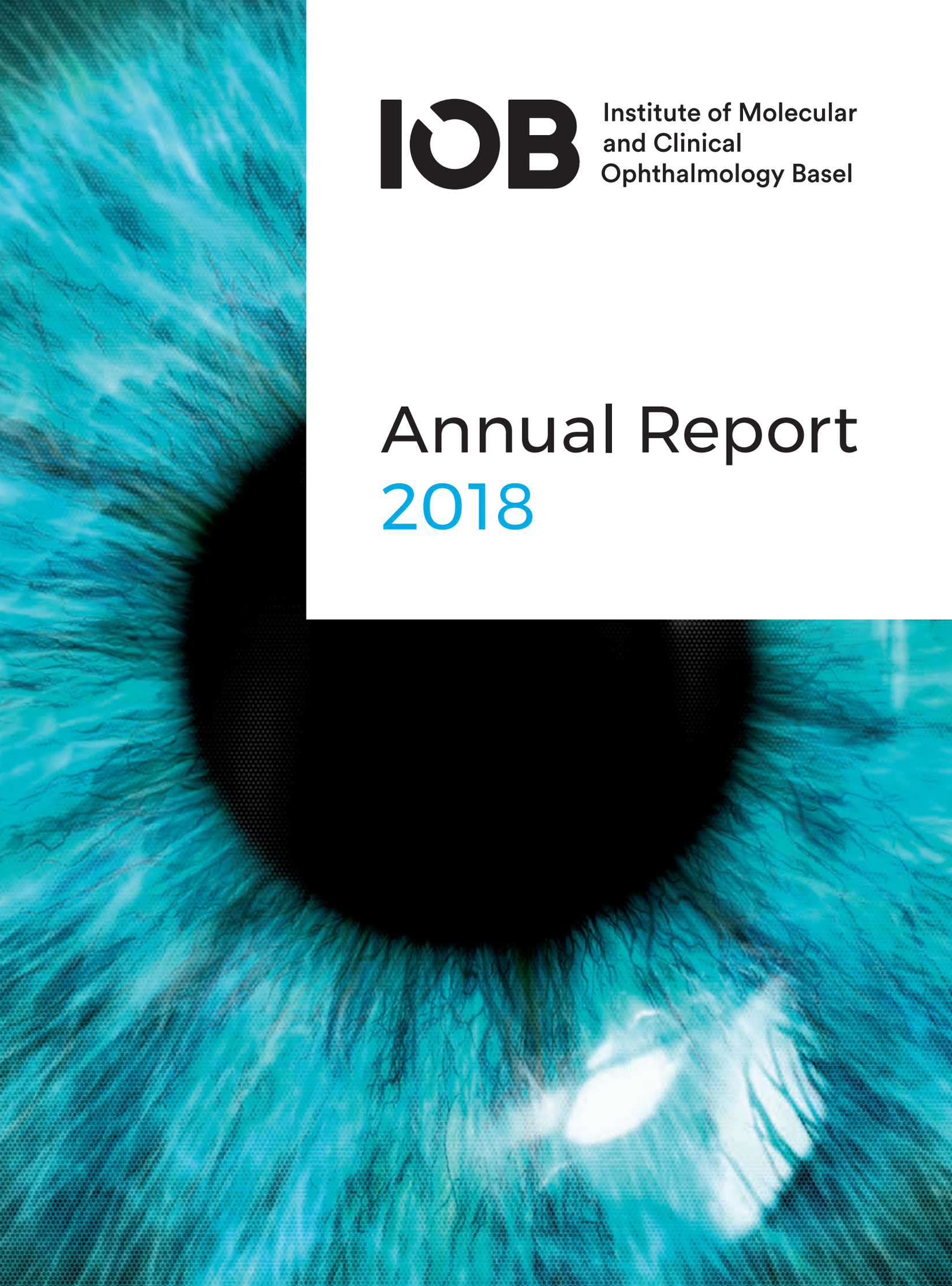


IOB Institute of Molecular and Clinical Ophthalmology Basel

Annual Report 2018

2018 IN BRIEF

Number of scientists: more than 60

Income 2018: CHF 10.76 m

Key Achievements in 2018:

- Developed novel approaches to delivering genes to cells in the eye
- Created digital tools to visualize the retina during surgery
- Strengthened the methods for measuring disease progression

MISSION

We accelerate the conversion of basic research into innovative treatments, which change the standard of care of ophthalmic therapy.

Our work promises hope to millions of patients worldwide suffering from currently incurable forms of vision impairment or vision loss.

CONTENTS

The aim of IOB is to conduct basic and translational research in human health.

In order to counter degeneration and to treat impaired vision and blindness hereby we foster Basel as a center of life science research. We also aim to improve society's understanding of the function and diseases of the human eye.

Chairman's letter

Dear Reader,

The Institute of Molecular and Clinical Ophthalmology Basel has completed its first year of operations, and has accomplished its goals for the year. IOB started the year as a concept, and now at the end of 2018, is a team of more than 60 individuals. We are proud of the progress IOB made in 2018.

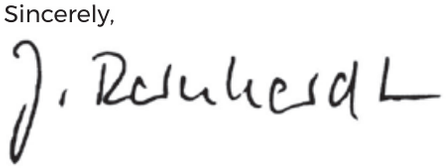
IOB's founding premise is that meaningful progress in biomedical research can only be achieved through collaboration. Today, no single person can possess the breadth of knowledge, skill and experience required for success. The strong partnership between Botond Roska, a globally recognized expert in the biology of the eye, and Hendrik Scholl, a world renowned expert in clinical research and patient care, gives IOB a strong foundation for cross-disciplinary collaboration. Already, the interactions between the clinical and molecular sides of IOB have generated important results, potentially altering our understanding of some pathobiology of the human retina.

IOB is itself a collaboration: its founders are Novartis, the University Hospital of Basel and the University of Basel. My colleagues on the Board and I have taken great pleasure in the opportunity to work more closely together, and to strengthen the community of researchers in Basel.

People rely on vision for most of their activities in life, it is an important source of social connection, and vision is a huge source of pleasure for most of us. Despite its importance, vision has been a challenging field for biomedical researchers. The human retina is unlike most animal retinas, making it much more difficult to understand diseases in the eye. Novel capabilities such as organoid technology, gene therapy, and improved imaging of the eye are enabling a new wave of research in ophthalmology. IOB has been founded just as that wave starts to rise, and is already a leader in some of these fields.

I am confident that the IOB will generate new knowledge about eye diseases, and will take important steps in 2019. Through a rich collaboration, I am hopeful that IOB's research will lead to novel therapies for diseases of the eye in the coming years.

Sincerely,



Jörg Reinhardt
Chairman of the Board of Trustees

Directors' letter

Dear Reader,

In our first year of operations, IOB has achieved important milestones.

Most importantly, IOB has contributed to advancing our knowledge of ophthalmic diseases. Clinical research at IOB has helped to develop better ways to measure how vision is impacted by Stargardt disease and retinitis pigmentosa. IOB researchers have also developed technology to image the retina and choroid with better quality and visualize the data three-dimensionally.

On the molecular biology side of the Institute, IOB researchers have made important progress in developing living models of the retina, known as organoids, which can be used to test novel therapies. Several projects are converging on methods to deliver gene therapies very precisely in the eye – either to a specific cell type, or to a particular location as small as a single cell. Computational methods have also been applied to understanding the circuitry of the retina, which is providing fundamental understanding of how the retina works, and may offer novel approaches to treatment.

In parallel with the scientific work, IOB operations are off to a good start. IOB now has the infrastructure to administer its finances, manage employees, explore legal questions, communicate its achievements and raise grant funding.

Our priorities in 2019 are in three areas: 1) continue to progress on the scientific side, particularly those efforts that combine the forces of the fundamental biologists and the clinicians on the IOB team, 2) build up IOB's scientific talent by hiring senior scientists with an international reputation as well as recruiting outstanding junior researchers, and 3) strengthen our operational capabilities, especially by moving into new laboratory space to integrate all laboratory research in one place.

With IOB, we have the chance of a lifetime to work together to develop novel therapies to address as yet untreatable ophthalmic diseases. We are grateful to our Founders and our many partners for their support.

Sincerely,

Botond Roska
Co-director

Hendrik Scholl
Co-director

Norbert Spirig
Director of Operations

IOB: ITS CONCEPT AND FOCUS

Around the world, millions of patients suffer from currently incurable vision loss. The new Institute of Molecular and Clinical Ophthalmology Basel (IOB) was created to help them.

We accelerate the conversion of basic research into innovative treatments to change today's standards of care in ophthalmic therapy.

At the IOB, interdisciplinary teams of researchers and clinicians work hand in hand. These problem-solvers and innovators have in-depth knowledge of unmet medical needs and daily exposure to patients. Together, they improve the understanding of vision, and of the cells involved in eye disease. In this highly collaborative environment, the IOB turns discoveries and technologies into clinical benefits for patients with blinding conditions.

We help change the practice of delivering care for ophthalmic disease based on the genetic, structural and functional understanding of the cell types and their interactions within the human eye.

Unmet medical need in ophthalmology

Vision is precious. All over the world, people rely on vision for their daily life and to enrich their interactions with one another. Recently, a survey was conducted in the United States asking people what would be their worst clinical condition, and strikingly, blindness topped the list.[1]

Globally, 36 million people are blind[2], and more than 1 billion people experience a significant degree of vision impairment. The major causes of vision impairment[3] include uncorrected visual refractive errors, cataract, age-related macular degeneration (AMD), glaucoma and diabetic retinopathy, but also include rarer blinding genetic diseases such as retinitis pigmentosa and Stargardt disease.

Globally, 80% of vision impairment can be corrected with existing technology. For most patients, access to established treatments is the most important gap. But many patients experience vision impairment or blindness due to diseases that cannot be treated effectively, or even at all.

Many of these diseases are most common in older individuals, particularly illnesses such as age-related macular degeneration and glaucoma. But the most common causes of blindness in younger people are retinal dystrophies. Important examples of those are Stargardt disease and retinitis pigmentosa, which begin to harm vision in childhood, and can lead to blindness in early adulthood.[4]

Innovation in treatments for blinding diseases has been frustratingly slow. There have been important breakthroughs over the last decades in lens replacement for cataract treatment, and the use of anti-VEGF agents for the management of wet age-related macular degeneration. Very recently, gene therapy for one genetic form of Leber congenital amaurosis has been introduced that has a dramatic benefit for patients with this rare and devastating disease. But these therapies address only a small fraction of the unmet need in vision, and these three innovations stand out in part because they are so few.

Why has this process been so slow? There are five critical factors that have slowed innovation in vision treatments:[5]

- First, the retina, once damaged, does not regenerate. Unlike some other tissues in the body, which can recover after an injury, the retina cannot recover on its own.
- Second, the retina is complex, making it difficult to understand precisely how diseases harm the retina, and also suggesting that therapeutics for the retina need to reach the right parts of the retina in order to function as designed.
- Third, the eyes of most animals differ significantly from human eyes, which makes it difficult to draw conclusions about human vision from studies of animal models. For instance, some of the features of the human eye which enable high resolution vision are completely absent in common research animals such as mice.
- Fourth, human eyes have a membrane barrier between the retina and the inner eye, which protects the retina. This membrane is biologically important but makes it more difficult to deliver therapies to the retina, particularly gene therapies which have the potential to correct some of the most important blinding diseases.
- Finally, the human retina has a very large surface area, almost 100 times larger than that of the mouse, also making delivery of therapeutics more difficult.

New tools and approaches are emerging which can address these challenges, and this is why IOB has been founded now, as the capabilities of these tools grows.

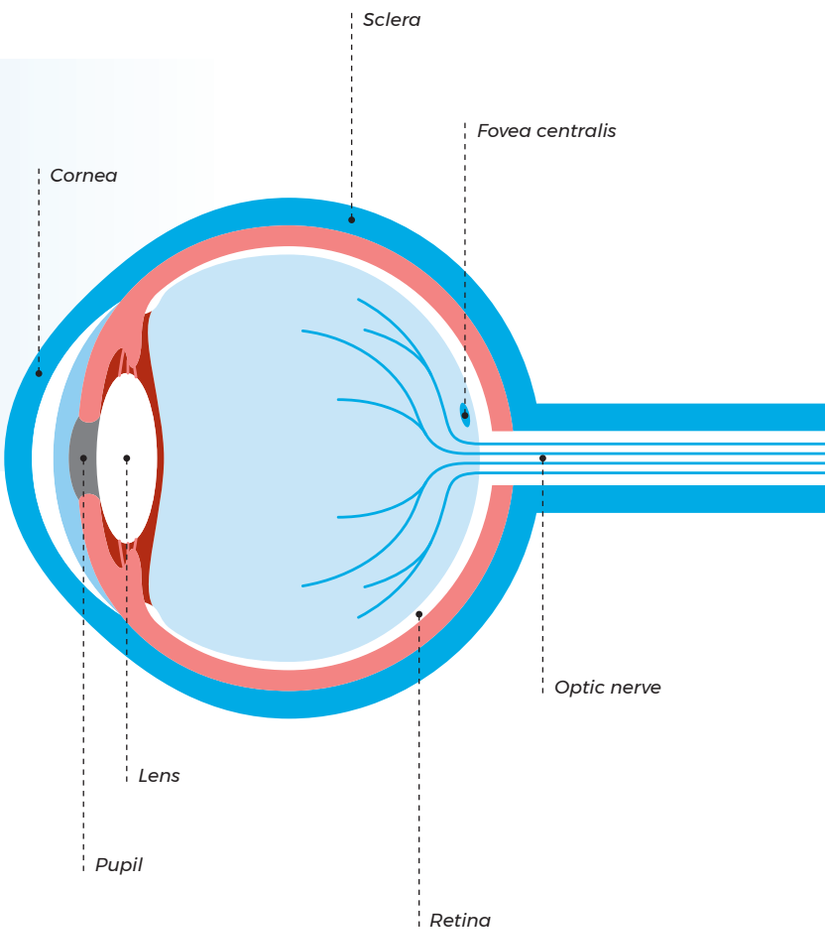
The four cornerstones of progress are discoveries in:

- human and animal genetics and genetic engineering,
- the development of patient-derived organ models,
- the understanding of the physiology of complex tissues, and
- the development of technologies to target specific cell types with biological or chemical materials.

The eye has been at the forefront of these developments, and is also at the forefront of turning these developments into innovative therapies. This is because of its accessibility through light-microscopy-like *in vivo* and *in vitro* imaging, its immune privilege, and new delivery methods to treat the target tissue extremely efficiently while having minimal or no systemic side effects.

IOB aims to change the practice of translational ophthalmology by using the understanding of the structure, function, and molecular composition of the cell types of the human eye and its organoid models as a starting point for developing therapy.

Human eye anatomy



1. Scott et al., JAMA Ophthalmol. 2016;134(10):1111–1118 – 2. Bourne et al., Lancet Global Health. 2017;5:e888–97 – 3. WHO. Visual Impairment and Blindness. http://www.who.int/mediacentre/factsheets/fs282/en/ (2017) – 4. Finger et al., Br J Ophthalmol. 2011;95:1061–1067; Liew et al., BMJ Open 2014;4:e004015 – 5. Roska & Sahel, Nature. 2018;537:359–367

SCIENTIFIC ACHIEVEMENTS 2018

In 2018, IOB scientists made substantial contributions to the understanding of the eye, of human disease, and to the creation of tools and potential therapeutics. A selection of these is presented on the following pages.

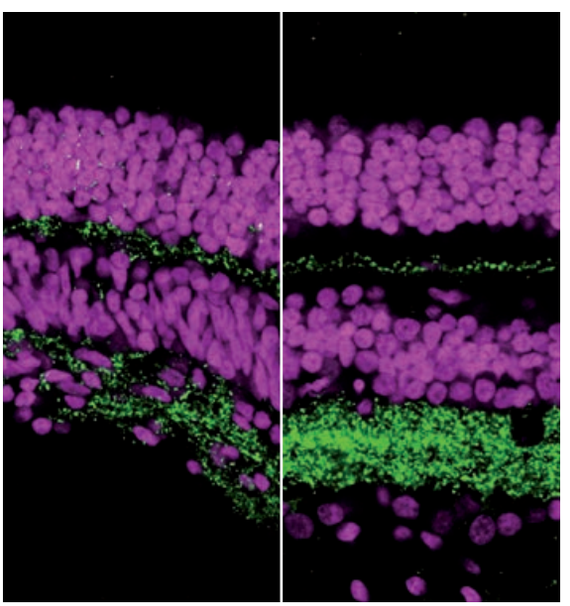
Laboratory-grown human retinas for personalized medicine

Magdalena Renner

Scientists at IOB have generated highly organized human retinas from human skin cells *in vitro*.

These so-called retinal organoids can be the starting point for developing personalized treatments for patients.

Vision is a key sense in humans and losing eyesight has been regarded as the condition with the greatest effect on day-to-day life. Most visual diseases originate in the retina, a biological image processor built from many different cell types organized in five retinal layers. Scientists have so far relied on animal models to study retinal function and disease; however, it is often difficult to translate findings in animal models to humans. This may be due to structural differences and/or to species-specific differences in gene expression. A model system consisting of human retinal cell types would be highly beneficial to the study of human disease and the development of new therapies.



200-day human retinal organoid (left) and a human donor retina (right)

Synaptic layers

Nuclear layers

Scientists at the IOB have succeeded in generating highly organized human retinal organoids in culture. Skin fibroblasts were used that can be programmed into pluripotent stem cells. These pluripotent cells can be induced to differentiate into most cell types of the human body. Following a specific culture protocol, IOB scientists induced a process very similar to human eye development. Over a period of several months, tissues formed that are strikingly similar to the human retina. Their work allowed the generation of a large number of retinal organoids from stem cells, that not only contain all major cell types of the human retina, but are also arranged into five layers. Moreover, the photoreceptor cells of the organoids possess a highly developed outer segment consisting of the light sensors that are often damaged in human disease.

Retinal organoids can also be generated from skin fibroblasts of patients suffering from specific genetic diseases. Thus, the effects of mutations on retinal cells can be directly studied in a culture dish. Furthermore, different therapies could be tested specifically on a patient's own retinal organoids.

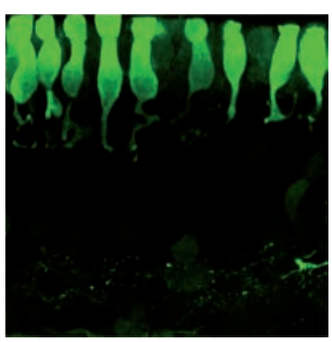
Targeting cell types with gene therapy vectors for therapy

Josephine Juettner

Targeting genes to specific neuronal or glial cell types could be essential in making gene therapies for the eye, or indeed for other neural systems in the brain or elsewhere. Adeno-associated viral vectors (AAVs) are the most promising approach for delivering gene therapy into the retina or the brain, but targeting expression to specific cell types is a challenge. If such therapies are not targeted to specific cell types, it is possible that they will be ineffective or even harmful.

At the core of cell targeting specificity is a DNA control element – promoter or enhancer – that when embedded into the AAV genome drives transgene expression in a cell-specific fashion.

An international team led by IOB scientists have created a library of 230 AAVs, each with a different synthetic promoter designed using four independent strategies. First, AAVs were tested for cell-type-specific expression in the eyes of mice. Next, a subset was analyzed in mouse brain and in the eyes of non-human primates. Finally, the library was tested in human post-mortem retinas. Remarkably, scientists identified a collection of AAVs that specifically targeted gene expression to neuronal and glial cell types in the mouse retina and brain, as well as in non-human primate and human retinas. The cell-type-specific AAVs target many retinal cell types or classes, including the photoreceptors, pigmented epithelium cells and ganglion cells affected in human blinding diseases like macular degeneration, retinitis pigmentosa and glaucoma.



Human cone photoreceptors targeted by specific AAV

In basic research, genetic labeling allows the isolation and molecular characterization of neuronal or glial cell types. Genetically encoded sensors and electrical recording targeted to neuronal cell types allow monitoring of activity; cell-type-targeted optogenetic or chemogenetic tools permit modulation of this activity. Using cell-type specific AAVs, the team demonstrated applications for recording, stimulation, and molecular characterization of targeted cells.

Furthermore, the scientists invented an approach using combinations of AAVs to target individual cell types that could not be marked by any one AAV alone. In addition, they successfully targeted particular sets of cells by using more than one AAV. This strategy may be used to analyze connectivity across different neuronal cell types.

The results demonstrate that different neuronal and glial cell types of mice, non-human primates, and humans can be efficiently targeted using AAVs. These resources and methods provide economic, fast, and efficient cell-type targeting in a variety of species, both for fundamental science and for the gene therapy of cell-type-specific human blinding diseases.

Interactive live imaging of human eyes

Peter Maloca

Optical coherence tomography (OCT) is an imaging technology used in the eye, which gives extremely detailed, almost cellular level information about the retina using non-invasive, low energy light. OCT images can be generated very rapidly. However, the technology generates so much information that it can be difficult to interpret and use the data in clinical practice. One very desirable application of OCT imaging is integration into the operating microscope during ophthalmic surgery and neurosurgery. The rapid collection of data does not disturb the surgeon's workflow, and can offer important information on the state of the retina during surgery.

However, OCT scans are difficult to interact with, and are typically displayed as a series of flat two dimensional B-scans. These characteristics make it more difficult for the surgeon to use the OCT-derived information as a guide.

Scientists from IOB and the University of Basel have introduced a novel virtual reality (VR) imaging technique for instant volume OCT data rendering, enhanced with real-time ray casting of shadows. It enables the visualization of the vitreoretinal interface, particularly the retina and its layers, with a cross-sectional and three-dimensional (3D) display. This digital transformation could alter how OCT and other imaging information are displayed and transform the medical field by providing clinicians with an environment that augments their training, facilitates surgical planning, and supports clinical decision-making intraoperatively. Trained ophthalmologists with a mean of 15 years of post-graduate professional sub-specialization rated the application positively.

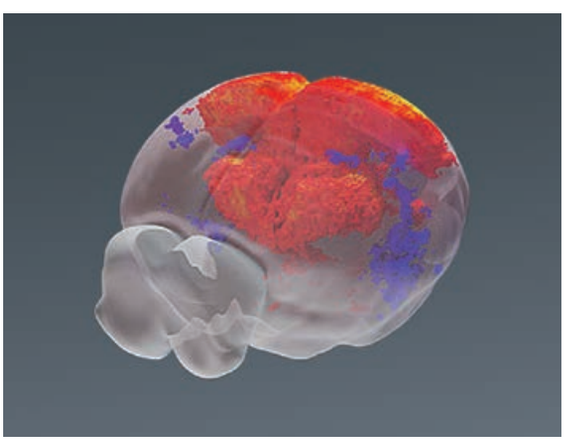
The system empowers the user to switch promptly between the 3D-OCT VR model and the corresponding original OCT data by means of the cutting plane. Instantly, the user can focus on any space, section and junction, and selectively hide or display particular structures. This combined feature of synchronized mapping of original, highly complex, 3D-OCT point-cloud volume data and plane view offers an unprecedented and meaningful VR environment. This kind of 3D data modeling and data representation mitigate the risk of masking pathologic tissue, such as intracranial aneurysms, which has been shown for VR rendering. The combined, multidimensional feature in the software avoids missing critical information, because the VR image is immediately correlated and compared with corresponding OCT images.

The combination of VR and machine learning can process high-end data in real time. The Ophthalmic Imaging Research Group at IOB showed that the developed system was at least as good as humans in retinal zone segmentation – but much faster. This enables further development of the technology for the early detection and monitoring of eye tumors. The technology will be made available to doctors free of charge.

Whole-brain imaging of animal models of disease during behavior

Emilie Mace

Visual perception only starts in the eye – and IOB's studies of vision, its ailments and potential therapies extends also into the way the brain processes visual information. The IOB team is particularly interested in the neuro-ophthalmological disease congenital nystagmus, which has an incidence of 1 in 1,500. One symptom of this genetic disease is lack of the horizontal optokinetic reflex that stabilizes images drifting on the retina both horizontally and vertically by moving the eye in the direction of image drift. An example of this is the reflexive movement of the eye following the landscape seen from a moving train. This reflex is inborn and well-conserved across species from mice to humans. Mutations in the FRMD7 gene on the X chromosome have been detected in 70% of recorded cases of the disease. In the retina, expression of the FRMD7 gene is localized in starburst amacrine cells, a retinal cell type that detects the direction of visual motion. In animal models of congenital nystagmus, FRMD7 mutation leads to abnormal starburst cell connectivity, lack of horizontal direction selectivity, and lack of the horizontal optokinetic reflex, as found in humans.



Brain regions involved in optokinetic reflex

Collaborating with scientists at the Friedrich Miescher Institute, and the Neuro-Electronics Research Flanders, IOB scientists have explored brain function in animal models of congenital nystagmus. Initial studies have shown that functional ultrasound imaging can yield high-resolution, brain-wide activity maps of mice during specific behaviors. This non-invasive technology has promising applications for ophthalmologic, neurologic and psychiatric diseases. This approach is superior to older technologies such as fMRI, since older methods have limited resolution and are difficult to apply to awake and behaving mice.

To determine changes in the brain of an animal model of congenital nystagmus, the team compared whole-brain activity in control and diseased animals. Of the 181 brain regions consistently identified in all animals, 87 regions were modulated during the optokinetic reflex. Remarkably, 70 brain areas were modified in the diseased animals. These areas were distributed in two brain modules. One module depended on the motor output of the reflex and the other was independent of the motor output.

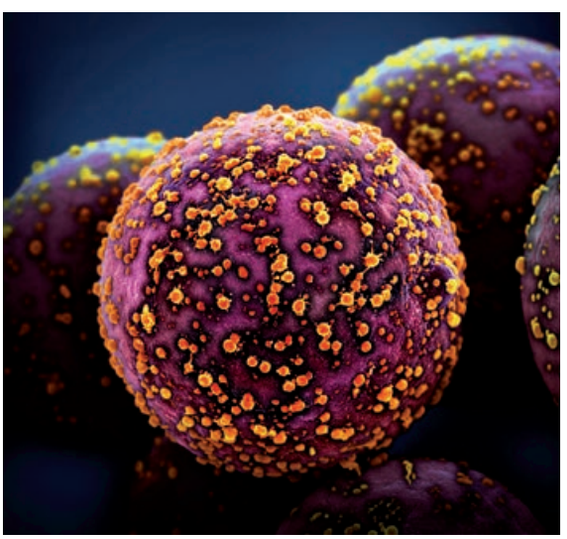
The major value of this study is the introduction of a simple, low-cost, sensitive, and practical whole-brain imaging method that generates an unbiased view of brain activity during many types of behavior, as well as in animal models of ophthalmic, neurologic and psychiatric diseases.

Virus stamping – a versatile new method for genetic engineering of single cells

Rajib Schubert

Adenovirus- and lentivirus-based vectors are promising methods for delivery of gene therapy in the eye. However, a key challenge is delivering the viral vector to the cells that need to be targeted but no others. Precise targeting of viral vectors could be important in the case that broader delivery of the vector could eliminate its effectiveness, or even be harmful. Precise targeting of viral vector delivery is also a powerful research tool, which could enable a range of more sensitive experiments.

Scientists at IOB, ETH Zurich and the Friedrich Miescher Institute have developed a novel method to efficiently deliver genes into single cells of whole tissues. The novel method, known as "virus stamping", is simple, versatile, and applicable for a variety of cell types and viruses *in vivo* and *in vitro*.



Virus-bound nanoparticle for virus stamping

In this method, viruses are reversibly bound to a delivery vehicle that is then brought into the vicinity of the target cell. Both mechanical and magnetic forces may be used depending on whether the cell is on the surface or within the tissue. For surface cells, an unshielded virus "stamper" is used, i.e., the virus is bound to a blunt glass pipette tip that is brought into physical contact with the target cell. For cells within an organ or tissue the stamper must be shielded and the virus is first bound to magnetic nanoparticles inside a glass pipette. When the pipette tip reaches the target cell, the viruses are delivered by pulling the nanoparticles to the tip of the pipette with a magnetic force.

This method has been used to infect single cells in cell cultures, tissues, animals and organoids. Furthermore, the method has been used successfully in complex structures such as the brain. It is also possible to infect a single cell with multiple viruses, either simultaneously or at different time points.

Virus stamping thus allows examination of the role of specific genes in clearly defined cells, offering a versatile solution not only for fundamental biomedical research but also, potentially, for gene therapy.

A computer model of the retina

Antonia Drinnenberg

Human eyes host a powerful 'biological computer', the retina.

Understanding how images from the outside world are transformed in the retina into signals that the brain interprets may not only result in insights into brain computations, but may also be useful in medicine. As machine learning and artificial intelligence develop, eye diseases will soon be described in terms of perturbations of the computations performed in the retina.

Vision starts in the retina, where light falling on the eye excites photoreceptor cells and is transduced into neuronal activity. Visual signals then reach the brain via ganglion cells, the output neurons of the retina. However, the retina is much more than just a camera and a cable. Between photoreceptors and ganglion cells, the retina includes intricate neuronal circuits made up of many different neuronal cell types. Incoming signals are processed in these circuits in a complex way, which defines important features of the visual scene. At the output level of the retina, the computations of the retinal circuits result in ~30 different neuronal representations of the visual scene. These then travel in parallel to the brain. Thus, the retina acts like a powerful computing device that shapes visual representation in a profound way.

To understand the mechanisms of vision and to predict the outcomes of visual diseases, it is essential to understand how the ~30 retinal output channels represent the visual world and how their different functional properties arise from the architecture of the retinal circuits. To address this question, IOB members together with collaborators at the Friedrich Miescher Institute, ETH Zurich, and the Ecole Normale Supérieure perturbed a specific retinal circuit element while studying how this perturbation changes the functional properties of the different retinal output channels.

The team developed a method to control the activity of horizontal cells, which are retinal circuit elements involved in feedback inhibition at the first visual synapse between photoreceptors and bipolar cells. The method involves a specific set of viruses, transgenic mice, and engineered ligand-gated ion channels that together allow the feedback at the first visual synapse to be switched on and off. To measure the effects of this perturbation on the retinal output, the team recorded electrical signals of hundreds of ganglion cells simultaneously. Surprisingly, the perturbation resulted in a large set of different changes in the output.

To understand how change in a single element of the retinal circuitry can lead to such a variety of effects, the team built a computer model of the retina that simulates the different pathways that the signal can take through the retina. Studying whether current understanding of the retinal circuitry (i.e., the model) can account for the effects observed during the perturbation experiments, the researchers found that it could reproduce the entire set of changes measured experimentally. In addition, it made five further predictions about the role of horizontal cells not seen previously in the data.

Thus, an efficient way to test our understanding of the retina is to perturb one of its elements, measure all the outputs, and see whether our 'understanding' can predict the observed changes. The next step will be to use the model to predict the outcome of eye diseases.

A natural history study of Stargardt disease

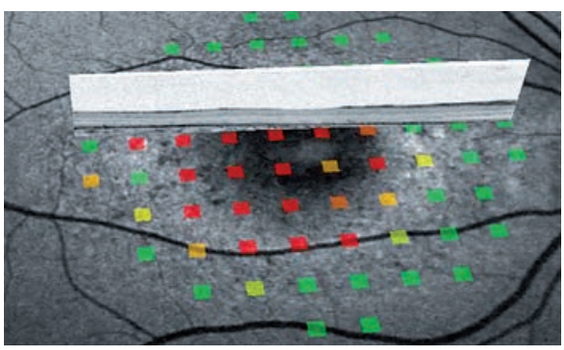
Hendrik Scholl

Stargardt disease is a blinding disease that affects children and young adults. It is a genetic disease, indeed, the most common juvenile macular degenerative disease. It is inherited as an autosomal-recessive trait associated with mutations in the ABCA4 gene.

Clinically, Stargardt disease is characterized by fundus flecks in the retinal pigment epithelium (RPE) and by macular atrophic lesions. Visual acuity and central visual fields deteriorate progressively, commonly leading to legal blindness in adulthood. Currently there is no treatment for Stargardt disease.

Clinician scientists at IOB are participating in an international collaboration, known as ProgStar, to study the natural history of Stargardt disease progression, and to help determine clinical outcome measures that could be used in clinical trials of future therapies.

The primary aim was to assess the yearly rate of progression of Stargardt disease using the growth or the development of atrophic lesions as measured by fundus autofluorescence (FAF) imaging. Other measures for assessing disease progression were also explored, such as using optical coherence tomography (OCT) to measure the loss of photoreceptors, and microperimetry to measure the loss of retinal sensitivity.



Central retina of a patient with Stargardt disease, superimposing FAF and OCT images with color-coded retinal sensitivity measurements

The primary clinical endpoint of the ProgStar study was the yearly rate of progression using the growth of atrophic lesions as measured by FAF imaging. In 458 eyes from 251 study participants, mean progression of definitely decreased autofluorescence (DDAF) lesions was 0.51mm^2/year. This finding led to the conclusion that the growth rate of atrophic lesions as determined by FAF imaging may be a suitable primary outcome measure for treatment trials. In actual fact, the first clinical trials have started that refer to these findings and use DDAF growth rate as the main outcome measure.

Microperimetry was used to create a detailed map of patients' retinas, showing their sensitivity to light. In the ProgStar prospective cohort, microperimetric mean sensitivity was lower in the fovea than in the peripheral macula. Overall mean sensitivity was lower in older patients and those stating longer disease duration. Overall mean sensitivity per eye was 0.086 dB lower per year of additional age ($p<0.001$) and 0.21 dB lower per additional year of duration of Stargardt ($p<0.001$). Some patients showed surprising discrepancies – for instance, individuals with low light sensitivity but good visual acuity. In these unusual cases, it was often possible to show that, while there was extensive damage to the retina, the fovea had been spared. It is reasonable to conclude that microperimetry allows a more comprehensive assessment of the function of the central retina, and it may serve as an outcome measure in future clinical trials for Stargardt disease and other macular diseases.

The ProgStar study also confirmed the large spectrum of ABCA4 sequence variants: In the 345 patients studied, 245 ABCA4 variants were detected. In ProgStar alone, 50 novel variants were found to be associated with Stargardt disease.

IOB PRIORITIES

Scientific plan

In recent years, biomedicine has witnessed a wealth of breakthrough discoveries, technologies, and concepts. The four cornerstones of progress are discoveries in human and animal genetics and genetic engineering, the development of patient-derived organ models, the understanding of the physiology of complex tissues, and the development of technologies to target specific cell types with biological or chemical materials.

The eye has been at the forefront of these developments, and is also at the forefront of turning these developments into innovative therapies. This is because of its accessibility through light-microscopy-like *in vivo* and *in vitro* imaging, its immune privilege, and new delivery methods to treat the target tissue extremely efficiently while having minimal or no systemic side effects.

The scientific goals of IOB are to:

- Understand vision at the level of cell types and circuits
- Gain mechanistic insights into diseases that lead to vision loss
- Design new therapies to restore vision in blinding diseases

Current approaches in translational ophthalmology start with understanding animal models of disease, as well as the normal structure and function of the eye in these animals.

There are several limitations to this starting point:

- First, with the exception of non-human primates, all current animal models of disease lack the fovea (or macula), the part of the human retina that is used for high-resolution vision necessary to read and recognize faces.
- Second, the gene expression patterns of human cell types are different from those of animal models.
- Third, gene therapy vectors are species-specific.

Due to these limitations, a number of diseases, including Stargardt disease and AMD, either do not manifest in animal models, or have a different manifestation: it has been difficult to develop safe and efficacious gene therapies targeting human retinal and other eye cell types.

A further limitation in translational ophthalmology is its current culture: there is a lack of daily communication and common planning between basic researchers, clinician scientists, and clinicians. This has two potential consequences. First, basic researchers sometimes study diseases and conditions for which there is no unmet medical need. Second, important insights, discoveries, and technologies are propagated slowly to clinician scientists and clinicians, meaning that relatively simple problems only slowly find solutions in clinical practice.

IOB aims to change the practice of translational ophthalmology by using the understanding of the structure, function, and molecular composition of the cell types of the human eye and its organoid models as a starting point for developing therapy. A key departure from previous approaches is that IOB focuses on a 'cell type' not a tissue and that it creates understanding and targeting of human cell types.

The reason for focusing on cell types is that in the last decade it has become increasingly clear that the functional units of the retina and other brain tissue are the genetically, functionally, and morphologically different cell types. Moreover, many if not all retinal diseases are narrowly or broadly cell-type-specific. More than 80 cell types have been described in the vertebrate retina alone. Additionally, IOB aims to create a unique environment in which daily interactions between clinicians, clinical researchers, and basic scientists is the norm, and in which project teams assemble dynamically and incorporate members from each faculty.

IOB's goal is to create a research environment where innovative thinking, quantitative argumentation, a trial-and-error approach, and bold ideas are rewarded. It aspires to achieve success by putting together problem solvers, innovators and those who have deep knowledge of, and daily exposure to, unmet medical need. In this research environment, there will be a constant definition of the unmet clinical need and proposed solutions, as well as exploration of the applicability of discoveries and technologies in basic science for current and future clinical care in ophthalmology.

The scientific plan of IOB can be broken down into:

- Projects that are performed as collaborations between IOB's Molecular Research Center and Clinical Research Center
- Projects that are more specific to the Molecular Research Center
- Projects that are more specific to the Clinical Research Center

The collaborative projects focus around three specific objectives

The first objective is to create tools and resources describing and controlling the different cell types of the human eye, with special emphasis on the retina. This also includes technologies for target-specific clinical testing in proof-of-concept and first-in-man clinical trials.

Second is to develop gene therapy for Stargardt disease and cell-type-targeted optogenetic therapy for complete blindness secondary to retinitis pigmentosa or Leber congenital amaurosis.

Third is to understand the pathomechanisms of glaucoma, myopia, retinitis pigmentosa and Leber congenital amaurosis as well as retinal diseases of motion detection, and use this understanding to define molecular and cellular targets for therapy. Every project is performed as a collaboration between clinicians, clinical researchers, and basic scientists.

Specific examples of transfer of materials and knowledge between the Molecular and Clinical Center are:

- Biobanking, where *ex vivo* material is transferred to the Molecular Research Center to both develop patient-derived retinal organoids for understanding the pathomechanism of genetic diseases and to understand the molecular, physiological and structural composition of donor retinae and eyes.
- Ophthalmic surgery, where surgical expertise is applied to animal experimentation.
- Gene replacement or gene editing therapy, where new methods for gene delivery and gene editing are developed at the Molecular Center and transferred to the Clinical Center as proof-of-concept studies.
- Optogenetic therapy, where new cell-type targeted optogenetic therapies, developed at the Molecular Center, are transferred to the Clinical Center.

Projects at the Molecular Research Center

The scientific goal of the Molecular Research Center is to combine different disciplines and technologies including genetics, virology, molecular biology, organoid technology, electrophysiology, two-photon imaging and computational tools to understand the structure and function of visual circuits at different stages of processing, to understand the mechanism of visual diseases, and to develop innovative therapies to slow the progression of vision loss or to restore vision when it is lost.

Our basic understanding of vision focuses on the retina, on one hand, and on higher visual centers on the other hand. We aim to describe the structure and function of the human retina using new methodologies that allow us to study function in post mortem retinas.

We also aim to understand how higher visual centers interpret signals that arrive from the retina. As far as disease mechanism, the central theme is to understand selective vulnerability of specific cell types in different diseases, such as the selective vulnerability of rods in Leber congenital amaurosis and retinitis pigmentosa, and the selective vulnerability of ganglion cells in glaucoma.

Further, we are interested in obtaining molecular insights into the pathomechanism of myopia and of retinal diseases of motion detection. Some of this understanding will come from personalized disease models in the form of human retinal organoids, grown *in vitro* from patient-derived cells.

- Our efforts in developing new therapies focus on cell type targeted optogenetics and on gene editing in hereditary blinding diseases.

Projects at the Clinical Research Center

Neurodegeneration of the retina such as in dry AMD, diabetic eye disease, retinal dystrophies and glaucoma remains untreatable. Lack of efficient outcome measures and endpoints for clinical trials and health outcomes showing the value for patients have limited the translation of basic science discoveries to human therapy and thus clinical development of new therapies.

The Clinical Research Center will address these shortcomings and focus on in-depth characterization of patient cohorts that will likely benefit from emerging therapies.

Improvements and new developments in high-resolution imaging of the retina and underlying tissues will be achieved by the Ophthalmic Imaging Research Group. Using *in vivo* high-resolution imaging, structure-function correlation will be studied and the functional consequences of morphological findings studied. Imaging the molecular signature of compounds will be achieved by building a new two-photon instrument with integrated, synchronized capabilities to measure visual sensitivity, scanning laser ophthalmoscopy and optical coherence tomography (OCT). Improved imaging of the retina, retinal pigment epithelium and choroidal layers will be achieved by new OCT technologies.

Visual function testing in the Visual Neurophysiology Research Group will allow visual performance to be tested at a microscopic level and to correlate the findings with retinal morphology. The latest technology of objective (such as electrophysiology) and subjective (such as microperimetry) vision testing will be established.

Genetic testing performed by the Ophthalmogenetics Research Group will allow the identification of underlying disease causes, risk for disease and probability to benefit from therapy and will allow the implementation of true personalized medicine.

Outcome measure research, such as currently being performed in the worldwide multi-center ProgStar Study, will allow the identification of new and more efficient endpoints for clinical trials, and research into patient-reported outcomes will help to evaluate the benefits of new therapies for the patients' daily activities and visual quality of life.

The Clinical Trial Center for Ophthalmology of IOB will cover the most important areas of therapy development in the field. Multi-center clinical (including phase 3 registration) trial coordination will be established and the chairmanship of the European Vision Institute Clinical Research Network (EVICR.net) taken over, the largest platform for clinical trial research in ophthalmology in Europe and a useful industry resource, in order to promote the development of new drugs and medical devices.

Letter from the Chairman of the Scientific Advisory Board

Dear Reader,

IOB convened a Scientific Advisory Board in September 2018 to review its scientific plans.

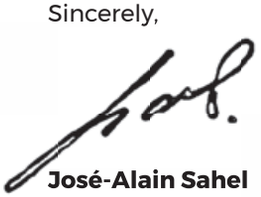
The SAB regards the plan as exemplary and in keeping with the reputation of Professors Scholl and Roska. It is highly encouraging for the future of this field that the IOB is being created to delve into disease studies with the intent of converting knowledge into therapy.

The unique, integrated approach of IOB is grounded in the highest quality of science, a focus on human disease benefiting from both excellent phenotyping capabilities, development of models derived from human tissues and organoids, optimized, cell-specific vectors and analyses, and innovative therapeutic strategies.

The SAB noted that the scientific plan is very ambitious, which is very appropriate at this stage of early development. The realities of clinical and basic laboratory observations will shape this research and direct it into successful avenues in due course. The SAB also noted that the intended joint new IOB building integrating the basic, translational and clinical science of IOB and patient care in ophthalmology of the Department of Ophthalmology, University of Basel, will be crucial to fulfill IOB's mission.

In summary, the SAB was much impressed by the research program presented at the meeting in Cambridge. It is innovative, highly ambitious and truly collaborative. Together with the unique expertise and personalities of the two directors and their unlimited dedication to research, it is bound to succeed and to provide breakthroughs in our understanding of the human retina and in therapies for retinal diseases.

Sincerely,



José-Alain Sahel
Chairman of the Scientific Advisory Board

Scientific Advisory Board

José-Alain Sahel, M.D.

Chairman of the Scientific Advisory Board

Dr. Sahel is the chair of the Department of Ophthalmology at the University of Pittsburgh School of Medicine, director of the UPMC Eye Center, and the Eye and Ear Foundation Chair of Ophthalmology. Dr. Sahel is also the founder and director of the Vision Institute in Paris and Professor of Ophthalmology at Sorbonne Université Faculty of Medicine. He was Professor of Biomedical Sciences at the Institute of Ophthalmology-University College London (2011-2017). He trained in Paris, Strasbourg and at Harvard University. Dr. Sahel is among the pioneers in development, advancement and clinical evaluation of emerging therapeutic strategies, such as neuroprotection of cone photoreceptors, visual prostheses and gene and cell therapies including optogenetics, for blinding eye diseases. He co-ordinates a large ERC-Synergy program on morpho-functional imaging of the visual system and is developing innovative technologies for assessing and fighting visual handicap. He is an elected member of the Académie des Sciences-Institut de France (2007) and of the German Academy of Sciences Leopoldina (2016).

Alexander Borst, Ph.D.

Dr. Borst is director at the Max Planck Institute of Neurobiology in Martinsried and head of the department “Circuits – Computation – Models”. Dr. Borst received his PhD in Biology at the University of Würzburg under the supervision of Martin Heisenberg, and completed a postdoctoral fellowship at the Max Planck Institute of Biological Cybernetics in Tübingen, where he remained until 1999 to lead a Junior Research Group at the Friedrich-Miescher-Laboratory of the Max Planck Society. He then became Professor at the University of California at Berkeley.
Dr. Borst is renowned for his work on visual motion processing in the fruit fly Drosophila, and in particular the discovery that motion direction is computed in parallel ON- and OFF-pathways where T4 and T5 cells represent the elementary motion-sensing neurons, respectively.

Constance Cepko, Ph.D.

Connie Cepko is the Bullard Professor of Genetics and Neuroscience in the Departments of Genetics and Ophthalmology at Harvard Medical School, and an Investigator of the Howard Hughes Medical Institute. She trained in virology with Phil Sharp at MIT for a PhD and later with Richard Mulligan at the MIT Whitehead Institute. She was an early developer of retroviral vectors for transduction into the nervous system for lineage analysis and for studies of gene function *in vivo*.
Her laboratory has focused on the topic of cell fate determination in the retina through the analysis of the behavior of progenitor and stem cells. More recently, they have been studying the mechanisms of photoreceptor death in diseases that cause blindness, such as retinitus pigmentosa and macular degeneration.

Cynthia Grosskreutz, M.D., Ph.D.

Dr. Grosskreutz is Vice President & Global Head of Ophthalmology at the Novartis Institutes for Biomedical Research (NIBR) and an Associate Professor of Ophthalmology at Harvard Medical School. She leads NIBR Ophthalmology Research whose goal is to discover new ophthalmic medicines for patients with blinding eye diseases. She practices ophthalmology and teaches at the Massachusetts Eye and Ear Infirmary, Harvard Medical School. Dr. Grosskreutz received her undergraduate degree in Physics from Washington University in St. Louis followed by an M.S. in Space Physics at the University of Iowa with James A. Van Allen. She received her M.D. and Ph.D. in Pharmacology from the University of Iowa and did her Ophthalmology residency and Glaucoma fellowship at the Massachusetts Eye and Ear Infirmary, Harvard Medical School.

Paul Sieving, M.D., Ph.D.

Dr. Sieving is director of the National Eye Institute, NIH, with responsibility for an $800M budget that supports basic and clinical vision research in the USA and internationally. Under Dr. Sieving, the NEI developed the Audacious Goals Initiative (AGI) in Regenerative Medicine, a 10-15 year strategic research program to restore neural function in the retina and visual system and thereby reverse vision loss in age-related macular degeneration and glaucoma. Dr. Sieving is known for his own studies of human inherited retinal and macular neurodegenerative diseases. He trained in medicine and bioengineering, and obtained MD and PhD degrees from the University of Illinois. After ophthalmology residency, he studied retinal physiology with Roy Steinberg at the University of California, San Francisco and trained in genetic retinal degenerations with Eliot Berson at Harvard Medical School. He holds elected membership in the US National Academy of Medicine (2006) and the German National Academy of Sciences, Leopoldina (2014).

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

Dr. Zrenner is Senior Professor of Ophthalmology at the Institute for Ophthalmic Research of the University of Tübingen. His research interests span neuro-ophthalmology and retinal electrophysiology, to ophthalmogenetics and gene therapy. He coordinates EU projects, serves as Principal Investigator on clinical trials, and has 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. He worked at the Max-Planck-Society for 16 years, and received a Fogarty fellowship (1977/78) at the National Eye Institute (NIH). After his PhD, Dr. Zrenner received an associated professorship at the University Eye Hospital in Munich. He became full professor and chairman at University Eye Hospital in Tübingen in 1989, now Center for Ophthalmology. There he served as founding Director at the Institute for Ophthalmic Research and runs a special clinic for hereditary retinal degenerations.

GOVERNANCE

Governance report

Dear Reader,

2018 was the inaugural year for IOB and for the Board of Trustees, and therefore of particular importance.

IOB has been established as a foundation (Stiftung) under Swiss law, meaning that the assets granted to IOB by its founders can only be used for the foundation's purpose, and are granted irrevocably. IOB has been recognized by the Basel Stadt foundation authority (BVG- und Stiftungsaufsicht beider Basel) as charitable, and therefore tax exempt.

The Board of Trustees for IOB is responsible for the overall direction and supervision of management, and holds the ultimate decision-making authority for IOB, within the purpose of the foundation. The Board has delegated operational responsibilities to the Directors of IOB, and the Scientific Advisory Board of IOB supports the Board of Trustees on scientific questions, both as defined by the Regulations of the IOB and the Management Authorization Levels approved by the Board of Trustees.

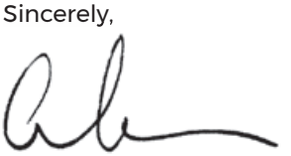
The Board of Trustees for IOB meets the legal requirements for a Swiss foundation: it has three members, all of whom are representatives of the three founders of IOB (Novartis AG, Universitätspital Basel, and Universität Basel); two of the three are resident in Switzerland, and all three have Swiss or EU passports. The Board of Trustees has the strength, diversity and independence to effectively govern the activities of IOB. The Board of Trustees meets four times each year, which has proven sufficient to govern the activities of IOB in its start-up period. Decisions are reached by consensus; in case of tie, the Chairman has the casting vote. Board members received no compensation in 2018.

The Founders of IOB remain strongly committed to IOB's success. In addition to the Founders' participation in the Board, strong links between IOB and its Founders are in place, and are expected to continue. Part of the Molecular Center is based at the Friedrich Miescher Institute, a research foundation partially funded by Novartis; the University of Basel is engaged in the recruitment of senior IOB faculty, and has extended its accreditation to IOB as a teaching and research entity; the Clinical Center is based at the Eye Hospital of the University Hospital Basel, which is also providing important operational support to IOB as it is established.

The executive leadership of IOB is made up of three individuals, Norbert Spirig, the Director of Operations; Hendrik Scholl, Director of the Clinical Center; and Botond Roska, Director of the Molecular Center.
The executive leadership is responsible for recruiting and appointing staff, in collaboration with the University of Basel for tenure track faculty; for ensuring the efficient operation of IOB; for setting policies and scientific plan for Board approval and implementing those approved; and submitting important investments, contracts, or other matters of fundamental significance to the Board for approval; and dealing with any other matters delegated by the Board.

The Board has appointed PricewaterhouseCoopers AG, Basel as the auditor for 2018.

Sincerely,



Charles Gubser
Secretary of the Board of Trustees

The Board of Trustees

Jörg Reinhardt, Ph.D.

Chairman of the Board of Trustees • **Nationality:** German • **Year of Birth:** 1956

Jörg Reinhardt Ph.D. has been Chairman of the Board of Trustees for IOB since its inception in January 2018. He has been Chairman of the Board of Novartis AG since 2013. From 2010 to mid-2013, he was chairman of the board of management and the executive committee of Bayer HealthCare, Germany. Prior to that, he was with Novartis and its predecessor company Sandoz since 1982. He graduated with a doctorate in pharmaceutical sciences from Saarland University in Germany.

Werner Kübler, M.D., MBA

Member of the Board of Directors • **Nationality:** Swiss • **Year of Birth:** 1962

Werner Kübler has been a member of the Board of Trustees of IOB since its inception in January 2018. Since 2008 he has been the Director of the University Hospital Basel, Chairman of the hospital management board and responsible for the operational management of the University Hospital Basel. Werner Kübler is also Vice-chairman of H+ Die Spitäler der Schweiz; board member and Vice-chairman of SwissDRG AG and board member of the Association of Northwestern Swiss Hospitals VNS. Werner Kübler studied Human Medicine at the University of Zurich and obtained his doctoral thesis in Experimental Immunology in 1989. He also completed an MBA at the University of Rochester.

Professor **Andrea Schenker-Wicki,** Ph.D.

Member of the Board of Directors • **Nationality:** Swiss • **Year of Birth:** 1959

Andrea Schenker-Wicki has been a member of the Board of Trustees of IOB since its inception in January 2018. She has been President of the University of Basel since 2015. She was Vice Rector for Law and Economics at the University of Zurich from 2012 to 2014, and a Full Professor of Business Administration at the University of Zurich from 2001-2015. She holds a Ph.D. in Operations Research and Computer science from the University of Fribourg (Switzerland), and an honorary doctorate from the University of Natural Resources and Life Sciences in Vienna.

The Directors of IOB

Professor **Botond Roska,** M.D., Ph.D.

Co-director of the IOB • **Nationality:** Hungarian • **Year of Birth:** 1969

Prof. Botond Roska is one of the two founding directors of the IOB, the Institute of Molecular and Clinical Ophthalmology Basel. Prof. Roska received his M.D. degree at the Semmelweis Medical School in Budapest, Hungary. He completed his Ph.D. studies in neurobiology at the University of California, Berkeley, USA, before becoming a Harvard Society Fellow in genetics at Harvard University and Harvard Medical School, USA. In 2005, he joined the renowned Friedrich Miescher Institute in Basel, Switzerland, where he leads an interdisciplinary group of scientists working in the area of neuroscience, genetics and physiology with a focus on vision.

Professor **Hendrik Scholl,** M.D., Ph.D.

Co-director of the IOB • **Nationality:** German • **Year of Birth:** 1969

Hendrik Scholl is one of the two founding directors of the IOB. He is also Professor and Chairman of the Department of Ophthalmology, University of Basel, and Adjunct Professor of Ophthalmology at the Wilmer Eye Institute, Johns Hopkins University. Prof. Scholl is a graduate of the Medical Faculty of the University of Tübingen, Germany and holds a Master of Arts from Tübingen's Faculty of Philosophy. He completed a residency at Tübingen's University Eye Hospital, and a fellowship at Moorfields Eye Hospital & Institute of Ophthalmology in London. After having held several academic positions at the Medical Faculty of the University of Bonn, Germany from 2004, he was appointed Professor of Ophthalmology in 2010 and Endowed Chair in 2011 at the Wilmer Eye Institute of John Hopkins University Medical School in Baltimore, USA.

Norbert Spirig, Ph.D.

Director of Operations of the IOB • **Nationality:** Swiss • **Year of Birth:** 1959

Norbert Spirig has been director of operations for the IOB since its founding. He studied Chemistry at the ETH in Zürich and received his PhD in the field of intramolecular dynamics at the Institute of Physical Chemistry of ETH Zürich. He held positions in different industrial companies including a leading producer of high level instruments in chemical spectroscopy. For the last decade he was Head of the department Specialty Clinics at the University Hospital Basel and member of the management board.

FINANCIAL STATEMENT FOR 2018

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 to hereby 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 receives no payment for its work.

Supervisory Authority

BVG- und 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 the Swiss accounting legislation of the Swiss Code of Obligation (SCO).

Currency

IOB presentation currency is CHF (Swiss francs).

Foreign currency positions

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

31.12.2018	*Foreign currency*	*Balance*
	EUR	1.1092

Trade account receivables

Trade account receivables and other short-term receivables are initially recognized at their invoiced amounts including any related VAT. Provision for doubtful trade receivables are established once there is an indication that a loss will be incurred. The remaining amount is adjusted by a general allowance of 5%.

Non-current assets and leasing

Property, plant and equipment are carried at cost less accumulated depreciation. Assets financed by long-term leasing contracts are not recognized in the balance sheet.

The following useful life spans and depreciation methods are used to calculate the depreciation amounts:

Non-current assets	*Durability*	*Method*
Research equipment	8 years	25% degressively

Notes to the financial statements

1 Accounts receivable and accounts payable

CHF 4,684,950 of the accounts receivable from affiliated parties correspond to the contributions of Novartis for the year 2018 (including 7.7% VAT). Most of the IOB research activities took place in facilities of FMI including seconded research personnel. All FMI expenses were charged through Novartis. Therefore, the in-kind contributions of CHF 5,404,419 exceeded the agreed financial contribution. It was agreed that the accounts would be balanced in 2019.

2 Unrestricted funds

The unrestricted funds contain available funds that have not yet been directly allocated to any project. In 2018, the income from fund raising amounted in total CHF 442,954.36, whereof CHF 117,210.74 were allocated to projects. As a result the total net amount of unrestricted funds is CHF 325,743.62.

31.12.2018	*Net amount of funds received from*	*CHF*
	Private entity	244,454
	Legal entities (Novartis AG, Universität Basel, USB)*	81,289

** The "Legal entities" is a pool fund of various legal entities.*

3 Difference between gross and net amount

The net column shows the amounts that are directly financed by IOB funds. The delta (Δ) are the expenses financed by income from third parties that has not yet been released from FMI.

4 Income from contributions

31.12.2018	*Income from contributions*	*CHF*
	Novartis AG	4,350,000
	Canton of Basel-Stadt	2,177,500
	USB	1,306,500
	University of Basel	771,000
	Total income from contributions	**8,605,000**

5 Research expenses

31.12.2018	*Research expenses*	*CHF*
	Consumables	889,344
	Non-capital equipment	1,560,370
	External services*	1,153,845
	Total research expenses	**3,603,559**

** The position "External services" includes a usage-fee of CHF 1,070,436 for the research facilities of FMI.*

6 Administrative expenses

31.12.2018	*Administrative expenses*	*CHF*
	Planning expenses for modular building IOB	484,434
	Legal and consulting expenses*	743,686
	Transport and travel expenses	79,042
	IT expenses	43,024
	Other expenses	99,715
	Total administrative expenses	**1,449,901**

** The position "Legal and consulting expenses" includes an overhead charge of CHF 410,634 for the usage of the facilities of FMI.*

Balance sheet

31.12.2018	*Assets*	*Notes*	*CHF*
	Cash and cash equivalents		1,925,336
	Accounts receivable	1	4,760,348
	from third parties		*3,770*
	from affiliated parties		*4,756,578*
	Other short-term receivables		500,174
	from third parties		*500,174*
	Prepaid expenses		123,276
	Current assets		**7,309,134**
	Property, plant and equipment		567,331
	Non-current assets		**567,331**
	Total assets		**7,876,465**

31.12.2018	*Liabilities and equity*	*Notes*	*CHF*
	Accounts payables	1	6,130,818
	from third parties		*662,080*
	from affiliated parties		*5,468,738*
	Accrued expense and deferred income		64,958
	Short-term liabilities		**6,195,777**
	Total liabilities		**6,195,777**
	Foundation capital		500,000
	Unrestricted funds	2	325,744
	Net result of the year		854,945
	Total equity		**1,680,688**
	Total liabilities and equity		**7,876,465**

Income statement

Accounting period 13.12.2017–31.12.2018

	Notes 3	net CHF	Δ CHF	gross CHF
Income from contributions	4	-8,605,000	0	-8,605,000
Income from third parties		-442,954	-1,685,780	-2,128,735
Other income		-31,054	0	-31,054
Total operating income		**-9,079,008**	**-1,685,780**	**-10,764,789**
Personnel expenses		2,279,566	957,960	3,237,526
Research expenses	5	3,155,334	448,225	3,603,559
Rent and utility expenses		891,016	0	891,016
Administrative expenses	6	1,444,333	5,568	1,449,901
Other expenses		93,380	15,203	108,583
Depreciation on non-current assets		35,936	258,824	294,759
Total operating expenses		**7,899,565**	**1,685,780**	**9,585,345**
Operating result		**-1,179,443**	**0**	**-1,179,443**
Financial income		-8,071		-8,071
Financial expenses		6,826		6,826
Financial result		**-1,245**		**-1,245**
Net result for the period		**-1,180,688**		**-1,180,688**
Net allocation to unrestricted funds	2	325,744		325,744
Net result for the period after net allocation to unrestricted funds		**-854,945**		**-854,945**

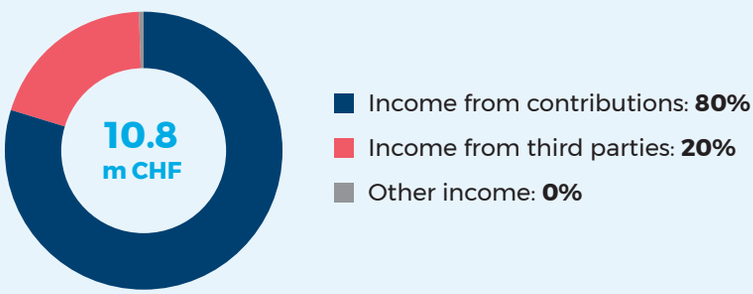
Cash flow statement

Accounting period 13.12.2017–31.12.2018

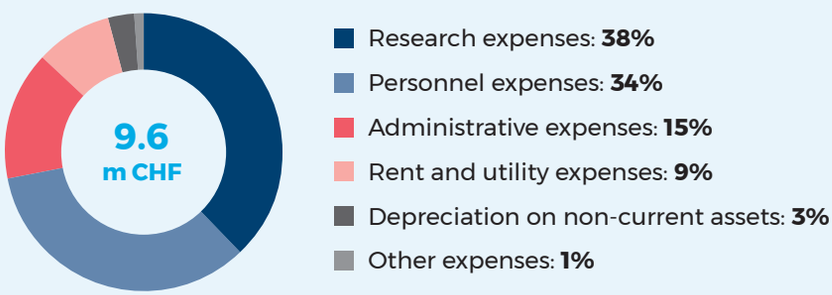
	CHF
Net result for the period before allocation to unrestricted funds	1,180,688
Depreciation on non-current assets	35,936
Changes in accounts receivable and other short-term receivables	-5,260,522
Changes in prepaid expenses	-123,276
Changes in short-term liabilities	6,130,818
Changes in accrued expenses and deferred income	-260,785
Cash flow from operating activities	**1,702,859**
Capital expenditure on property, plant and equipment	-603,267
Cash flow from investing activities	**-603,267**
Increase in foundation capital	500,000
Increase in unrestricted funds	325,744
Cash flow from financing activities	**825,744**
Changes in cash and cash equivalents	**1,925,336**

Verification of changes in cash and cash equivalents	
As of 13.12.2017	0
As of 31.12.2018	1,925,336
Changes in cash and cash equivalents	**1,925,336**

Funding 2018



Expenses 2018



Report of the statutory auditors

on the limited statutory examination to the Board of Institute of Molecular and Clinical Ophthalmology Basel

As statutory auditors, we have examined the financial statements of Institute of Molecular and Clinical Ophthalmology Basel, which comprise the balance sheet, income statement, cash flow statement and notes, for the period 13 December 2017 to 31 December 2018.

These financial statements are the responsibility of the Board. Our responsibility is to perform a limited statutory examination on these financial statements. We confirm that we meet the licensing and independence requirements as stipulated by Swiss law.

We conducted our examination in accordance with the Swiss Standard on Limited Statutory Examination. This standard requires that we plan and perform a limited statutory examination to identify material misstatements in the financial statements. A limited statutory examination consists primarily of inquiries of foundation personnel and analytical procedures as well as detailed tests of foundation documents as considered appropriate in the circumstances. However, the testing of the operational processes and the internal control system, as well as inquiries and further testing procedures to detect fraud or other legal violations, are not within the scope of this examination.

Based on our limited statutory examination, nothing has come to our attention that causes us to believe that the financial statements do not comply with Swiss law and the foundation's deed.

PricewaterhouseCoopers AG

Roy Bächinger
Audit expert
Auditor in charge

Petar Lesic
Audit expert

Founders, partners and affiliations

Founders

Novartis AG

University Hospital Basel

University of Basel

Partner institutions

Canton of Basel Stadt

University Hospital Basel

University of Basel

Novartis Institutes for Biomedical Research (NIBR)

Friedrich Miescher Institute for Biomedical Research, Basel

Department of Biomedicine, University of Basel (DBM)

OCT research group for OCT technology, Virtual Ophthalmology, Artificial Intelligence (AI) and Robotics of the Department of Ophthalmology at the University of Basel

Department of Biomedical Engineering, University of Basel (DBE)

Department of Clinical Research, University of Basel (DKF)

European Network of Clinical Research in Ophthalmology (EVICR.net)

Retina International

Retina Suisse

PRO RETINA Deutschland e. V.

Foundation Fighting Blindness

European Vision Institute EEIG

ProgStar study group

Wellcome Trust

Bertarelli Foundation

Spectrum Foundation

Affiliations

IOB is proud to be affiliated with the University of Basel.

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Researchers and Clinicians united to restore vision.

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