Centre for Ophthalmology

Eberhard-Karls-Universität
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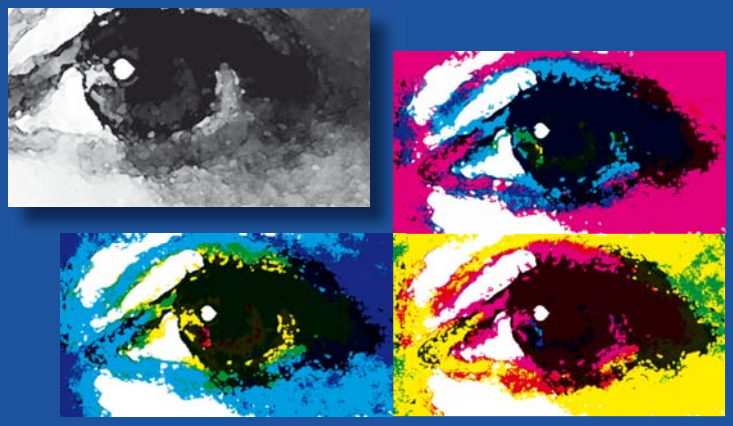
Universitätsklinikum Tübingen

Institute for Ophthalmic Research



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Editor: A. Werner
Cover: A. Werner
Layout: A. Werner & R. Hofer
Printed by Maier Press, Rottenburg

Centre for Ophthalmology

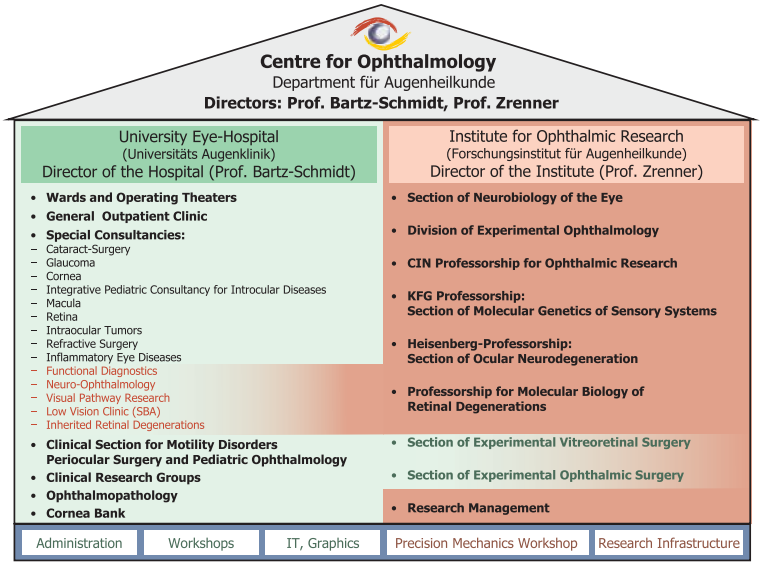
Institute for Ophthalmic Research

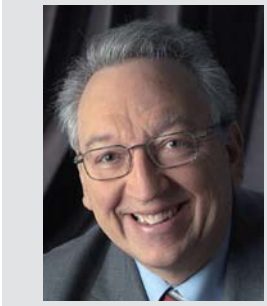
Content

Overview

Prof. Dr. med.
Karl Ulrich Bartz-Schmidt,
Director of the Eye Hospital

The Institute for Ophthalmic Research is headed by Prof. Dr. med. Eberhart Zrenner and cooperates closely with the University Eye Hospital (head: Prof. Dr. med. Karl Ulrich Bartz-Schmidt) under the common roof of the Centre for Ophthalmology. The Institute, founded in 2007, aims at uncovering the causes for degenerative, inflammatory, neoplastic, and vascular diseases of the eye and the visual pathways at molecular, cellular and systemic level.





Prof. Dr. med.
Eberhart Zrenner,
Director of the Institute
for Ophthalmic Research

The University Eye Hospital provides health care in all areas of ophthalmology at highest quality level with more than 60.000 consultations of patients and more than 13.000 surgeries annually. In close cooperation with the Institute, it develops novel therapeutic approaches for diseases of the eye.

The Institute houses several teams of scientists who work together to develop and evaluate concepts for therapy and treatment and optimise clinical and research diagnostics. Thus, the Institute provides an efficient infrastructure which supports research and education and mediates contacts to other research institutions and to industry.

Neurobiology of the Eye

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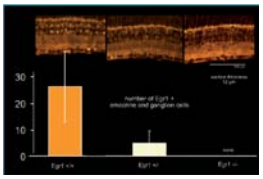
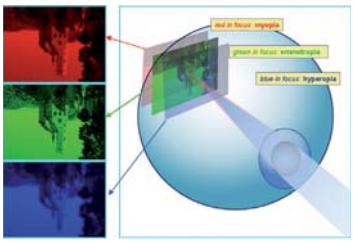
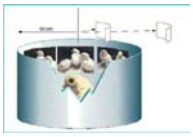
Our goal is to uncover the biological mechanisms of myopia development and to develop strategies to inhibit its progression. Development of new optical techniques to measure eye growth and optical properties of eyes in animal models for myopia and in humans.

Methods: Measurement of refractive state and accommodation with high temporal resolution, binocularly and including pupillography and gaze tracking: infrared photoretinoscopy; optical measurements in eyes: new phacometry and fast automated peripheral photorefraction; measurement of ocular dimensions: low coherence interferometry and A-scan ultrasonography; measurement of gene expression in different fundal layers: realtime RT-PCR; screening for candidate genes for myopia with mouse and chicken microarrays; description of activity and gene expression in individual cells: quantitative immunohistochemistry and laser microdissection with RT PCR; testing of visual function in transgenic and wildtype mice: automated optomotor experiments and pupillography; recording from retinal ganglion cells in vitro: MEA; measurements of contrast adaptation due to defocus: psychophysical measurement of supra-threshold contrast sensitivity.

Recent major results of our research: Demonstration that the retina can detect amount and sign of defocus and use this information to control the axial growth rate of the eye. Identification of the glucagon amacrine cells as a major carrier of this information and demonstration that glucagon can act as an axial eye growth inhibitor in the chicken. Analysis of the central role of the transcription factor Egr1 as an initial trigger in the signalling cascade for visual eye growth control in chickens and mice. Description of mechanisms of atropine and other muscarinic antagonists during the inhibition of myopia in animal models. Role of insulin during myopia development. Demonstration of the importance of peripheral refractive errors for the development of myopia in the central visual field in humans and chickens.







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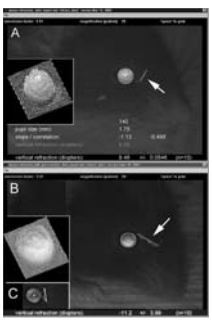

Experimental Ophthalmology

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Inherited retinal degenerations such as Retinitis Pigmentosa (RP) are a major cause of blindness in industrialized countries. In the Division of Experimental Ophthalmology we are seeking to develop treatments for RP and related diseases that affect photoreceptors. We argue that neuroprotection or cell replacement as a survival- and function-upholding regime is a feasible approach to preserve functional vision in patients affected by inherited retinal degenerations. Based on our findings on cell death mechanisms, we believe that neuroprotective treatments combined with a replacement of diseased cells constituts the most promising approach to preserve and restore functional vision.

We use different animal models for RP as well as retinal explant cultures to study signalling pathways that are involved in photoreceptor cell death or survival. Insights into these mechanisms are crucial for the successful development of potential therapies. Based on these, different neuroprotective strategies are evaluated for their capacity to prevent or delay photoreceptor cell death. Another approach to preserve vision is the replacement of diseased cells by transplantation of retinal progenitors that are induced to differentiate into functional photoreceptors and integrate into the pre-existing retinal networks.

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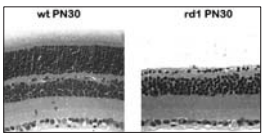

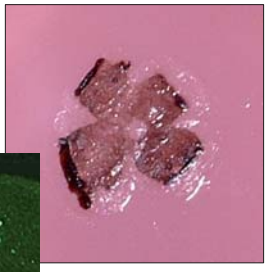

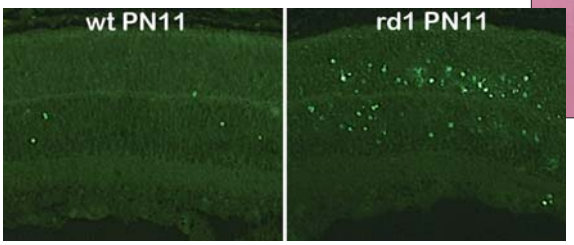

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Research Groups associated to Experimental Ophthalmology

Colour and Visual Psychophysics Group

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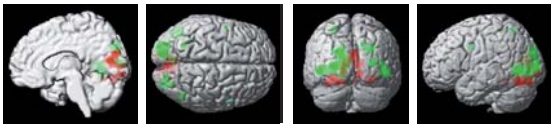
Colour is a particularly sensitive indicator for visual dysfunctions. By developing sophisticated psychophysical methods and combining them with fMRI, we investigate visual performances and pathways in normal and dysfunctional vision. Current topics include the testing of visual functions in congenital stationary night blindness, visual deficiencies associated with dyslexia, the effects of ageing and colour vision at high altitudes. We also offer procedures for use in clinical and research testing. Furthermore, we investigate the functional organization of cortical colour processes, adaptive mechanisms (colour constancy), and visuo-motor integration.



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Biomedical Engineering Laboratory

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The biomedical engineering lab has three main areas of focus, clinical trials software development, biosignal analysis in ophthalmology, and developing retinal prostheses by answering basic scientific and clinical questions. The group contributes to design and conduct experiments aimed at testing the safety and efficacy of Subretinal Active Microphotodiode Arrays (MPDAs) to replace degenerated photoreceptors in blind human patients. Basic research in this field is focused on the understanding of electrodynamic- and biological effects that occur during electrostimulation of the retina.

Research Groups associated to Experimental Ophthalmology

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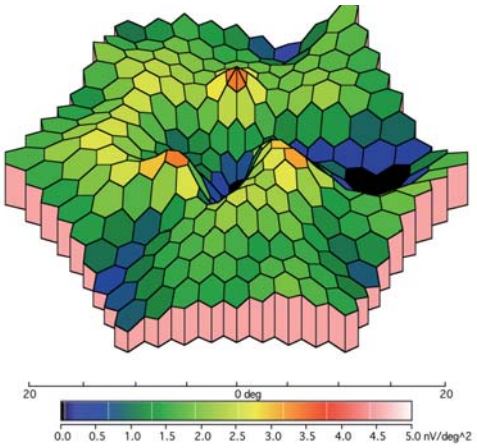
Retinal Function Research Group

The research of this group deals with the function of the normal retina and the pathological alterations associated with inherited and acquired retinal disease. The focus is on the detection of early functional alterations using psychophysical and electrophysiological methods.

The illustration shows a representation of the topography of the first order kernel(left) and second order, first slice, kernel (right) response amplitudes of multifocal oscillatory potentials over the central 50 degrees of the visual field. The responses are thought to be generated at the amacrine-bipolar synapses of the inner retina.



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Research Groups associated to Experimental Ophthalmology

Laboratory for Cellular Electrophysiology and Imaging Techniques

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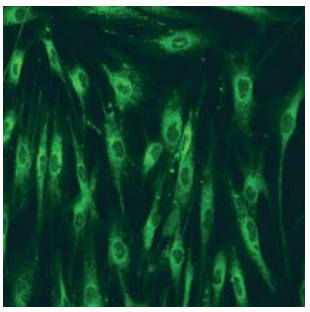
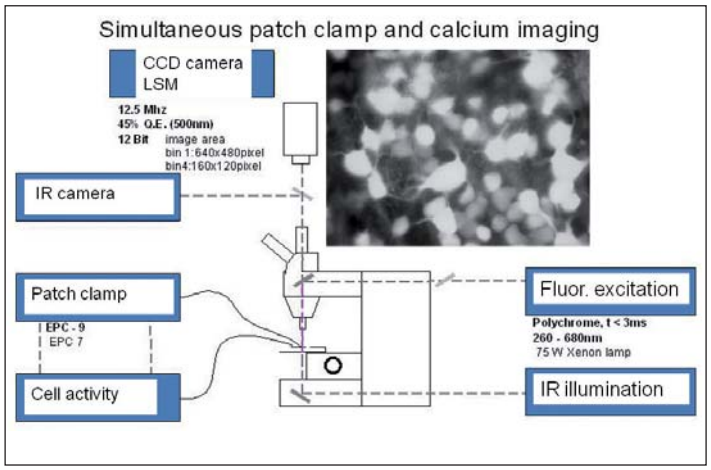
Our lab combines imaging (Calcium Imaging, Laser Scanning Microscopy, FRET) and electrophysiological techniques (Patch Clamp) to study cellular questions related to retinal sensory processing and mechanisms leading to cell degeneration in retinal diseases. Our specific fields of interest are the calcium homeostasis in retinal ganglion cells and photoreceptors investigated under physiological and pathophysiological conditions.

Finally, we want to give new insights into the cellular mechanisms underlying diseases like the autosomal-dominant optic nerve atrophy or achromatopsia and retinitis pigmentosa.





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Molecular Genetics of Sensory Systems

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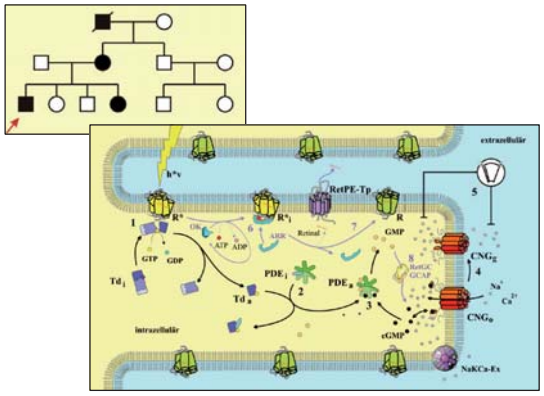
The Molecular Genetics Laboratory has a well documented research record in the field of hereditary retinal disorders (HRD). Beginning in the early 1990s we have established a large biobank of DNA and RNA samples from patients and families suffering from HRD. This biobank currently comprises ~4000 DNA samples of affected patients and thus represents the largest sample collection for HRD in Germany. We have been involved in the first description of several "disease genes" (CNGA3, CNGB3, GNAT2, PDE6C, RBP4, NYX) as well as numerous follow-up mutation screenings in a variety of retinal disease genes and clinical subtypes. Another main research project focuses on the causes of hereditary optic neuropathies. In the past we have worked intensively on the maternally and mitochondrial inherited Lebers Hereditary Optic Neuropathy (LHON). Currently we are working on the autosomal dominantly inherited forms of Optic Atrophy Type Kjer (ADOA).



Our lab was substantially involved in the identification, cloning and characterisation of the first causative gene OPA1.

Our most recent project deals with the identification of hereditary factors in glaucoma. In the last years our group has also been engaged in transcript analyses and the characterization of retinal gene promoters.

As there is a large gap concerning the knowledge of the pathomechanisms between genetic cause and clinical phenotype, a major aim of our group is to evaluate the physiologic properties of mutant gene products. In that context we have been able to establish enzymatic and biochemical assays to measure enzyme activity and channel function of mutant proteins. We are also working on the characterization of homologous animal models on a functional, histological and molecular level in order to elucidate the pathology of these disorders and the underlying molecular processes and signalling pathways.

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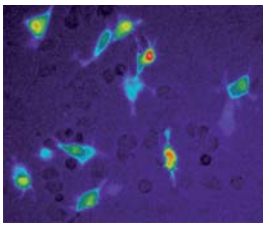

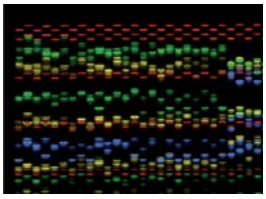

Ocular Neurodegeneration

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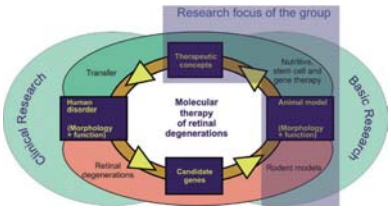
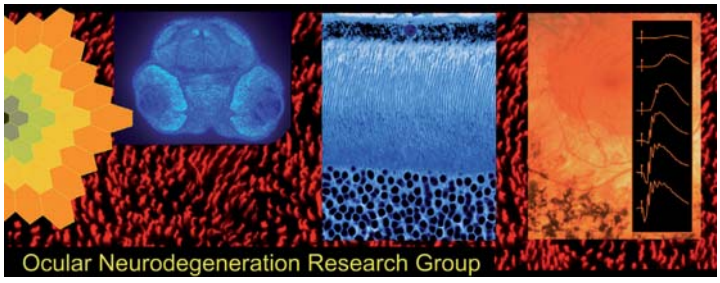
Our mission is to uncover the pathophysiology of ocular neurodegenerative processes, to develop and test therapeutic strategies and to understand and model normal retinal function. The basis of our work is in-depth functional and morphological phenotyping of genetic models of blinding human neurodegenerative disorders with electroretinography (ERG), scanning-laser ophthalmoscopy (SLO), and optical coherence tomography (OCT), the same non-invasive techniques used in affected patients.





Neurodegeneration research: We investigate the causes of and the disease mechanisms in retinal degenerations, and relate the findings in human patients to those in animal models with homologous genetic defects. Also, we examine animal models generated by groups worldwide for their relevance in this regard.

Systems biology: As many aspects of normal retinal function are still unclear, we assess functional pathways, particularly in the outer retina, by means of mouse lines with specific genetic defects in photoreceptor function and/or connectivity. Cross-breeding of such lines enables us to investigate isolated pathways, to obtain new insights about their nature and to model their behaviour.

Molecular therapy: Recent advances in therapeutic research (particularly gene and stem cell therapy) have led to collaborations with many leading groups on the evaluation of therapy in affected models. Our main field is the development of optimal application procedures and the evaluation of the therapeutic success by short- and long-term follow-up in vivo.

Methodological innovation and refinement: Since more than a decade we are involved in the development and refinement of innovative diagnostic strategies in human patients and animal models. In addition, we are regularly contributing to ERG standards/guidelines issued by the International Society for Clinical Electrophysiology of Vision (ISCEV).

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Section for Experimental Vitreoretinal Surgery

We are especially interested in processes that lead to a loss of sight in age-related macular degeneration (AMD). There are several questions we are working on, e.g. why does the RPE partially lose its function in elderly people? How can the function of the RPE be maintained or even restored? What role does melanin play in the eye? And what about the lipofuscin formed during a lifetime? We recently found in monkey eyes that lipofuscin can be removed from the RPE by drug treatment.

Moreover, we have developed a model (in rats and rabbits) for VEGF-induced choroidal neovascularization in order to compare different anti-VEGF strategies. We apply several methods, such as gene therapy, subretinal transplantation of genetically modified cells (e.g., stem cells) to replace the defective RPE, and administration of therapeutic antibodies and pharmacologic compounds. A broad range of experimental techniques is performed in our lab on experimental animals, ranging from surgery and drug treatment, electrophysiology (ERG and VEP), functional diagnostics with OCT and SLO, and finally analysis of tissues on histological, immunohistochemical and ultrastructural levels including immunogold and analytical electron microscopy.

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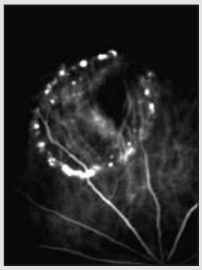
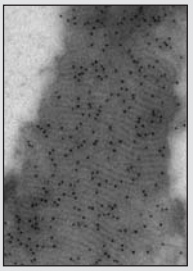
Zeiss Leo 912 omega electron microscope with complete analytical equipment



Our new SLO and OCT for small animal use

Transduced RPE cells in an eye of a living rat viewed by SLO

Fenestrations in the choriocapillaris of a monkey eye



Immunogold-labelling of rhodopsin in a monkey eye

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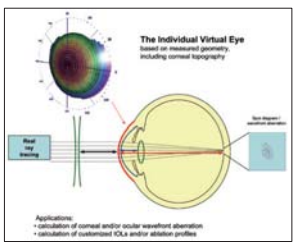
Experimental Ophthalmic Surgery

The Division <Experimental Ophthalmic Surgery> is one of the very few interdisciplinary research units in Europe where ophthalmologists, engineers, physicists and software engineers develop concepts for future innovative diagnosis and treatment under the roof of a University Eye Hospital. Historically, its personnel has been involved in the earliest steps of the development of refractive laser surgery since 1989; its continuation is a clinical refractive laser unit, specialized in complex patterns of visual impairment, high ametropia or complicated retreatments.



Own hard- and software developments for excimer lasers – partly in cooperation with leading international laser companies - as well as an own technology platform for advanced high resolution corneal topography allow for individualized custom treatments, often not available elsewhere.

Present research focuses on a simultaneous total eye morphometry system and the first model of a real data based <Individual virtual eye> (Real Ray Tracing), enabling the planning and calculation of combined refractive laser- and IOL- based procedures; it likewise provides a basis for the calculation of future true individually optimised IOLs. Other research topics include models, studies and applications of laser tissue interaction in the UV and IR spectral range, on-line feedback concepts for optimising laser treatment parameters and OCT research and imaging.

The division´s interdisciplinary approach provides attractive opportunities for young physicists and engineers on their way to graduation, MA or PhD qualifications in the neighbourhood of experimental and clinical medicine.

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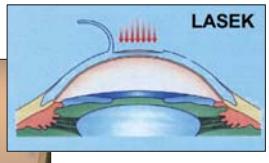
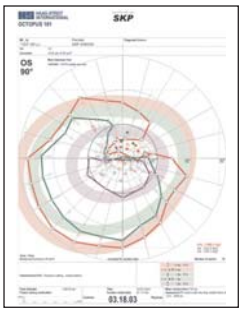


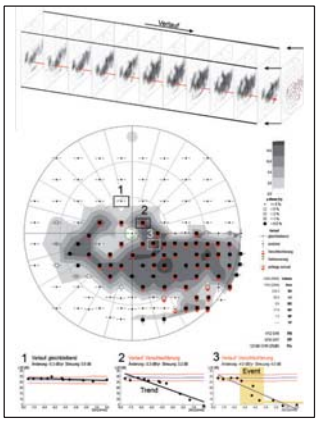
Running cooperations with Univ. of Vienna, Medical Physics; Belarussian Institute of System Analysis, Minsk.

Research Group Visual Pathway: Neuro-Ophthalmology & Perimetry

Detection of functional and morphological interrelationship of circumscribed visual pathway lesions, in order to evaluate their natural course and individual effect as well as to facilitate statements in regard to indication and prognosis of therapeutical methods. Clinical studies concerning glaucoma, neuroprotective strategies and early diagnosis of tumours affecting the visual pathway are pursued by refined techniques of visual field assessment developed by the group.

- Investigation of the functional and morphological interrelation of lesions in the ascending visual system aiming at understanding the consequences for prognosis
- Development of semi-automated kinetic perimetry (SKP), which allows for a considerable standardization of kinetic perimetry with additional assessment of and correction for individual reaction time of a patient
- German adaptive threshold estimating (GATE): development of a fast static perimetric thresholding algorithm, which is independent of stimulus grids and applicable to all kinds of ophthalmologic pathologies
- Enhanced evaluation and visualization of progressive visual field loss, using pointwise linear regression (PLR), event analysis and other procedures
- Visual Field Reading Center for multicenter clinical studies (consultation service, certification service, data processing service, data analysis, reports)
- Scotoma oriented perimetry (SCOPE): application of individually condensed grid for locally enhanced spatial resolution, especially in glaucomatous optic neuropathy (in co-operation with the Hamilton Glaucoma Center, University of California, San Diego)
- Assessment of compensatory exploration and driving performance under "virtual reality conditions" in patients suffering from homonymous visual field defects





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Clinic for Hereditary Retinal Degeneration

Hereditary retinal degenerations, e.g. retinitis pigmentosa (RP), are the most common cause of blindness in young adults. Since 1989 a special clinic for patients suffering the various forms of these diseases has been established with the aim to help elucidating the causative gene mutations, to develop elaborate methods of function testing for correct diagnosis and to advise and treat patients. Novel methods of electrophysiology and imaging techniques have been developed to allow for multimodal mapping and refined phenotype analysis. Approximately 500 patients are investigated and counseled annually. In close cooperation with the Molecular Genetics laboratory of the Institute, the DNA of these patients is analyzed in conjunction with the clinical research group, supported by the German research council since 2005. This allows not only for classifying patients in careful studies but for establishing a huge network of cooperation with other special RP clinics and molecular genetic laboratories. This has led to the discovery of many new genes and to major contributions in developing novel therapeutic strategies based either on pharmacological agents or medical devices. Since 1995 a subretinal multiphotodiode chip has been developed, carefully investigated in animal experiments and applied in the meantime in a clinical study that has shown the feasibility of this approach to restore useful visual sensations in completely blind RP patients.

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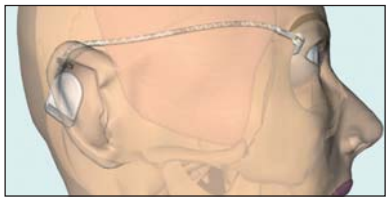

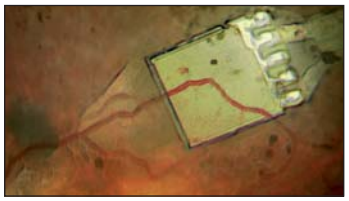

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Clinical Function Testing

The aim of Clinical Function Testing is to access the function of the various parts of the ascending and descending visual pathway by refined methods of psychophysics, electrophysiology and imaging. Emphasis is placed on further development of such methods as well as its application in patients with lesions of the visual pathways. This includes also the determination of normal values in large cohorts of volunteers as well as the development of standardization, including standard operating protocols and application in monocenter and multicenter clinical studies. Methods include Autofluorescence, Optical Coherence Tomography (OCT), Electroretinography, Rod-ERG, Cone-ERG, ON-OFF ERG, Multifocal Electroretinography ON-OFF Multifocal ERG, Electrooculography, refined Static and Kinetic Perimetry, Visual Evoked Cortical Potentials, and Pupillography .

We examine patients with hereditary diseases of the retina and optic nerve, toxic lesions of the visual system, loss of function due to glaucoma, stroke, trauma, tumours and degenerative diseases. Presently studies are done on glaucoma, Retinitis Pigmentosa patients, and restitution of vision in blind by subretinal microphotodiode arrays.

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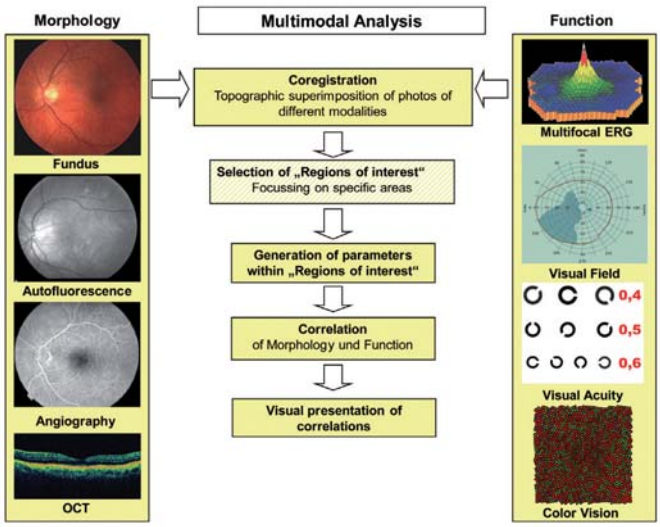

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Low Vision Clinic and Research Lab

This group focuses on the assessment, optimization and rehabilitation of visual functions, which are relevant for daily living skills, such as reading and orientation. In the research lab, the main focus lies on the analysis of reading disorders and motor control, eye movement recording (by video eye tracker and Scanning Laser Ophthalmoscope) in patients with visual field defects, psychophysical methods and development of standardized low vision tests.

Another group of patients are children with developmental dyslexia.

The residual function in patients with visual impairment is examined in order to analyze cortical adaptive mechanisms and to optimize the function by means of visual aids and new training programs. In the Low Vision Clinic the patients receive detailed diagnostics, consulting, visual aids and training. The Low Vision Clinic and Research Lab are interlocked very closely and have an active network of interdisciplinary and international cooperation.

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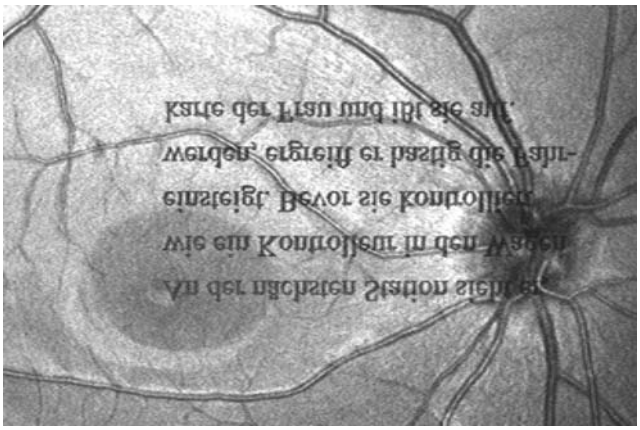

Pupil Group

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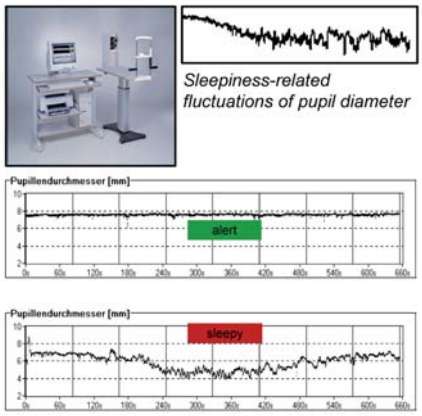
The pupil provides plenty of information about vision, emotional state, vigilance state and function of the autonomic nerve system. The Pupil Research Group does basic and clinical research and applies special knowledge in clinical routine. The afferent visual system is examined by the swinging flashlight test, even with an automated pupillographic method that has been developed by this group. Additionally a pupillographic pupil campimetry has been developed. This is used in basic research to provide a better understanding of the visual pathways, in clinical research to develop early diagnostic procedures in glaucoma and in daily routine clinic as an objective perimetric tool to disclose malingering.

Pupillography is done by different devices to obtain objective information about retinal function, e.g. in patients with subretinal implants and to investigate different branches of the visual system.

A major topic in research and clinical application is pupillographic testing of central nervous activation by means of the Pupillographic Sleepiness Test, PST, which has been developed and patented by this group. Pupillary oscillations in darkness provide direct information about the state of the central sympathetic nervous system and allow objective assessment of the alertness level. Quantitative analysis of pupillary oscillations in darkness has opened a wide field of research and clinical applications. Both in occupational medicine and pharmacological research PST gives insight on the effects of working environments and drugs influencing wakefulness. In sleep medicine the PST has already become a routine clinical application and is provided by this group as a service for other clinics within and outside the University Hospital.

The Neuro-ophthalmology clinic serves as a country-wide reference centre for pupillary disorders by applying all diagnostic features provided by the pupil group.



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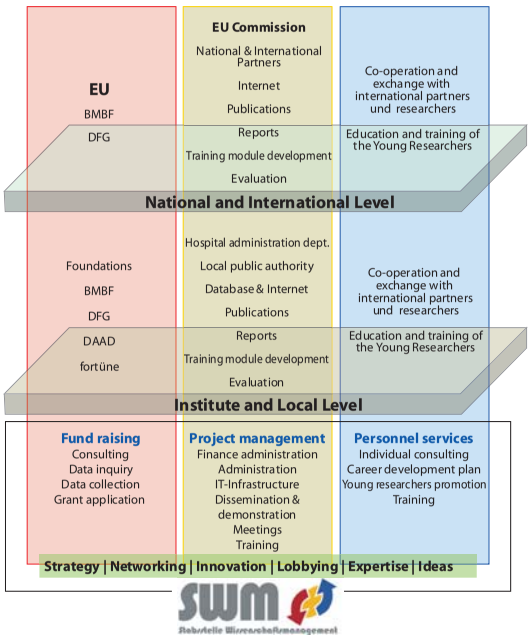
Research Management

In the course of an increased national and international crosstalk in R&D, the requirements on the professional organization and management of the Institute for Ophthalmic Research are mandatory. In order to ensure the high competitiveness and the quality of the research, the scientists need efficient instruments as provided by the 'Unit for Research Management (URM; Stabsstelle Wissenschaftsmanagement (SWM))'.

The URM supervises a wide and diverse portfolio of local, national and international projects, including several EC-projects. Its team is cooperating with nearly hundred research-partners in all European countries. The Unit for Research Management at the Institute for Ophthalmic Research initiated numerous applications and is presently involved in the coordination of 12 international research projects. Some of the projects coordinated by the URM are exclusively dedicated to transfer of knowledge and the training of young researchers. The URM has proved its ability to manage successfully and effectively this level of diversity and consists of an established team of professional project managers, who are focused on professional, cost effective and efficient science-driven management.



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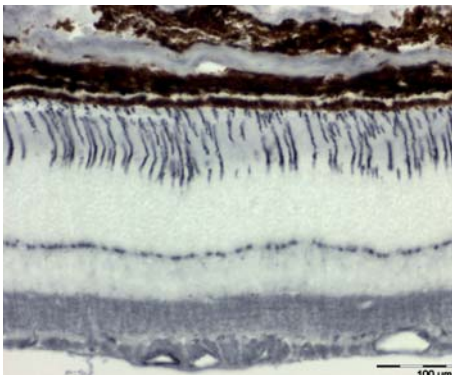
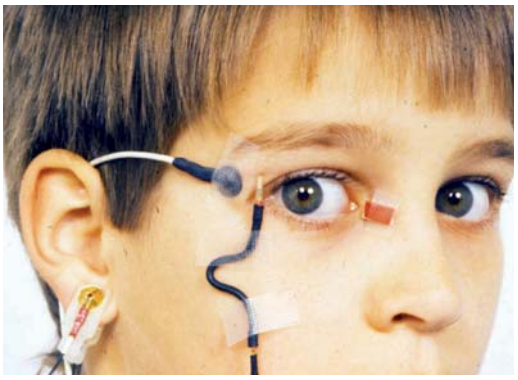
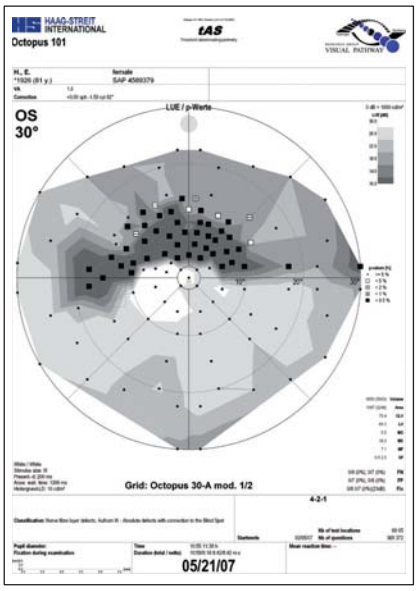
Education at the Institute

The Research Institute offers numerous training activities for students from medicine as well as from biology and other related natural sciences. The training ranges from teaching in Ophthalmology to specialist workshops on applied methods (e.g. the famous FUN course, an interactive course for application of advanced neuro-ophthalmological techniques; Basic Science Course in Vision, Research Colloqium, Lab Rotation Program, Glaucoma workshop; Interactive courses on [kinetic] perimetry, function testing in neuro-ophthalmology, Electroretinography Course) as well as soft skills, such as project and laboratory management.

Training at the Centre for Ophthalmic Research has in the past received top evaluations in the Tuevalon rankings. Prof. Dr. med. U. Schiefer has been awarded the medal for excellence in teaching from the State of Baden-Wuerttemberg. The Institute also participates in lectures and courses at the Graduate School for Neural and Behavioural Neurosciences, Max-Planck-Research School, and the faculty of biology. Several theses Doctoral Students have been marked with a summa cum lauda from the faculty of biology and medicine.







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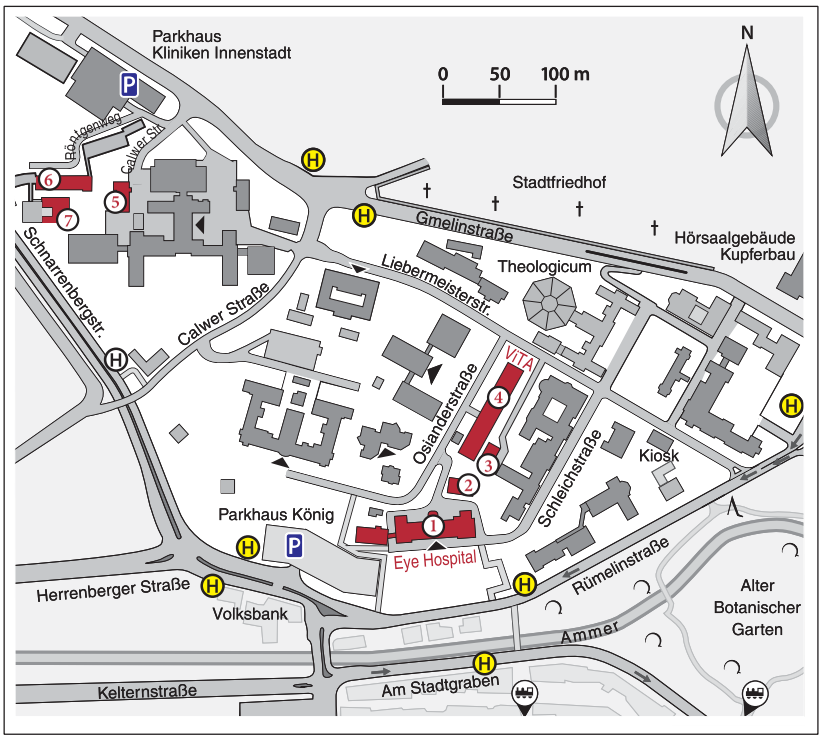

① Schleichstr. 12–16: Clinical Function Testing, Biomedical Engeneering Laboratory, Research Group Visual Pathway

② Schleichstr. 12/1: Section for Experimental Vitreoretinal Surgery

③ Schleichstr. 4/3: Ocular Neurodegeneration

④ Osianderstr. 5: Low Vision Clinic and Research Lab, Pupil Group

⑤ Calwerstr. 7/1: Neurobiology of the Eye

⑥ Röntgenweg 11: Research Management, Molecular Genetic of Sensory Systems, Experimental Ophthalmology

⑦ Röntgenweg 13: Colour and Visual Psycho Physics Group

Centre for Ophthalmology

2008