The resulting clinical interventions then are expected to significantly improve eye care and decrease the social and economic burden of ocular conditions. We would like to discover new pharmacological interventions to elucidate the contribution of specific molecules to retinal degenerative diseases.

To test new findings and monitor results of novel treatments either on animal models or humans we need to develop new functional methods of in vivo retinal imaging to track changes in retinal function over time, for individual subjects with well-defined health conditions.

Another challenge for this ambitious project is to deliver new compounds to the retina in an effective and controlled way. These challenges can be solved twofold: either by smart and targeted designing of chemical drug delivery systems or by development of new automated robotic instrumentation that will enable the delivery of drugs to locations of focal retinal changes.

To complete the picture, it is also necessary to monitor the plasticity of retinal tissue especially in the context of immune system reactions – required for characterizing the pharmacodynamics of new therapies and their potential side effects.
The last decade has seen an impressive expansion of our knowledge regarding the morphology and function of both the posterior (retina and choroid) and anterior (cornea, lens, and sclera) segments of the eye. One area of advancement pertains to retinal photoreceptor signal transduction and the regulation of the visual cycle required for normal eyesight. Substantial progress in human genetics now allows the identification of candidate genes and more complex genomic loci responsible for a variety of common retinal diseases. Technical innovations and improved methodologies in proteomics, macromolecular crystallization, and micro-imaging create the conditions for making even greater advances.

Pharmacology, combined with structural biology, holds the key for developing innovative and accessible therapies for millions of people robbed of their sight or those progressing toward blindness.

Diagnostic tools such as Scanning Laser Ophthalmoscopy (SLO), fluorescein and indocyanine green angiography, microperimetry, multifocal electroretinography, adaptive optics imaging and Optical Coherence Tomography (OCT) have advanced rapidly over the last two decades and improved our understanding of retinal diseases and their treatments. Improved monitoring of medical treatments enabled the introduction of new ophthalmic therapies including laser photocoagulation and anti-VEGF therapy helping to stop progressing visual impairments in millions of people. Also, new therapies for refractive errors using laser corneal surgeries have improved the quality of life for millions of people sometimes helping to correct complex corneal aberrations that prevented people from their full professional and personal activities.

The global impact of blindness and visual impairment is enormous, especially in the aging population. The major causes of visual impairment and blindness in addition to cataract and refractive defects are more severe and usually irreversible eye diseases including age-related macular degeneration (AMD), glaucoma and other retinal disorders. Further, the increased incidence of Type II diabetes is leading to an escalation in blindness due to retinopathy.

As the human life-span increases in developed countries by a year every decade, the already substantial burden of vision loss will continue to escalate, a concern which is acknowledged on a global scale by healthcare partnerships such as the World Health Organisation (WHO) and the International Agency for the Prevention of Blindness (IAPB). Their findings are incorporated into the Vision 2020 global initiative (http://www.iapb.org/vision-2020).

Main Causes of Visual Impairment in Global vs. Developed Countries.

Rationale

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The broad scope of activities can be covered by one or a few interdisciplinary groups composed of experts in medical biology, physical chemistry, organic chemistry, biotechnology or biophysics.

GROUP 1
SYSTEMS PHARMACOLOGY
OF VISION

Professor Krzysztof Palczewski and his team of collaborators have been studying the pharmacology of vision for over 30 years, and by targeting specific stages of the visual cycle they have been able to restore vision to animals which have the same mutations as patients with retinitis pigmentosa and other congenital mutations that result in early stage blindness.

Applying a new approach referred to as Systems Pharmacology, Prof. Palczewski’s research has identified new and powerful mechanisms to treat complex diseases. Systems Pharmacology identifies and connects different biochemical signal transduction pathways that culminate in a common effector molecule/second messenger that can be manipulated through GPCRs. GPCRs such as the adrenergic, adenosine, and muscarinic receptors and 600 others in the human genome, play essential roles in fundamental cellular processes and are the most common types of receptors targeted by medications for disease treatment. An approach involving expression profiling on a genomic scale was used to guide rational targeting of specific pathways by novel therapeutics, and to bring repurposed drugs to the forefront in combating complex. This novel approach is also of interest to those pursuing mechanism-based pharmacological development and how more comprehensive systems approaches can enhance rational therapeutic strategies for treating disorders of complex etiologies.

The approach can be applied to key eye diseases and other biological systems. Physiological phenotypes are defined by a tightly regulated flow of events evolving from genetics, RNA transcripts and regulatory RNAs, proteins, and metabolites to interacting networks that contribute to the complexity of biological information. This information provides a rationale for selecting pharmacological interventions to elucidate the contribution of these molecules to retinal degeneration, which in turn is tested in mouse models of retinal degeneration (Chen et al. JCI, 2013).
To follow the progression and treatment of degenerative diseases, new in vivo imaging modalities are required. Building on state-of-the-art technology and recent advances in biochemical/functional aspects of vision, the group led by prof. Maciej Wojtkowski develops new methods for repeated, safe, retinal imaging to assess morphological and functional aspects of individual cells of the retina and retinal pigment epithelium (RPE).

Optical coherence imaging techniques like OCT, SLO, AO-SLO can provide phase and amplitude sensitive information about the morphology and function of the human eye offering higher speed and sensitivity than any other methods. However, limitations include the deterioration of spatial resolution due to the presence of speckle noise. Therefore, existing techniques are unable to provide high quality reconstructions of important types of cells in vivo. In this project we propose developing a speckle-less OCT technique that will enable us to visualize retinal microstructure at the cellular level.

Retinyl condensation products have been identified as native fluorophores in the human retina and the source of a strong two-photon excited fluorescence (TPEF) signal. These fluorophores undergo chemical changes during the visual cycle. Monitoring their concentration in retinal layers will provide unprecedented and unique opportunities in ophthalmology by providing information about functional changes in response to age and pharmacological treatments. Currently such techniques can be applied only to animal models due to limited sensitivity of detection.

Along with novel measurements of retinal function, these unique diagnostic tools will offer major advantages for the early detection and monitoring of treatments for human blinding retinal diseases. Thus, these novel instruments will allow early detection of age- and disease-related changes in the retina long before they become discernible by existing methods. Such real-time retinal imaging will also be critical for evaluating various drug candidates for the treatment of retinal degeneration and other retinal pathologies. Finally, these instruments will shorten the time of clinical trials, and in turn the cost for evaluating innovative therapies to halt the progression of blinding diseases.

SPECKLE PATTERNS PREVENT RESOLVING RETINAL CELLS

A. Scheme showing the formation of the speckle pattern: back-scattered light waves reflected from a rough surface have random phases causing the intensity distribution in the imaging plane to vary randomly.  
B. Exemplary OCT cross-sectional retinal image.  
C. Zoomed details of panel B compared to in-scale light micrographs. Due to the presence of speckles the corresponding regions look different in OCT and light micrograph images even if the nominal resolutions of both techniques are comparable.
GROUP 3
TARGETED DRUG DELIVERY

Critical area determining the treatment specificity, safety and efficacy is related to targeted drug delivery.

Depending on the physical-chemical properties of new drugs it is necessary to engineer correctly the properties of the administration route of a drug and its delivery system. Pharmacokinetic and pharmacodynamic factors determine the required dosing rates and doses that are needed for drug action. Currently, intravitreal injections are the method of choice to administer drugs to the retina, but this approach is applicable only in selected cases like for example anti-VEGF antibodies and soluble receptors. Alternatively, there are other routes of drug administration, such as pericocular, suprachoroidal, sub-retinal, systemic, or topical. There is still open space for development of retina targeted delivery of intravitreal drugs. Unfortunately, tolerability factors limit the use of many materials that can be adopted to improve retinal drug delivery making this task even more challenging. That is why unorthodox approaches are desirable for this project.

GROUP 4
ROBOTIC MEDICINE

There is now a worldwide movement toward evaluating robotic systems in an expanding number of clinical applications. Coincident with this expanding application is growth in the number of laboratories committed to "robotic medicine". Recent technological advances in conventional retina treatments have led to tremendous progress in the surgeon’s capabilities, enhanced outcomes, a reduction of patient discomfort, limited hospitalization and improved safety. The emergence of robotic technology into this rapidly advancing domain is expected to further enhance the patient’s comfort and improve the efficacy of therapies. For example, robotic retinal surgery is a rapidly emerging technology that has witnessed an exponential growth in capabilities and applications over the last decade. Toward this challenge we would like to expand the idea of robotic surgery to robotic and fully automated intravitreal injections to limit the administration of drugs to focal retinal locations and monitor the therapy with better accuracy. Exceptional precision is required to operate on retinal targets on a micron scale while also maneuvering in a tightly constrained and fragile workspace. These challenges are compounded by inherent limitations of the unassisted human hand with regard to dexterity, tremor and precision in positioning instruments. The human ability to visually resolve targets on the single-digit micron scale is a further limitation. The inherent attributes of robotic approaches therefore provide logical, strategic and promising solutions to the numerous challenges associated with retinal microsurgery and drug delivery.

GROUP 5
EXPERIMENTAL BIOLOGY OF RETINAL DEGENERATION

Over the last decade, several therapeutic strategies involving neuroprotective agents, corrective gene therapy, and immunotherapy have been developed with the goal of preventing photoreceptor degeneration. Retinal degeneration is evidenced by the progressive death of photoreceptor cells in the retina. Importantly, the decline of rod cells is greater than that of cone cells, primarily in the area surrounding the fovea. If the decline is slow, this can be the result of a natural aging process. Normally, the annual loss of photoreceptor, RPE and ganglion cells is about 0.2 to 0.4%. If the loss of photoreceptor cells is greater, a pathological process is likely responsible. A comprehensive understanding of all biological processes responsible for the loss of photoreceptors is critical for implementation of new therapies.
The proposed research program represents a multidisciplinary effort, which enables vertical integration of fundamental scientific studies, applied optics, new technology, engineering, biology, and medicine, to improve medical diagnostics and develop novel and innovative treatments for eye diseases.

ICTER provides a multidisciplinary research plan, supported by extensive preliminary data, to develop novel therapies and diagnostic tools for retinal degeneration based on the concept of Systems Pharmacology developed in prof Palczewski’s laboratory over the past 5 years. We now need to further validate and advance this concept by testing specific combinations of drugs, introducing more reliable and specific imaging tools and developing therapeutic procedures that could provide a durable alternative to small molecules in treating retinal disorders. The first general outcome of the proposed research will be a new and comprehensive protocol for clinical trials of therapeutic agents targeting GPCRs.

ICTER will recruit a collaborative team of scientists, engineers, chemists and medical biologists with expertise in multiple disciplines related to retinal disorders to conduct this fundamental research and accelerate its translation into clinical applications.

Newly recruited PIs will creatively contribute to the project – therefore we prefer not to specify a detailed workplan for new groups but rather set the goals that should be achieved by the collaborative effort based on very specific scientific aims.
The International Centre for Translational Eye Research project is carried out within the International Research Agendas programme of the Foundation for Polish Science co-financed by the European Union under the European Regional Development Fund.