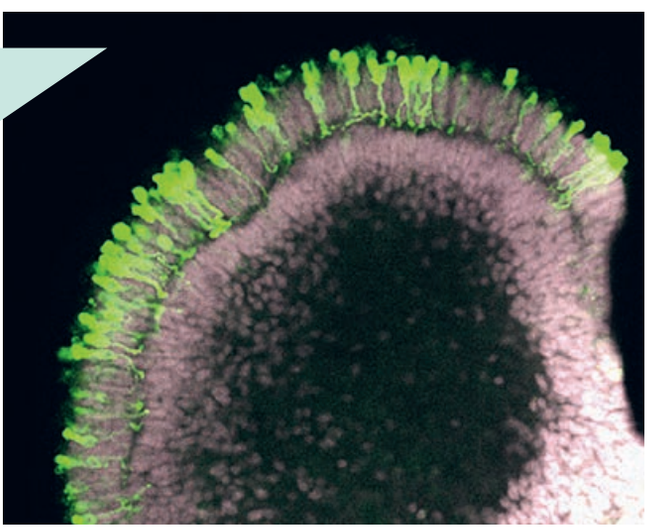
The goal of our first screen is on the one hand to find compounds that delay or decrease the degeneration of cone photoreceptors, and on the other hand to find compounds that induce cone death. The rationale of finding compounds that are toxic to cones is to prevent the medical use of molecules that damage cones as a side effect.

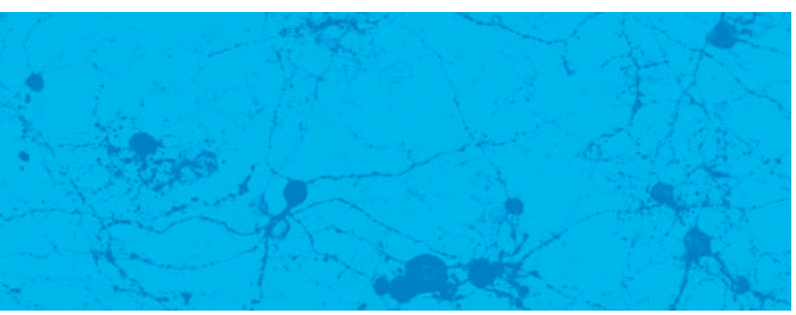
We generated ~17 000 human retinal organoids, each with cones that were labeled with GFP, a fluorescent marker. We induced cone degeneration and measured the number of cones using imaging. We searched across ~3 000 compounds with known modes of action to find those that decrease degeneration and those that increase degeneration. We identified many compounds that are protective of cones and several that damage cones. We are analyzing the action of these molecules in both retinal organoids and animal models of photoreceptor degeneration. ■

GROUP LEADER
Botond Roska

» *New technologies allow us to perform screens for molecules affecting disease in human retinal organoids.* «

A human retinal organoid with cones expressing a green fluorescent marker





CENTRAL VISUAL CIRCUITS GROUP

How does the visual cortex encode objects?

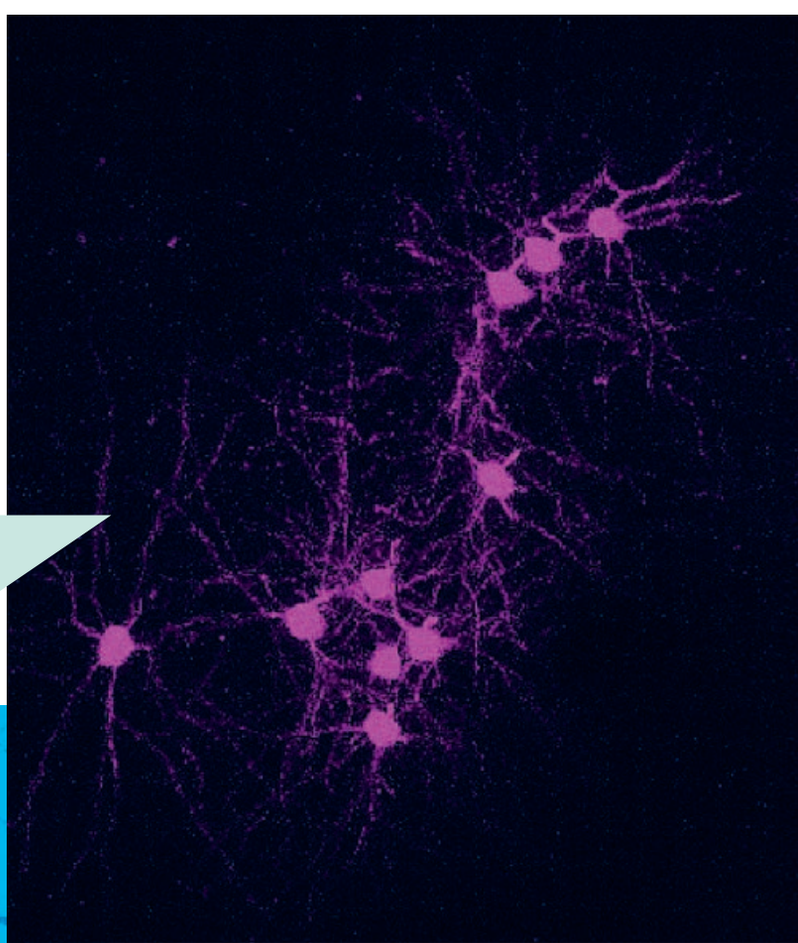
The visual cortex incorporates neurons that respond selectively to certain visual stimuli. How does the cortex achieve this selectivity?

The activity of neurons in the cortex of the brain can represent complex stimuli such as faces, the location of the animal or its motion. We are interested in understanding how the neurons in the visual cortex encode specific visual objects. We performed a large-scale screen of the activity of neurons across many visual cortical areas of mice to search for cells that respond to particular visual objects. We found highly specific object-selective cells in different visual areas with activity independent of object location.

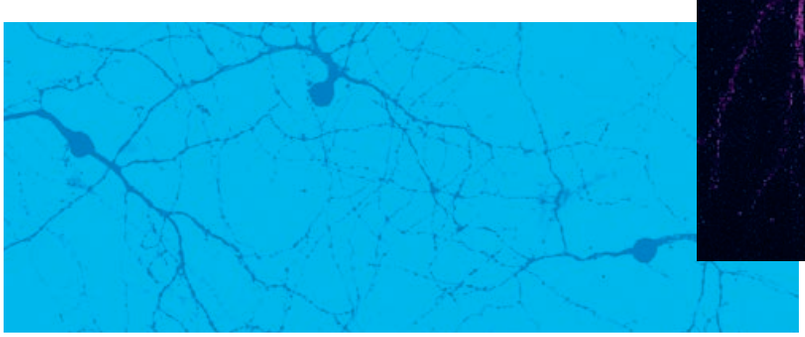
To understand how these cells become sensitive to objects, we performed targeted patch-clamp recording from object-selective cells and compared inhibitory and excitatory inputs during visual stimulation. We then developed a method to target molecular tools to these cells and interfere with inhibition only in the targeted cells. These investigations reveal the role of inhibition in creating object selectivity in the visual cortex. ■

GROUP LEADER
Botond Roska

» We aim to understand how our brain recognizes visuals objects. «

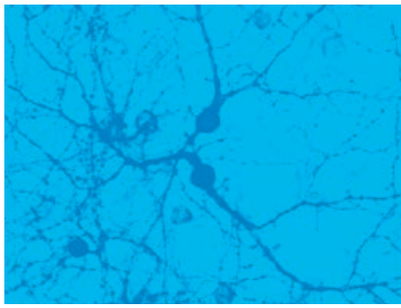


Ten cortical cells selectively marked after high-throughput imaging of hundreds of cortical cells

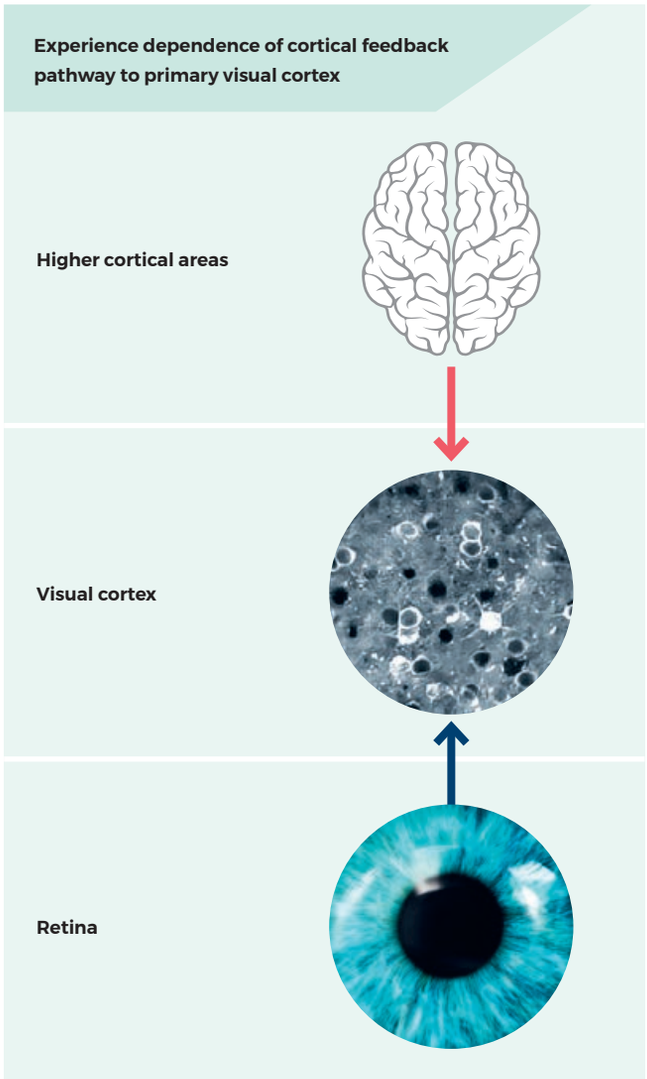


VISUAL CORTEX PLASTICITY GROUP

Experience dependence of visual processing in cortex



Blindness due to retinal disease affects the brain beyond the malfunction of the retina itself. The proper development of cortical visual processing requires visual experience.



How do neurons become specialized to extract features from visual scenes and to integrate this information with contextual signals, such as those from the visual surround? In normal mammalian vision, information is passed forward from the retina to the primary visual cortex and then to the higher visual areas. This feedforward pathway allows neurons to extract basic features from visual scenes, such as lines or edges.

In addition to this feedforward pathway, the opposite flow of information plays a crucial role in normal vision – the feedback pathway linking higher cortical areas to the primary visual cortex. When information is lacking, for example due to obstruction, the missing information is inferred based on the surround through the feedback pathway. Therefore, both these pathways are necessary for normal visual processing.

Here, using a mouse model, we investigate what visual input is required for these pathways to form. To this end, we will raise mice in complete darkness and then test whether neurons in the visual cortex can still extract visual features in the center, based on feedforward pathways, and features in the surround, based on feedback pathways. This work will help us understand how to support the visual cortex in learning to process visual information. ■

GROUP LEADER
Andreas Keller

» *Our eyes capture the visual scenes around us, but visual perception arises only in cortex. In other words, we do not see with our eyes – we see with our brains.* «

THEORETICAL & COMPUTATIONAL NEUROSCIENCE GROUP

Jittery eye motion as active sensation for high visual acuity

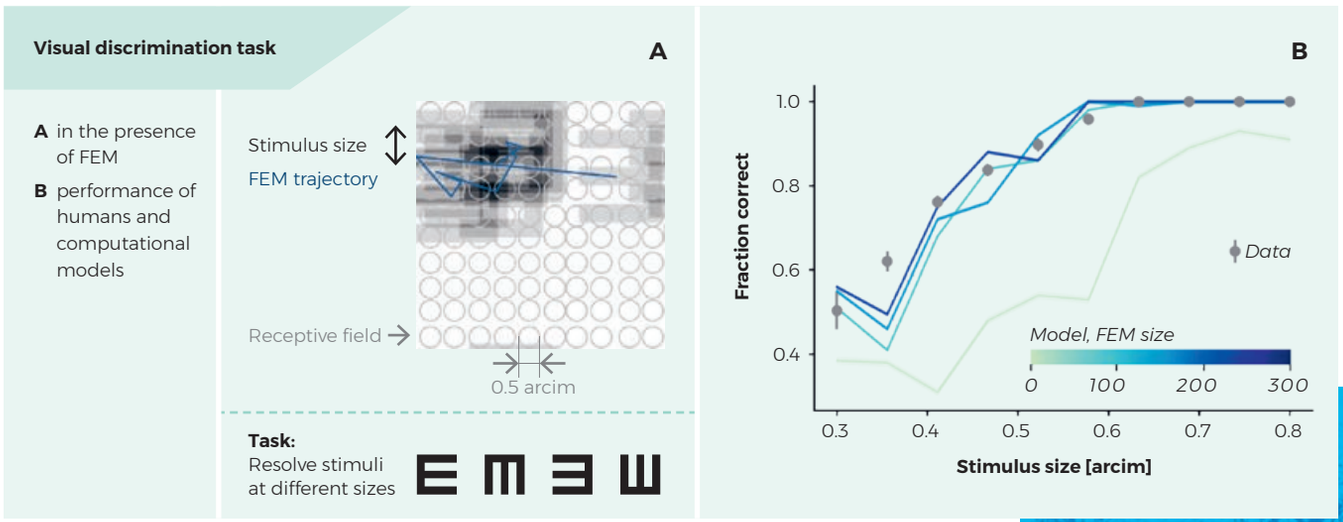
Our perception of the world is shaped by how we move our eyes. Even when trying to fixate on a static object, our eyes make small, involuntary movements.

Fixational eye movements (FEM) render a stable world jittery on our retinae, which could contribute noise and harm human vision. Yet, one can resolve details finer than FEM size and empirical evidence suggests that FEM help rather than harm visual acuity. We investigated in which contexts FEM may improve or impair information-encoding in the retina and accuracy in visual tasks. To this purpose, we considered the analysis of human eye-tracking and performance in a visual discrimination task together with a theoretical investigation. The latter involved a model of retinal responses alongside Bayesian learning to quantify visual acuity on the basis of simulated retinal activity.

Comparing experimental and modeling results, we quantitatively accounted for how FEM support fine detail resolution. In addition, we observed that the subjects' FEM statistics vary depending on stimuli, and our model indeed suggested that changing FEM amplitude enhances acuity as compared to maintaining FEM amplitude constant. Overall, our findings suggest that visual perception may be active even at the exquisitely fine level of FEM statistics, which may non-trivially change with stimuli and support retinal coding and human behavior. ■

GROUP LEADER
Rava Azeredo da Silveira

» Noise is ubiquitous in biological neural networks. Here, we study an example of how noise from jittery eye motion can sculpt and, in certain cases, support visual coding. Our results suggest that beyond overcoming noise due to FEM, neural coding may take advantage of FEM to enhance visual acuity. «



OPHTHALMIC GENETICS GROUP

Advancing knowledge of hereditary visual loss

Usher syndrome is a genetic disease characterized by the simultaneous loss of hearing and vision. To date, 16 different genes have been identified in association with this condition, including the one studied by our team.

In mice and dogs, mutations in the arylsulfatase G gene (ARSG) cause a particular lysosomal storage disorder characterized by severe neurological problems. In humans, for unknown reasons, mutations in the same gene lead to Usher Syndrome Type IV, a new subtype of deafblindness characterized by a relatively late onset of symptoms.

In our work, we investigated the genetic makeup of a large cohort of patients with hereditary visual impairment and identified two individuals from Portugal who were positive for three mutations in ARSG.

Clinical follow-up confirmed that these patients suffered from Usher syndrome, displaying typical signs and symptoms of the disease. Further biochemical analyses, performed in collaboration with the group of Dr. Markus Damme at Kiel University, revealed that all mutations abolished the activity of the ARGS protein and resulted in its localization in a wrong subcellular compartment.

Our new data enable us to definitely associate mutations in ARSG with Usher Syndrome Type IV and to establish that the molecular pathology of this disorder is tightly linked to the loss of ARSG enzymatic function. ■

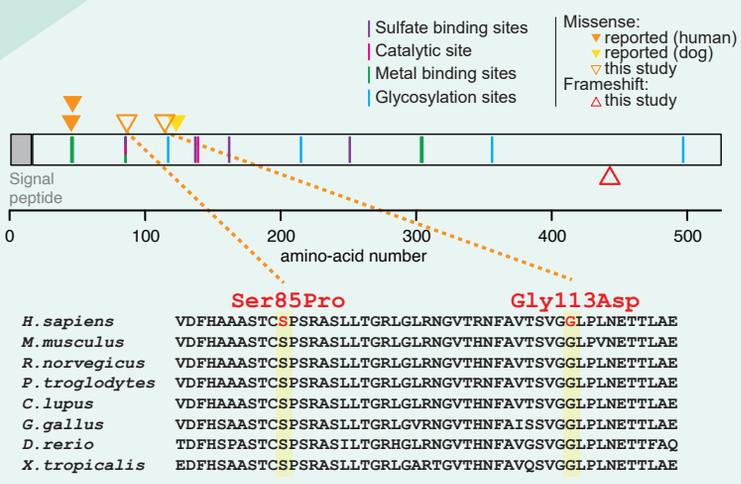
GROUP LEADER
Carlo Rivolta

» *By a combination of computer-based analysis and functional studies of cultured cell lines, we confirmed the association between mutations in the ARSG gene and a deafblindness condition.* «

Schematic representation of the ARSG protein with specific functional sites (in color) and its partial alignment with homologous sequences

Sequences from:

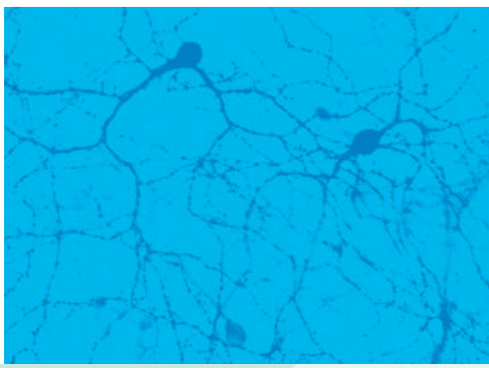
- mouse *(M. musculus)*
- rat *(R. norvegicus)*
- chimpanzee *(P. troglodytes)*
- dog *(C. lupus familiaris)*
- chicken *(G. gallus)*
- zebrafish *(D. rerio)*
- frog *(X. tropicalis)*



GENETIC EPIDEMIOLOGY OF OPHTHALMIC DISEASES GROUP

Save your sight by eating your genetic risk away

It is well established that age-related macular degeneration is caused by nature (genetics) and nurture (lifestyle). This study aimed to investigate the potential of lifestyle factors to save people from a grim genetic outlook.



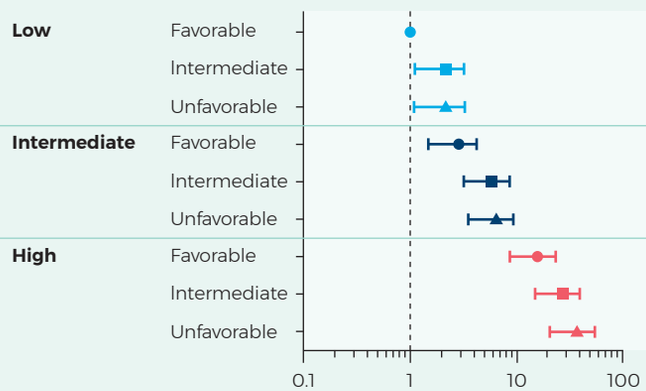
Age-related macular degeneration (AMD) is one of the commonest eye diseases in the elderly. Despite current treatment options with intraocular injections for some forms of AMD, this disease often ends in blindness. AMD has a remarkably strong genetic basis, but lifestyle factors such as smoking and diet are also important.

It is clear that a person's genetic make-up can't be changed, but is it possible to change the fate of genes? We examined this question in 17 174 elderly persons from nine different studies across Europe. Study participants underwent eye screening at regular intervals, were tested for all 52 AMD genetic variants, and filled in extensive questionnaires about their lifestyle.

We found that genetic variants for AMD were common in the general population. Half of the population appeared to be at least slightly at risk of AMD. People with many genetic variants, and thus a high genetic risk, had the most unfavorable prognosis: they were 35 times more likely to develop advanced disease. But where these people had stopped smoking or had never smoked, and where they had a diet rich in vegetables, fruit, and fish, their risk of developing AMD was only 15 times higher than that of the general population.

Although this risk is still considerable, the outcome for about half of these people was better. We observed the same trend for people with lower genetic-risk profiles. Our findings call for doctors to recommend that their AMD patients at risk of blindness 'eat their genetic risk away'. ■

Lifestyle determines the outcome of genetic risk



GROUP LEADER
Caroline Klaver

» *Lifestyle factors have a great influence on the outcome of the genetic risk of age-related macular degeneration and should be a strong focus in patient management.* «

OPHTHALMIC TRANSLATIONAL RESEARCH GROUP

New study reveals that many blind patients have dormant photoreceptors that can be re-activated

The worldwide multicenter study EyeConic reveals that at least one third of blind patients would be eligible for the IOB cone-based optogenetics vision-restoration approach.

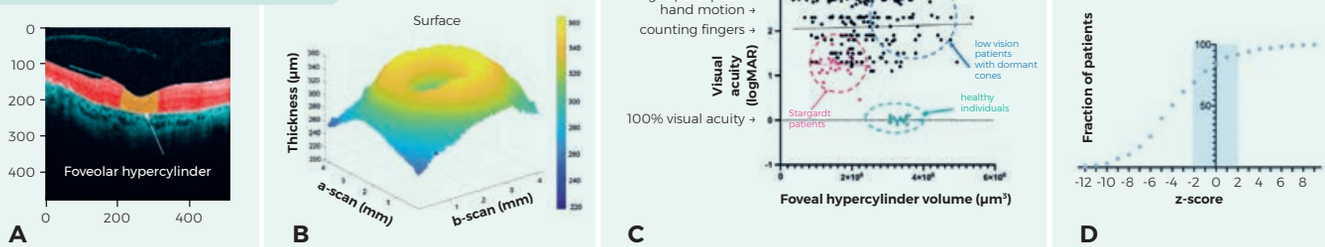
GROUP LEADER
Bence György

» *The results were very surprising: a few years ago it was thought that blind patients infrequently have photoreceptors that can be reactivated. Our study puts this into a different perspective.* «

IOB is developing cone-based optogenetics, a vision-restoration approach that aims at re-sensitizing remaining dormant cone photoreceptors in the blind retina. However, the proportion of blind patients who carry non-functional (dormant) cone photoreceptors was unknown. Together with researchers at ETH Zurich, our team developed machine-learning approaches to automatically segment images from the retina in patients with low vision. These data were used to perform a three-dimensional reconstruction of the fovea, the cone-rich region that allows us to read, drive or recognize faces.

Using this novel method, we have set up a worldwide imaging study and enrolled patients from 12 centers on three continents. Based on 274 eyes from 174 patients, we have found that one third of blind patients have normal foveal cone volumes, but as many as one half of blind patients could potentially benefit from IOB's vision-restoration approach. Although the remaining dormant cone cells of patients cannot mediate vision, they may be made light sensitive using the IOB cone-based optogenetic program. ■

OCT analysis of low-vision patients



A Cone-only region in the fovea: We quantified the foveal volume (350 µm hypercylinder, shaded region) on OCT scans.

B Retinal volumetric reconstruction: Topographic representation of total retinal volume in a normal individual.

C Structure-function correlation plots in Stargardt patients, EyeConic study patients and healthy individuals.

D Cumulative frequency distribution of foveal volumes in EyeConic study participants (z-score is the normalized deviation from the mean of healthy individuals). About 30% of study patients are within two standard deviations from the mean foveal volume of healthy individuals.

MYOPIA RESEARCH GROUP

Optical defocus induces transient changes in choroidal blood flow

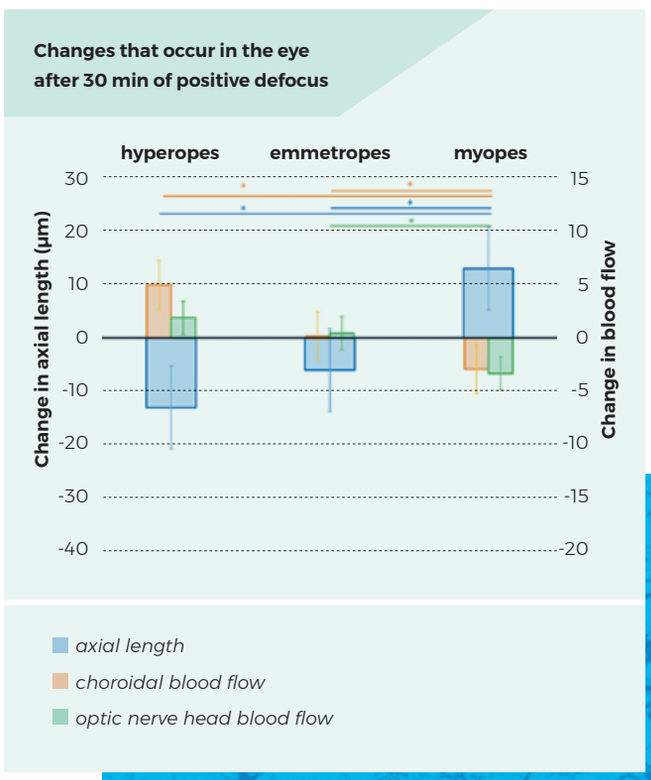
We have studied whether changes in choroidal and fundal blood flow can explain the changes in choroidal thickness that are induced when subjects wear positive lenses.

GROUP LEADER
Frank Schaeffel

» Our results show a link between changes in short-term axial length and choroidal thickness induced by imposing positive defocus and changes in fundal blood flow. «

We had previously found that the retina in myopes triggers transient axial eye elongation when positive defocus is imposed, whereas eye shortening is observed in emmetropes. Such changes in axial length result from changes in the thickness of the choroid, the highly vascular layer behind the retina. We have studied in young adult human subjects whether the induced changes in choroidal thickness are related to changes in choroidal and optic nerve head blood flow. A positive lens (+3.0D) was placed in front of the right eye of subjects while they were watching a movie in a dark room at 2 meters of distance for 30 minutes. The left eye served as control. Miniature transient changes in axial length were measured by the Lenstar (LS 900, Haag-Streit, Switzerland) and blood flow was monitored by laser speckle flowgraphy (LSFG, 820nm, Fukuoka, Japan).

As found in our previous study, hyperopes and emmetropes displayed thickening of the choroid with positive defocus, while myopes displayed thinning. Changes in choroidal blood flow were significantly correlated with changes in axial length, suggesting that changes in blood flow explained choroidal thickening or thinning. Our experiments are perhaps the first to show that choroidal blood flow is increased when positive defocus is imposed. The result suggests that inhibition of eye growth is metabolically costly and requires a higher level of retinal and choroidal perfusion. ■



OPHTHALMIC IMAGING & OCT GROUP

Ambiguous ground matters for machine learning output

Machine learning has enhanced optical coherence tomography image analysis. However, machine learning remains a black box. We want to better understand how a machine learning algorithm reacts to ambiguity in data collected from real-world scenarios.

GROUP LEADER
Peter Maloca

» *We unbox the internal workings of state-of-the-art machine learning.* «

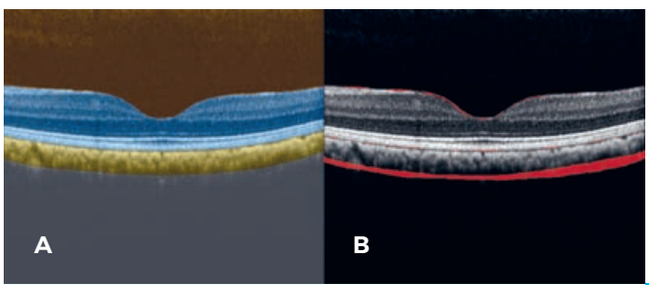
Optical coherence tomography (OCT) is a non-invasive imaging technology that utilizes low-coherence laser light to produce cross-sectional images in biological tissues.

Machine learning algorithms have enhanced OCT image analysis to perform a specific image-analysis task without it being explicitly programmed. However, the internal workings of machine learning are still not well understood, and the method has not yet been integrated into clinical routine.

To better understand the workings of machine learning, we trained a machine learning algorithm from ambiguous ground truth data – data collected from real-world scenarios to train algorithms on contextual information. The ground truth consisted of labels from three human graders who acted as three "teachers" for the convolutional neural network. In particular, we applied the proposed machine learning method to automated OCT image segmentation.

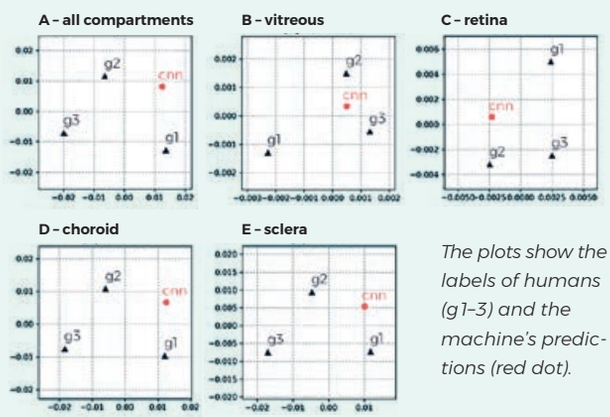
This machine learning technique, which we called T-REX, was able to record and visualize the predictive performance of a convolutional neural network with respect to ambiguous ground truth generated by multiple graders.

The findings revealed that a convolutional neural network trained on ambiguous ground truth learned a form of consensus among the human graders, which is specific to particular eye compartments (vitreous, retina, choroid, sclera), but was heavily influenced by the quality of the basic data. ■



A Illustration of the manual separation of the posterior eye pole into its four compartments (vitreous = brown, retina = blue, choroid = yellow, sclera = grey).

B Representation of the divergence between three human graders in image annotation. Regions where the graders do not completely agree with each other are highlighted in red. The disagreement was particularly pronounced in the area of transition from choroid to sclera.



The plots show the labels of humans (g1–3) and the machine's predictions (red dot).

Depending on the eye compartment, the convolutional neural network showed a balancing behavior compared to the human graders. This is an illustrative sign of some kind of intelligence.

CLINICAL TRIAL CENTER & VISUAL NEUROPHYSIOLOGY PLATFORMS

Investigating progressive neurodegeneration and vision loss in late dry AMD (OMEGA Study)

The OCT and Microperimetry Biomarker Evaluation Study in Patients with Geographic Atrophy (OMEGA) investigates progressive neurodegeneration and vision loss in late dry AMD.

In this investigator-initiated clinical study, funded by Boehringer Ingelheim Pharma GmbH & Co.KG, we are investigating the use of microperimetry and OCT in assessing the natural history changes of retinal sensitivity and anatomy in the perilesional zone of geographic atrophy (GA) areas in patients with dry age-related macular degeneration (AMD).

Patients with GA are followed for 12 weeks and their visual performance and retinal structure using various methods are being measured at baseline, 12, 24, and 48 weeks. Through structure-function correlation, we will investigate the consequences of degenerative changes on visual performance and thus establish the clinical significance of structural outcome measures. The functional measures include visual acuity, low-luminance visual acuity, and microperimetry, while the structural measures include OCT, OCT angiography, fundus autofluorescence, and near-infrared imaging.

As novel outcome measures for visual function, we will include the rapid measurement of the contrast sensitivity function (so called quick CSF method), and for retinal structure an adaptive optics fundus camera that allows imaging of individual photoreceptors and the RPE mosaic in vivo with a resolution of 1.6 µm with a 4×4 deg field of view. ■

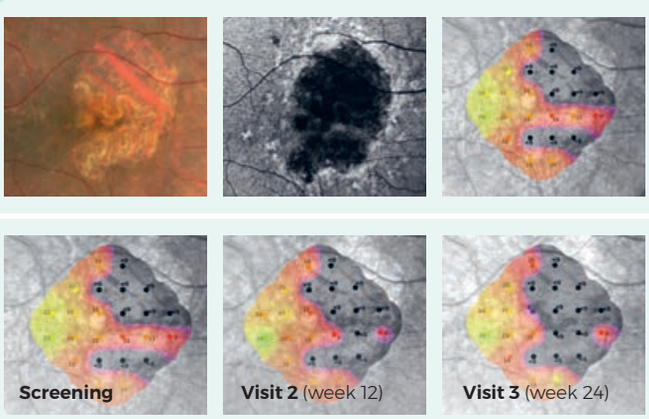
PLATFORM LEADERS
Christian Prünte
Hendrik Scholl

» With OMEGA we're tapping into the commonest cause of blindness in the Western industrialized countries and developing outcome measures for clinical trials to tackle one of the largest unmet medical needs. «

Fundus images and microperimetry results of the right eye of an 80-year-old male patient affected by geographic atrophy secondary to age-related macular degeneration

Visual acuity at baseline was 20/25. The upper row shows a color fundus photograph (left), a fundus autofluorescence image (middle) and the microperimetry interpolated map superimposed onto an infrared reflectance image (right). The extent of geographic atrophy is best seen in the fundus autofluorescence image as the central dark appearing area.

The lower left panel is the same as the upper right and shows the microperimetry results at baseline. At 12 (middle) and 24 weeks (right), there was significant loss of light sensitivity.



The microperimetry-derived sensitivity map:
normal moderate decrease *severely decreased* *complete loss of sensitivity/absolute scotoma*

Cooperation and communication within IOB

Name	*Purpose / Description*	*Frequency*	*Participants*
Annual Retreat	Fostering a cohesive institute culture by getting together for a three-day retreat that includes plenary presentations, panel discussions, educational sessions, flash talks, workshops, and poster sessions	*yearly*	all IOB Members
Basel Seminar Series on Vision Research	Disseminating cutting-edge science in the field of vision and ophthalmology by renowned speakers and fostering the integration and interaction of the Basel scientific community working in vision research	*multiple times a year*	Public
Friday Seminar	Presentations by PhD students / postdocs about their projects followed by informal discussion	*bi-weekly*	Groups and Platforms
Genetics Meets the Clinics	Discussing genetic findings and clinical phenotypes. Researchers acquire clinical knowledge from ophthalmologists, while clinicians have the opportunity to gain information on the latest developments in the field of diagnostic molecular genetics	*once every three weeks*	Clinicians and Researchers
Joint Clinicians & Researchers Meeting	Each meeting includes talks by researchers and clinicians that focus on a specific topic (such as Stargardt, Myopia and many more), followed by a discussion and a social gathering	*quarterly*	Clinicians and Researchers
Translational Lunch Meeting	Discussing progress on the translational programs and exploratory projects	*monthly*	Clinicians and Researchers
Basic Research Institute Meeting	One or two IOB research groups present their results, followed by a discussion	*monthly*	Research groups

Awards 2021

Awardee	*Award*	*Institution*
Bence György	SNSF Eccellenza Professorial Fellowships	*Swiss National Science Foundation*
Andreas Keller	2021 finalist of the Eppendorf & Science Prize for Neurobiology	*Eppendorf & Science*
Caroline Klaver	Oberdorfer Award in Low Vision Research (ARVO award)	*ARVO & Lighthouse Guild*
Dasha Nelidova	Alfred Vogt-Preis zur Förderung der Augenheilkunde	*Alfred Vogt-Stiftung*
	Bayer Early Excellence in Science Award	*Bayer Foundation*
	DOG – Retina Award	*Deutsche Ophthalmologische Gesellschaft & Novartis*
	German Chemistry Society (GDCh), Division of Medicinal Chemistry, Doctoral Award	*German Chemistry Society, Division of Medicinal Chemistry*
	Justus-Liebig University Giessen Radiography Prize	*Justus-Liebig University Giessen*
	Swiss Society of Experimental Pharmacology (SSEP), Bürgi prize for the best original publication in Experimental Therapeutics	*Swiss Society of Experimental Pharmacology*
	University Faculty of Science Faculty Prize	*University of Basel*
	Young Investigator Award ESCI – 2nd place	*European Society for Clinical Investigation*
	Dr. Holger Müller Preis 2020	*Dr. Holger Müller Stiftung*
	Vision Research Best Paper of the Year 2020 – 3rd place	*1Vision Research*
	Harold M. Weintraub Graduate Student Award	*Fred Hutch*
	UZH Brain Diseases Prize	*UZH Foundation*
	30th Pfizer Research Prize	*Pfizer*
	SwissNeuro Best Publication Award 2021 in cellular & molecular neuroscience	*SwissNeuro*
Mathieu Quinodoz	Swiss RetinAward 2021	*Swiss VitreoRetinal Group & Bayer*
Carlo Rivolta	Alfred Vogt-Preis zur Förderung der Augenheilkunde	*Alfred Vogt-Stiftung*
Barbara Swiatczak	ARVO-Swiss Travel Grant	*ARVO Swiss*
Arjun Bharioke & Martin Munz	Emerging Neuroscientists Seminar Series (ENSS) 2021	*Sainsbury Wellcome Centre*
Cameron Cowan & Magdalena Renner	SwissOphthAWARD for the best experimental work 2021	*Schweizerische Ophthalmologische Gesellschaft & Bayer*
	Bruno Speck Award in the category basic research	*Stiftung for Hämatologische Forschung*
	Basic Science Research Award 2021	*Deutsche Ophthalmologische Gesellschaft & PRO RETINA Deutschland e.V. & Retina Suisse*
	Vision Research Best Paper of the Year 2020 – 1st place	*Vision Research*

Key publications 2021

View all our papers listed in PubMed:

Title / Authors	Journal
Partial recovery of visual function in a blind patient after optogenetic therapy *Sahel JA, Boulanger-Scemama E, Pagot C, Arleo A, Galluppi F, Martel JN, Esposti SD, Delaux A, de Saint Aubert JB, de Montleau C, Gutman E, Audo I, Duebel J, Picaud S, Dalkara D, Blouin L, Taiel M, Roska B*	*Nat Med. 2021*
Charting human development using a multi-endodermal organ atlas and organoid models *Yu Q, Kilik U, Holloway EM, Tsai YH, Harmel C, Wu A, Wu JH, Czerwinski M, Childs CJ, He Z, Capeling MM, Huang S, Glass IA, Higgins PDR, Treutlein B, Spence JR, Camp JG*	*Cell. 2021*
The Progression of Stargardt Disease Using Volumetric Hill of Vision Analyses Over 24 Months: ProgStar Report No.15 *Schönbach EM, Janeschitz-Kriegl L, Strauss RW, Cattaneo MEGV, Fujinami K, Birch DG, Cideciyan AV, Sunness JS, Weleber RG, Ip MS, Sadda SR, Scholl HPN; ProgStar Study Group*	*Am J Ophthalmol. 2021*
Unraveling the deep learning gearbox in optical coherence tomography image segmentation towards explainable artificial intelligence *Maloca PM, Müller PL, Lee AY, Tufail A, Balaskas K, Niklaus S, Kaiser P, Suter S, Zarranz-Ventura J, Egan C, Scholl HPN, Schnitzer TK, Singer T, Hasler PW, Denk N*	*Commun Biol. 2021*
AutoMap is a high performance homozygosity mapping tool using next-generation sequencing data *Quinodoz M, Peter VG, Bedoni N, Royer Bertrand B, Cisarova K, Salmaninejad A, Sepahi N, Rodrigues R, Piran M, Mojarrad M, Pasdar A, Ghanbari Asad A, Sousa AB, Coutinho Santos L, Superti-Furga A, Rivolta C*	*Nat Commun. 2021*
Lineage recording in human cerebral organoids *He Z, Maynard A, Jain A, Gerber T, Petri R, Lin HC, Santel M, Ly K, Dupré JS, Sidow L, Sanchis Calleja F, Jansen SMJ, Riesenberg S, Camp JG, Treutlein B*	*Nat Methods. 2021*
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*	*Am J Ophthalmol. 2021*
Uncovering of intraspecies macular heterogeneity in cynomolgus monkeys using hybrid machine learning optical coherence tomography image segmentation *Maloca PM, Seeger C, Booler H, Valmaggia P, Kawamoto K, Kaba Q, Inglin N, Balaskas K, Egan C, Tufail A, Scholl HPN, Hasler PW, Denk N.*	*Sci Rep. 2021*
The Lancet Global Health Commission on Global Eye Health: vision beyond 2020 *Burton MJ, Ramke J, Marques AP, Bourne RRA, Congdon N, Jones I, Ah Tong BAM, Arunga S, Bachani D, Bascaran C, Bastawrous A, Blanchet K, Braithwaite T, Buchan JC, Cairns J, Cama A, Chagunda M, Chuluunkhuu C, Cooper A, Crofts-Lawrence J, Dean WH, Denniston AK, Ehrlich JR, Emerson PM, Evans JR, Frick KD, Friedman DS, Furtado JM, Gichangi MM, Gichuhi S, Gilbert SS, Gurung R, Habtamu E, Holland P, Jonas JB, Keane PA, Keay L, Khanna RC, Khaw PT, Kuper H, Kyari F, Lansingh VC, Mactaggart I, Mafwiri MM, Mathenge W, McCormick I, Morjaria P, Mowatt L, Muirhead D, Murthy GVS, Mwangi N, Patel DB, Peto T, Qureshi BM, Salomão SR, Sarah V, Shilio BR, Solomon AW, Swenor BK, Taylor HR, Wang N, Webson A, West SK, Wong TY, Wormald R, Yasmin S, Yusufu M, Silva JC, Resnikoff S, Ravilla T, Gilbert CE, Foster A, Faal HB*	*Lancet Glob Health. 2021*
Emmetropic But Not Myopic Human Eyes Distinguish Positive Defocus From Calculated Blur *Swiatczak B, Schaeffel F*	*Invest Ophthalmol Vis Sci. 2021*

Scientific Advisory Board

Letter from the Chairman of the Scientific Advisory Board

Dear Reader,

The Scientific Advisory Board of IOB held its second evaluation meeting in November 2021, three years after the first meeting in Cambridge, USA. The board has been extremely impressed, but not surprised, with the development of the overarching structure of IOB, the number and quality of the groups, and the progression of numerous projects.

Botond Roska and Hendrik Scholl, both world leaders in their own fields, have been able not only to continue advancing their own research at the highest level, but also to attract and inspire numerous researchers and clinicians at various stages of their careers. This allowed them to build an impressive continuum of basic, translational and clinical research with progressive integration, based on complementarity.

The research conducted at IOB is innovative, often published in top journals. It leads to a better understanding of the biology of vision in health and disease while paving the way for the development and validation of novel diagnostic and therapeutic tools. The commitment and vision of the directors ensure the synergy of all projects.

Moreover, IOB has established excellent platforms that enable many groups to benefit from tools and expertise in various technologies, including organoids, single-cell analyses and innovative imaging.

The Institute has secured important funding for numerous new projects and is clearly on a fast-ascending trajectory. Success will become even more obvious when all teams will be located in a single building. This step is of paramount importance to provide scientists, clinicians and – most importantly – trainees with the opportunity to share questions, ideas, and enthusiasm.

The Scientific Advisory Board commends IOB's supporters for giving its leaders the resources to build an institution that can now be considered one of the leading ophthalmology centers worldwide. The trust and investments in its founders' vision have proved exceptionally successful.

Finally, we want to emphasize the uniqueness of IOB – a place where world-class science and translation are at the heart of the whole enterprise – and thank all IOB members: their dedication and outstanding work led to this exceptional evaluation. We feel privileged to have the opportunity to observe and comment on this exceptional institute.

José-Alain Sahel, M.D.
on behalf of the Scientific Advisory Board

Members of the Scientific Advisory Board

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

Alexander Borst
Ph.D.

Director Max Planck Institute of Neurobiology,
Martinsried

Constance Cepko
Ph.D.

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

Cynthia Grosskreutz
M.D., Ph.D.

Global Head of Ophthalmology,
Novartis Institutes for BioMedical Research

Paul Sieving
M.D., Ph.D.

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

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

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

FINANCIAL STATEMENT FOR 2021

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, for example 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 hereby 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*
- Charles Gubser – *Secretary 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:

31.12.2021	*Foreign currency*	*Balance*
	EUR	1.0347

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/amortisation. Assets financed by long-term operating leasing contracts are not recognized in the balance sheet. In 2021, all non-current assets with an investment value above CHF 10 000 (instead of CHF 50 000) have been capitalised as property, plant and equipment, retrospective since 2018.

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

Notes to the financial statements

1 Unrestricted and restricted funds

In 2021, the income from fund raising amounted to CHF 6 824 186, thereof CHF 3 314 358 have already been used for projects. This results in net funds available as per 31.12.2021 in the amount of CHF 3 509 828, whereof CHF 1 227 274 are restricted (unrestricted: CHF 2 282 554).

	31.12.2021	31.12.2020
Net amount of funds received from	CHF	CHF
Private entity	902 003	1 398 066
Legal entities	1 380 551	450 899
Total unrestricted funds	**2 282 554**	**1 848 965**
Private entity	104 691	212 651
Legal entities	1 122 583	1 089 911
Total restricted funds	**1 227 274**	**1 302 563**
Total funds	**3 509 828**	**3 151 528**

2 Income from contributions

Income from contributions	**15 600 000**	**14 110 000**
Novartis	7 800 000	7 050 000
Canton of Basel-Stadt	3 900 000	3 530 000
University Hospital Basel	2 340 000	2 120 000
University of Basel	1 560 000	1 410 000

3 Research expenses

Research expenses	**5 553 445**	**4 630 797**
Consumables	3 745 329	2 392 681
Non-capital equipment	809 873	944 773
External services	877 551	1 293 343
Rent medical equipment	120 692	–

4 Administrative expenses

Administrative expenses	**2 962 725**	**2 341 222**
Legal and consulting expenses	1 230 861	1 016 151
Transport and travel expenses	58 715	54 478
Board and lodging expenses	74 856	36 854
IT expenses	1 207 773	1 024 576
Other expenses	390 520	209 163

Balance sheet

Assets	*Notes*	*31.12.2021* CHF	*31.12.2020* CHF
Cash and cash equivalents		525 084	1 671 307
Accounts receivable		900 012	631 823
from third parties		738 888	424 299
from affiliated parties		161 124	207 524
Other short-term receivables		243 807	133 631
from third parties		243 807	133 631
Prepaid expenses		529 851	634 239
Current assets		**2 198 753**	**3 071 000**
Property, plant and equipment		8 963 309	7 922 597
Intangible assets		393 424	0
Non-current assets		**9 356 734**	**7 922 597**
Total assets		**11 555 487**	**10 993 597**
Liabilities and equity			
Accounts payable		1 189 849	1 411 985
from third parties		979 826	883 218
from affiliated parties		210 022	528 767
Other short-term payables		455 723	291 720
from third parties		455 723	291 720
Short-term interest-bearing liabilities		1 000 000	500 000
from third parties		1 000 000	500 000
Accrued expense and deferred income		633 786	568 845
Restricted funds		1 227 274	1 302 563
Short-term liabilities		**4 506 632**	**4 075 112**
Long-term interest-bearing liabilities		7 000 000	6 000 000
from third parties		2 000 000	3 000 000
from affiliated parties		5 000 000	3 000 000
Long-term liabilities		**7 000 000**	**6 000 000**
Total liabilities		**11 506 632**	**10 075 112**
Foundation capital		500 000	500 000
Profit brought forward		-1 430 480	-136 288
Unrestricted funds	1	2 282 554	1 848 965
Net result of the year		-1 303 220	-1 294 192
Total equity		**48 855**	**918 485**
Total liabilities and equity		**11 555 487**	**10 993 597**

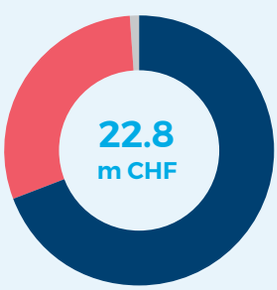
Income statement

	Notes	01.01.2021 – 31.12.2021 CHF	01.01.2020 – 31.12.2020 CHF
Income from contributions	2	-15 838 713	-14 258 934
Income from fundraising		-6 824 186	-5 563 062
Other income		-126 332	-248 844
Total operating income		**-22 789 231**	**-20 070 841**
Personnel expenses		11 532 149	9 227 121
Research expenses	3	5 553 445	4 630 797
Maintenance, repair, replacement		209 833	241 781
Rent and utility expenses		1 644 937	1 926 822
Energy, gas, water, disposal		246 797	153 938
Administrative expenses	4	2 962 725	2 341 222
Other expenses		49 662	62 133
Depreciation on property, plant and equipment		1 545 391	881 403
Total operating expenses		**23 744 939**	**19 465 217**
Operating result		**955 708**	**-605 624**
Financial income		-83 197	-60 537
Financial expenses		179 737	134 589
Ordinary result for the period		**1 052 247**	**-531 571**
Extraordinary, non-recurring or prior period income		-831 658	0
Extraordinary, non-recurring or prior period expenses		521 765	56 464
Net result for the period		**742 354**	**-475 108**
Net allocation to restricted funds	1	127 276	1 302 563
Net result for the period before net allocation to restricted funds		**869 630**	**827 455**
Net allocation to unrestricted funds	1	433 589	466 737
Net result for the period after net allocation to unrestricted funds		**1 303 220**	**1 294 192**

Cash flow statement

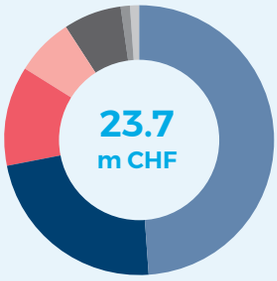
	01.01.2021 – 31.12.2021	01.01.2020 – 31.12.2020
	CHF	CHF
Net result for the period before allocation to unrestricted funds	-869 630	-827 455
Depreciation on property, plant and equipment	1 545 391	881 403
Changes in accounts receivable and other short-term receivables	-378 363	-119 870
Changes in prepaid expenses	104 388	-462 284
Changes in accounts payable and other short-term payables	-58 133	-298 862
Changes in accrued expenses and deferred income	64 942	616 548
Changes in restricted funds	-75 288	1 302 563
Post capitalisation of property, plant and equipment	-831 658	0
Cash flow from operating activities	**-498 353**	**1 092 043**
Capital expenditure on property, plant and equipment	-2 147 869	-3 918 331
Cash flow from investing activities	**-2 147 869**	**-3 918 331**
Proceeds from interest-bearing liabilities	2 000 000	3 500 000
Repayment of interest-bearing liabilities	-500 000	0
Cash flow from financing activities	**1 500 000**	**3 500 000**
Changes in cash and cash equivalents	**-1 146 223**	**673 712**
Verification of changes in cash and cash equivalents		
Beginning of period	1 671 307	997 595
End of period	525 084	1 671 307
Changes in cash and cash equivalents	**-1 146 223**	**673 712**

Funding 2021



- Income from contributions: **69%**
- Income from third parties: **30%**
- Other income: **1%**

Expenses 2021



- Personnel expenses: **49%**
- Research expenses: **23%**
- Administrative expenses: **12%**
- Rent and utility expenses: **7%**
- Depreciation on non-current assets: **7%**
- Maintenance, repair: **1%**
- Other expenses: **1%**

COLLABORATION

Advancing Europe's clinical research in ophthalmology

INTERVIEW
Hendrik Scholl

If new and improved treatments for eye diseases are the light at the end of the tunnel, clinical studies are the means to get there. EVICR.net is a network of 89 clinical research sites dedicated to perform multinational clinical research in ophthalmology with the highest standards of quality. IOB co-founder Hendrik Scholl, who has been leading the network's steering committee since 2017, talks about the aims and activities of EVICR.net, and shares his vision for the future of Europe's clinical research in ophthalmology.

What is the mission of EVICR.net?

→ Clinical trials help improve the quality of treatments available to patients. Many trials are initiated by sponsors, such as pharmaceutical companies, but others start at a research site. When researchers have an idea for a study – whether it's testing a new diagnostic procedure or assessing how a specific drug works on a particular disease, they may start a so-called investigator-initiated study. EVICR.net is committed to promoting investigator-initiated multinational clinical research in ophthalmology within Europe and guarantee the highest standards of quality and excellence according to harmonized standard operating procedures. The network's main activity is coordinating and conducting clinical studies to develop and optimize the use of diagnostic, preventative, and treatment approaches in ophthalmology.

Support for multinational clinical studies

IDENTIFYING CLINICAL SITES TO PARTICIPATE IN THE STUDY

- Recruitment capacity
- Human resources and equipment
- SOPs in place

feasibility assessment ▶

SCIENTIFIC REVIEW

- Expert committees
- Funding application submission

if approved € ▶

OVERALL COORDINATION OF MULTINATIONAL CLINICAL STUDIES

Pre-study activities

- Study design
- Study protocol development
- ICF development
- CRF design
- Database validation and implementation
- Study planning
- CS contracting

▶

Submission to RA and approval ▶

In-study activities

- Study management
- IMP management
- eCRF management and support
- Monitoring
- Data management
- Pharmacovigilance

▶

Post-study activities

- Biostatistics
- Medical writing
- Final study report
- Publication
- Archiving

What is the benefit of having a network for multinational clinical research?

→ There's always a shortage of patients for clinical trials, especially when it comes to rare conditions. So, it would be helpful if researchers could recruit patients out of the entire European population, which is nearly 750 million. But multinational studies are challenging, since European countries have different languages and regulations. To be able to recruit patients and conduct clinical studies across Europe, clinical researchers need a platform like EVICR.net, which serves Europe internationally through its network of 89 clinical research sites in 15 countries.

How is this achieved?

→ When researchers come up with an idea for a study, they can contact the Coordinating Center of EVICR.net in Coimbra, Portugal. The Coordinating Centre assigns the evaluation of the project to one of EVICR.net's expert committees. (EVICR.net has expert committees in different sub-specialties, including age-related macular degeneration, retinal dystrophies, and glaucoma.) The expert committee examines the idea and its feasibility. If the study is feasible, researchers have a platform that will allow them to conduct the clinical study across Europe. They can draw on the expertise and the patient population of the 89 centers that participate in the network, while the Coordinating Center helps to overcome language barriers and other challenges in order to allow such pan-European studies to take place.

What makes EVICR.net unique?

→ Currently, there is no other platform that would allow researchers to conduct pan-European clinical studies in ophthalmology. The European Organisation for Research and Treatment of Cancer, another established network for multinational studies, focuses on oncology research only. What makes EVICR.net unique is that it provides scientific independence: for example, a healthcare company has recently licensed a new gene therapy for inherited retinal diseases and contacted EVICR.net because they wanted to understand the current management of patients with such conditions in various European countries. The EVICR.net's expert committee for retinal dystrophies, which I'm chairing, found this research question interesting and important. So, the network performed an investigator-initiated survey that received funding from the company, but how the results were collected and how the data were put together was completely up to the network.

It was a win-win situation: EVICR.net received funding to conduct the research and disseminate the results through publications and presentations, and the healthcare company was able to access the survey results.

What other activities are organized by EVICR.net?

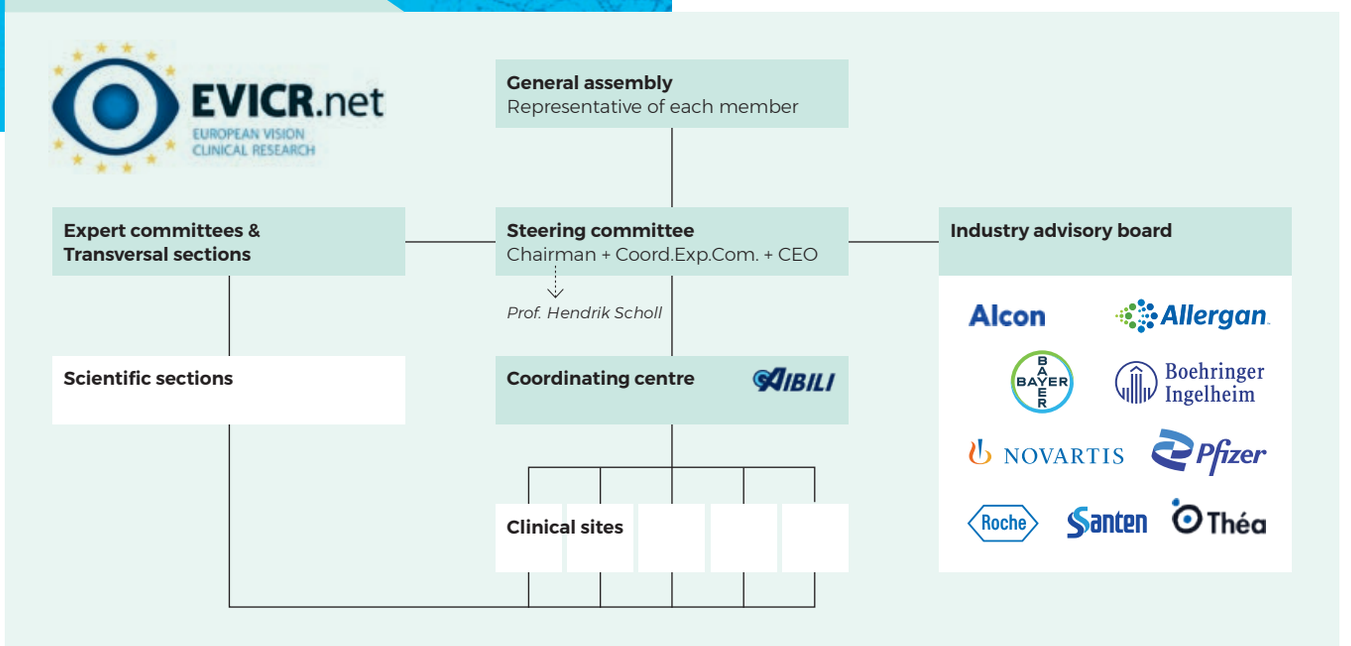
→ In 2017, we launched an educational program to share the network's experience and expertise with the broader clinical research community. We make educational webinars on ophthalmic clinical research that are available to nurses, technicians working in clinical practice, employees of clinical trials centers and so forth. There are all sorts of modules: how to implement clinical trials, good clinical practice, developments in specific fields such as glaucoma, current workup of patients with conditions such as retinal dystrophy – you name it. During the COVID pandemic, when we have little opportunity to meet and teach in-person courses, it turns out to be handy that information can be disseminated online and available to anyone anytime.

EVICR.net is also partnered with the European Clinical Research Infrastructure Network (ECRIN), an organization that facilitates the development of multinational clinical studies in Europe. EVICR.net serves as a resource to ECRIN in the area of vision and ophthalmology by providing scientific and medical expertise as well as access to patients and research centers.

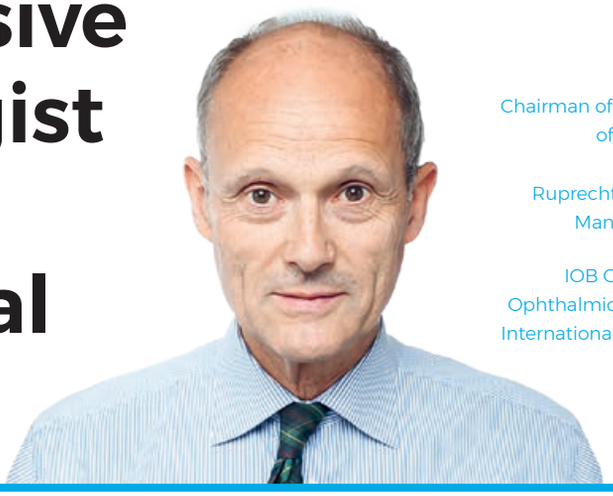
What is your vision for the future of EVICR.net?

→ The network can clearly offer the coordination of pan-European clinical research in ophthalmology. For example, EVICR.net is responsible for the overall coordination of the MACUSTAR multinational clinical study, which aims to characterize intermediate age-related macular degeneration and is funded by the European Innovative Medicines Initiative. In the future, I hope to see more such multinational studies funded by the European Union and coordinated by EVICR.net. However, over the five years that I've been serving as EVICR.net's chairman, it hasn't become easier to connect all European countries: we have witnessed Brexit and now Switzerland's access to European research funding is uncertain. When it comes to clinical research, these are hurdles that we need to overcome. ■

Organigram EVICR.net



A comprehensive ophthalmologist with interest in international research



PORTRAIT
Jost Jonas

Chairman of the Department of Ophthalmology, Medical Faculty, Ruprecht-Karls-University, Mannheim, Germany

IOB Guest Professor of Ophthalmic Epidemiology & International Ophthalmology

Jost Jonas is an accomplished eye specialist and surgeon, and one of the world's most cited researchers in ophthalmology – boasting an exceptional publication record. He is Professor of Ophthalmology at the Medical Faculty Mannheim of Heidelberg University, where he chairs the department of ophthalmology. Since 2021, he is also a guest professor at IOB.

As a researcher, Jonas focuses on a broad range of topics: from the biology of eye diseases to epidemiology – the study of the distribution and determinants of health-related conditions in specific populations. Among Jonas' main research interests is the diagnosis of glaucoma, a group of eye conditions that damage the optic nerve and one of the leading causes of blindness for people over the age of 60. He has also developed new methods to measure blood pressure in the eye, which can cause damage to the optic nerve when abnormally high. Jonas' work "really put German research in glaucoma on the world map," says IOB's co-director Hendrik Scholl.

Another key focus of Jonas' research is myopia, in particular high myopia, a severe type of nearsightedness that is becoming the most common cause of irreversible blindness worldwide. Myopia happens when a person's eyeballs grow longer than they should, Jonas explains. "We are looking for the factor that makes the eye longer, and we speculate that it is the epidermal growth factor, EGF," he says. Studies done in guinea pigs have shown that blocking the EGF receptor – a protein that is activated by binding of EGF – prevents excessive elongation of the eyeballs. Since drugs that block the EGF receptor are safely used to treat some types of cancer, Jonas set out to try these drugs on the eye. He recently co-led an early-stage clinical study, whose findings suggest that blocking the EGF receptor could have applications in the clinic.

Jonas speculates that EGF may also find uses in the treatment of age-related macular degeneration, a disease characterized by damage to the macula – the part of the retina that controls sharp, straight-ahead vision. Jonas explains that the retinal pigment epithelium – a cell layer that nourishes retinal visual cells – may be the main structure affected by age-related macular degeneration. Studies have shown that EGF can stimulate proliferation in cells of the retinal pigment epithelium grown in a lab dish. So Jonas and his colleagues assessed the safety of injecting EGF into the human eye and did not observe any major side effects. "Whether EGF is helpful, it's an open question," Jonas says, a question that he plans to address next. After all, one of his mottos is: Every question answered should raise at least two new questions.

Diverse interests

Jonas' scientific curiosity and enthusiasm have led him to establish numerous collaborations with institutions abroad, especially in Asia and Russia. There, he helped to design and organize several population-based studies. In these studies, researchers follow up a defined population to explore associations between health outcomes and factors such as age, sex, or lifestyle.

Population-based studies can provide important information on the prevalence and risk factors for specific

health conditions, Jonas explains. In collaboration with colleagues in China, India, and Russia, he assessed the prevalence and risk factors for eye diseases such as myopia, glaucoma and other health conditions, including cardiovascular events.

By exploring the prevalence of such conditions in areas where they had not been explored before, the studies filled a knowledge gap. They also revealed associations that had been previously unknown, for example that myopia may protect against age-related macular degeneration.

One recent population-based study that Jonas helped to design and organize is the Ural Eye and Medical Study, the first of its kind in Russia and Eastern Europe to assess a broad spectrum of conditions – including some, such as diabetes, that don't affect the eye directly but can increase the risk of eye diseases. Another unique population-based study that Jonas co-led is the Ural Very Old Study, which was conducted in the Russian city of Ufa and included participants over the age of 85. "Worldwide, there aren't many population-based studies on such an old group of people," Jonas notes.

Jonas' international collaborations often brought him abroad. Before the coronavirus pandemic hit, he used to travel outside of Europe every other week, for one or two days. "I used to work until Friday afternoon, get on the plane in Frankfurt, arrive in Beijing on Saturday morning and work there all day, go for dinner with my collaborators, and take a flight back to Frankfurt on Sunday morning," Jonas says.

For his work, Jonas has received many national and international awards, including the Life Achievement Honor Award of the American Academy of Ophthalmology. He is a member of prestigious scientific societies such as the German Academy of Science Leopoldina, the Academia Ophthalmologica Internationalis, the Macula Society, and the Retina Society.

Appointing Jonas as a guest professor has been one important achievement of IOB in 2021, Scholl says. "He is a very comprehensive clinician with expertise in different fields, and IOB's research priorities – macular degeneration, glaucoma, and myopia – all overlap perfectly with his expertise," Scholl adds.

Although the pandemic hampered in-person interactions, Jonas has already met with scientists at IOB and helped establish scientific collaborations with Ufa and Beijing. Scholl anticipates that in 2022, even more collaborations and scientific opportunities will materialize thanks to Jonas. "Junior clinicians and researchers at IOB will benefit enormously from being connected with such a prominent figure in the field." ■

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	Eidgenössische Technische Hochschule Zürich (ETH)	*Zurich/Basel*	Switzerland
	10	F. Hoffmann-La Roche Ltd, Pharmaceutical Research and Early Development (pRED)	*Basel*	Switzerland
	11	Fond'Action contre le cancer	*Lausanne*	Switzerland
	12	Fondation Leenaards	*Lausanne*	Switzerland
	13	Fondation Louis-Jeantet	*Geneva*	Switzerland
	14	Friedrich Miescher Institute for Biomedical Research	*Basel*	Switzerland
	15	Hedy Glor-Meyer Foundation	*Lucerne*	Switzerland
	16	Helbling Technik Bern AG	*Liebefeld-Bern*	Switzerland
	17	MaxWell Biosystems AG	*Zurich*	Switzerland
	18	Medical Image Analysis Center (MIAC)	*Basel*	Switzerland
	19	MIAC AG	*Basel*	Switzerland
	20	National Centre of Competence in Research (NCCR) of Molecular Systems Engineering	*Basel*	Switzerland
	21	Neuroscience Network Basel	*Basel*	Switzerland
	22	Novartis AG	*Basel*	Switzerland
	23	Palatin Foundation	*Basel*	Switzerland
	24	Professor Dr Max Cloëtta Foundation	*Zurich*	Switzerland
	25	ProgStar study group	*Basel*	Switzerland
	26	Retina International	*Zurich*	Switzerland
	27	Retina Suisse	*Zurich*	Switzerland
	28	Spectrum Foundation	*Lucerne*	Switzerland
	29	Swiss Tropical and Public Health Institute	*Basel*	Switzerland
	30	University Hospital Basel	*Basel*	Switzerland
	31	University of Applied Sciences and Arts Northwestern Switzerland	*Windisch*	Switzerland
	32	University of Basel	*Basel*	Switzerland
Middle East	**33**	Hebrew University of Jerusalem	*Jerusalem*	Israel
Asia	**34**	Nanyang Technological University, Ophthalmology and Biomedical Engineering	*Singapore*	Singapore
	35	Singapore Eye Research Institute	*Singapore*	Singapore
	36	Japan Eye Genetics Consortium	*Tokyo*	Japan

Europe	**37**	Department of Ophthalmology, Kepler University Clinic	*Linz*	Austria
	38	Department of Ophthalmology, Medical University of Graz	*Graz*	Austria
	39	Institute of Molecular Biotechnology of the Austrian Academy of Sciences (IMBA)	*Vienna*	Austria
	40	Medical University of Vienna	*Vienna*	Austria
	41	European Vision Institute	*Brussels*	Belgium
	42	Ecole Normale Supérieure	*Paris*	France
	43	GenSight Biologics	*Paris*	France
	44	Institut de l'Audition, Institut Pasteur	*Paris*	France
	45	Institut de la Vision Paris	*Paris*	France
	46	SILABE	*Strasbourg*	France
	47	Sparing Vision	*Paris*	France
	48	Boehringer Ingelheim	*Ingelheim*	Germany
	49	Forschungsplattform Degenerative Erkrankungen, Deutsches Primatenzentrum	*Göttingen*	Germany
	50	Heidelberg University	*Heidelberg*	Germany
	51	Institute for Ophthalmic Research, University of Tübingen	*Tübingen*	Germany
	52	Körber-Stiftung	*Hamburg*	Germany
	53	Max Planck Institute for Biophysics	*Frankfurt a. M.*	Germany
	54	Max Planck Institute of Neurobiology	*Martinsried*	Germany
	55	Okuvision GmbH	*Reutlingen*	Germany
	56	Peter und Traudl Engelhorn-Stiftung	*Weilheim*	Germany
	57	PRO RETINA Deutschland e. V.	*Bonn*	Germany
	58	STZ eyetrial, Department für Augenheilkunde, University of Tübingen	*Tübingen*	Germany
	59	University Hospital Freiburg	*Freiburg i. Br.*	Germany
	60	Femtonics	*Budapest*	Hungary
	61	Semmelweis University	*Budapest*	Hungary
	62	Erasmus Medical Center, Erasmus University Rotterdam	*Rotterdam*	Netherlands
	63	Radboud University Medical Center, Radboud University Nijmegen	*Nijmegen*	Netherlands
	64	European Vision Institute Clinical Research Network EVICR.net	*Coimbra*	Portugal
	65	Gyroscope Therapeutics Ltd.	*London*	UK
	66	Imperial College London	*London*	UK
	67	Institute of Ophthalmology, University College London	*London*	UK
	68	King's College London	*London*	UK
	69	Moorfields Eye Hospital	*London*	UK
	70	Novartis Pharma AG (CORE)	*London*	UK
	71	PINNACLE study group	*Southampton*	UK
	72	ReNeuron Group Plc/Ora Inc. and member of the Steering Committee of Novo Nordisk	*Bridgend, Bagsværd*	UK, Denmark
	73	Sainsbury Wellcome Center	*London*	UK
	74	University of Southampton	*Southampton*	UK
	75	Wellcome Trust	*London*	UK
USA	**76**	Affinia Therapeutics	*Waltham*	USA
	77	Allen Institute for Brain Science	*Seattle*	USA
	78	Astellas Pharma Global Development, Inc./ Astellas Institute for Regenerative Medicine	*Deerfield/ Marlborough*	USA
	79	Beam Therapeutics	*Cambridge*	USA
	80	Belite Bio	*San Diego*	USA
	81	Biogen MA Inc	*Cambridge*	USA
	82	Byers Eye Institute, Stanford University	*Palo Alto*	USA
	83	Cole Eye Institute, Cleveland Clinic	*Cleveland*	USA
	84	David Geffen School of Medicine, University of California	*Los Angeles*	USA
	85	Department of Ophthalmology, Case Western Reserve University	*Cleveland*	USA
	86	Doheny Eye Institute, University of California	*Los Angeles*	USA
	87	End Blindness by 20/20	*Washington DC*	USA
	88	Foundation Fighting Blindness	*Columbia*	USA
	89	Foundation Fighting Blindness (FFB) Consortium, coordinated by the Center at Jaeb Center for Health Research (JCHR)	*Tampa*	USA
	90	Greater Baltimore Medical Center	*Towson*	USA
	91	Harvard Medical School	*Cambridge*	USA
	92	Inscopix, Inc.	*Palo Alto*	USA
	93	Janssen Research & Development, LLC (Johnson & Johnson)	*Raritan*	USA
	94	Moran Eye Center, University of Utah	*Salt Lake City*	USA
	95	Novartis Institutes for Biomedical Research	*Cambridge, Basel*	USA, Switzerland
	96	Retina Foundation of the Southwest	*Dallas*	USA
	97	ReVision Therapeutics, Inc.	*Ridgewood*	USA
	98	Scheie Eye Institute, University of Pennsylvania	*Philadelphia*	USA
	99	Stargazer Pharmaceuticals, Inc.	*Boston*	USA
	100	State University of New York College of Optometry	*New York*	USA
	101	University Hospitals Clinical Research Center, Cleveland Medical Center	*Cleveland*	USA
	102	University of Houston College of Optometry	*Houston*	USA
	103	University of Michigan	*Michigan*	USA
	104	University of Pittsburgh	*Pittsburgh*	USA
	105	Wilmer Eye Institute, Johns Hopkins University	*Baltimore*	USA

Founders:
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Affiliations:
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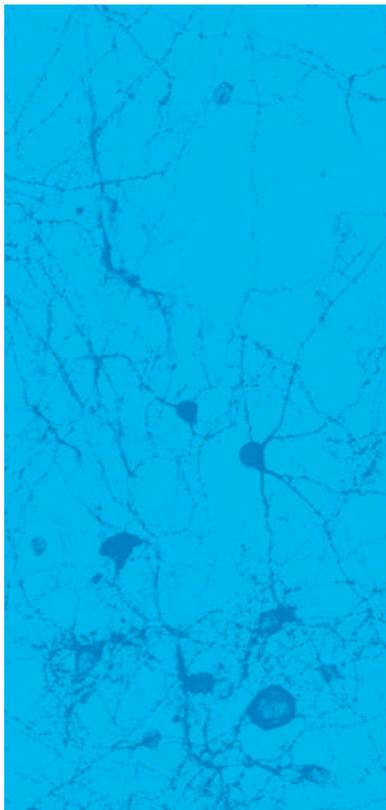

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IOB Mission

We advance the understanding of vision and human eye diseases and develop new therapies for vision loss.