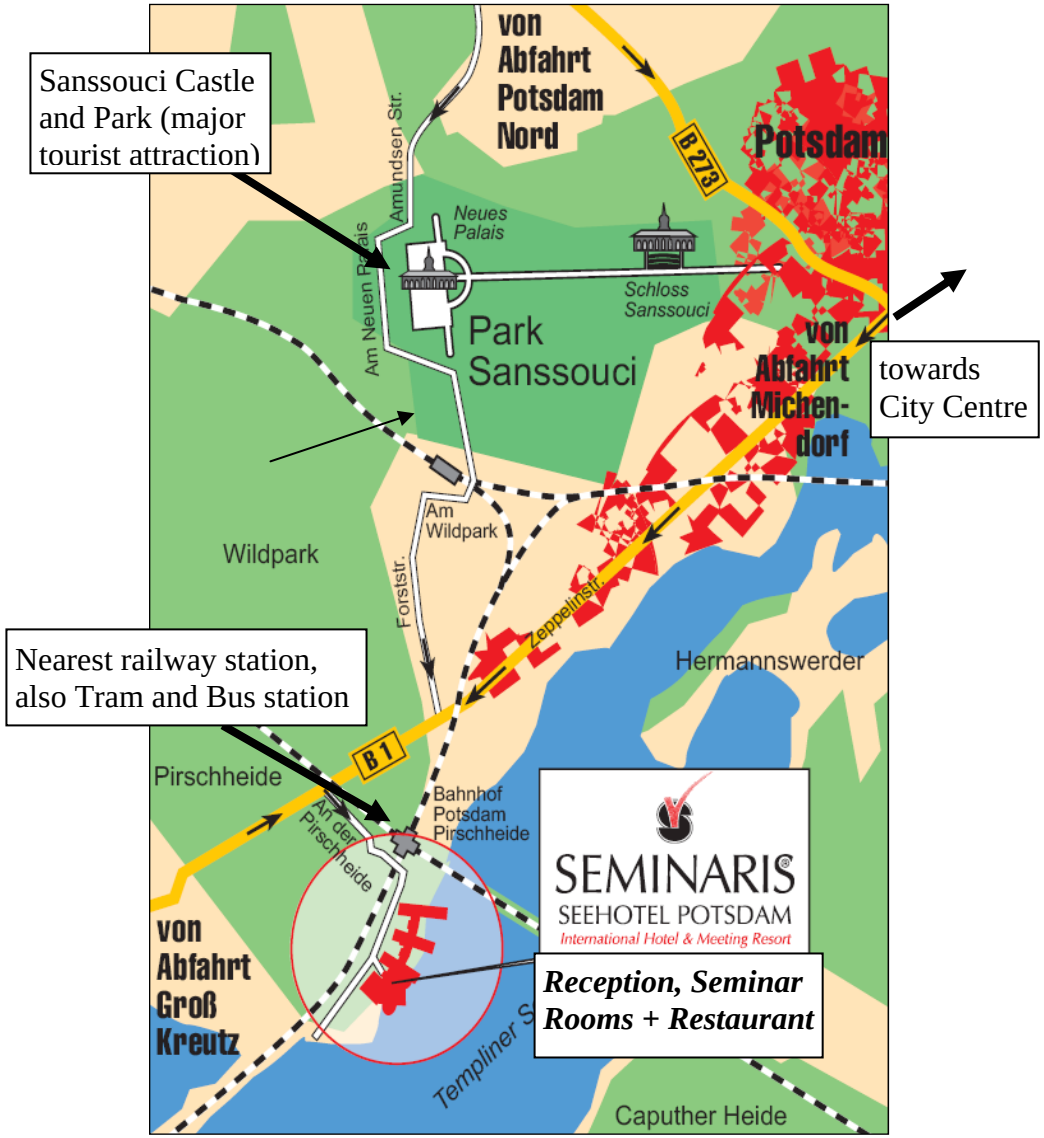
Area Map – Potsdam South-West



1st young researchers´ workshop on Vision and Neurodegeneration

Potsdam, Germany

March, 29. – 30. 2007

Organised by

European **Ret**inal Research Training **Net**work

Neurotrain - Early Stage Research Training

1st young researcher's workshop on
Vision and Neurodegeneration

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European **Ret**inal Research Training **Net**work

Neurotrain - Early Stage Research Training

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Dear fellow researchers,

We are very pleased to welcome you to our "1st young researchers workshop on Vision and Neurodegeneration" held at the Seminaris Seehotel am Templiner See **in Potsdam/Germany.** The aim of this workshop is to give young investigators an opportunity to present themselves and their work to fellow researchers to allow them to build and strengthen personal networks in an international environment.

The workshop is organized by fellows of the European Retinal Research Training Network – RETNET, a Marie Curie research training network (www.euro-ret.net). Additional help comes from some fellows of the Neurotrain research training network (www.neurotrain.org). Since the workshop is held just prior to the 3rd Pro Retina research colloquium 2007 (www.pro-retina.de) at the very same location, it is possible for participants to attend both events. Please note that you will have to register separately for the ProRetina meeting (Registration desk open from Friday, 30., 11.00h).

The intention of this workshop is to give as many young researchers as possible an opportunity to present. Unfortunately, time and resources are scarce and the time for the presentations is therefore limited to **5 minutes per person**. In order to emphasize interactions between participants, in each session there will be a combined discussion of approximately 20 min.

To warm up we will start with an evening of round table discussions with a number of senior scientists from the field. Several principal investigators from different European countries have agreed to participate in this event. Depending on interests, different topics such as "Careers in Research", "Family and Research", "Personal Motivation", "Medicine vs. Natural Sciences", "Dishonesty and Fraud", etc. may be discussed. We hope that these discussions will enable young scientists to benefit from the wealth of experience senior researchers have acquired during their careers.

We wish you an interesting and successful meeting,

On behalf of the organizers,
François Paquet-Durand and Kostas Nikopoulos

Programme

Thursday, March, 29.

16.30h Welcome coffee

17.00h Introductory remarks – Opening ceremony

17.30h Discussion 1 – Careers in science
- Do you have to go to the USA? – The American perspective (N. Katsanis)
- Where to go next? Academia vs. Industry. Other options? (W. Raffelsberger)
- Women in Science: Is there real equality? (MT. Perez, S. Hauck)

18.15h Discussion 2 – Careers in science
- How to be successful? How to stay motivated? Funding opportunities? (T. Wheeler-Schilling, N. Katsanis)
- Establishment in a foreign country – The European perspective (S. Bhattacharya, MT. Perez)

19.00h Discussion 3 – Other aspects of a Scientists life
- Combining Family and Work: The research scientist's perspective. (S. Hauck, F. Paquet-Durand)
- Dishonesty and Fraud: Could this happen to you? How to deal with it? (T. Wheeler-Schilling, MT. Perez)
- Medicine and Natural sciences: How to get along with each other? Is it all out war, peaceful coexistence or fruitful collaboration? (N. Katsanis, S. Bhattacharya)

19.45h Concluding remarks

Friday, March, 30.

9.00h Session 1: "**Genetics of neurodegenerative diseases**"
Chairs: W. Raffelsberger, Strasbourg/France, Arijit Mukhopadhyay, Nijmegen/The Netherlands

Alison Reynolds: "A QTL on mouse Chromosome 19 controls variation in the light adapted ERG"

Ciara O´Driscoll: "Candidate gene analysis for RP25"

Karin Littink: "Congenital blindness, retinitis pigmentosa and cone-rod dystrophy: Identification of causes and genotype-phenotype correlation."

The molecular basis of cell degeneration in Parkinson's disease: Studies with LRRK2

Zhi Yao

Institute of Neurology, University College London, United Kingdom

Parkinson's disease (PD) is the second most common neurodegenerative disease. Mutations in the leucine rich repeat kinase 2 (LRRK2) gene have recently been identified in families with autosomal dominant Parkinson's disease. The most common mutation of LRRK2 (G2019S) is present in approximately 5-6% of familial PD cases and in approximately 1-2% of sporadic cases in several European and US populations. The prevalence of LRRK2 mutations in PD suggests a critical role for LRRK2 in Parkinson's disease pathogenesis. The LRRK2 gene encodes a large, 2527 amino acid protein (dardarin), which has several identifiable domains. The function of LRRK2 and how mutations in this gene cause Parkinson's disease remains unknown. Some studies have showed that pathological mutations in LRRK2 can lead to cell death, aggresome formation and reduced neurite outgrowth in *in vitro* over-expression cell models. Moreover, mutations in the kinase domain of LRRK2 have been reported to lead to increased kinase activity which suggests a possible gain of function model for LRRK2 linked PD. The aim of this project is 1) to develop a range of stable overexpression and knock-down (by using siRNA techniques) cell models of LRRK2 in a primary human neuronal cell line and a human neuroblastoma cell line to gain insight into the effects (phenotypes) of loss and gain of function phenomena in PD *in vitro*; 2) to identify putative interactors and substrates of LRRK2 using those cell models and proteomic techniques, such as Tap tagging and 2D-DIGE.

Gene transfer into organotypic retina cultures via electroporation and ballistic transfection

Tobias Goldmann

Institute of Zoology, University of Mainz, Germany

Cells of highly the specialized neuronal network of the retina survive and maintain only in the connection to their neighbouring cells. Because of this, most retinal cells can not be studied in primary cell cultures. The organotypic retina culture provides an accessible *ex vivo* system for protein function analyses.
Cultured retinas were transfected with eGFP constructs by electroporation or ballistic transfection. The expression of eGFP fusion proteins in retinal cells were analyzed by fluorescence microscopy. Transfected cells were identified by co-labelling with cell type specific markers.
In retina cultures transfected via electroporation numerous eGFP fusion protein expressing cells were detected. In PN8 explants, transfected cells were localized in the outer nuclear layer and in the inner nuclear layer, whereas in maturate explants transfection was restricted to RPE cells. The ballistic gene transfer method revealed lower transfection efficiency, but did also deliver constructs to cells of the inner retina.
The organotypic retina culture is a suitable *ex vivo* system for gene transfers. The electroporation is appropriate for transfection of cells of juvenile retinas. Gene Gun™ transfer is applicable to transfect of single cells of all cell types of mature retinas.

Friday, March, 30.

Ronald Carpio: “Studies on Transcriptional Regulation in the Human Retina”

9.45h Session 2: “**The Retina: A window on neurodegenerative processes**”
Chair: T. Cronin, Paris/France, K. Nikopoulos, Nijmegen/The Netherlands

Balázs Varsányi: “The complex (clinical and molecular genetic) examinations of patients with congenital achromatopsia – from a clinician’s point of view”

Patricia del Rio Medina: “Identification of GDNF-induced retinal Müller glial cell-derived neuroprotective factors”

Francesca Fiocco: “The role of PRPF31 in Retinitis Pigmentosa”

Javier Sancho Pelluz: “Role of inflammation in photoreceptor degeneration”

10.30h Coffee Break

11.00h Session 3: “**Cell death mechanisms in neurodegeneration**”
Chairs: F. Paquet-Durand, Lund/Sweden, E. Körtvely, Munich/Germany

José Silva: “The PARP enzyme plays a role in the rd1 retinal degeneration”

Krzysztof Kucharz: “Cell on the crossroads”

Zhi Yao: “The molecular basis of cell degeneration in Parkinson’s disease: Studies with LRRK2”

Kirsten Wunderlich: “Role of the ubiquitin proteasome system in retinal degeneration”

11.45h Session 4: “**Therapeutic approaches for the treatment of CNS disorders**”
Chairs: N. Chadderton, Dublin/Ireland, C. Maubaret, London/UK

Manuel Falcao: “Effects of bevacizumab on HUVEC´s proliferation and apoptosis”

Tobias Goldmann: “Gene transfer into organotypic retina cultures via electroporation and ballistic transfection”

Julianne McCall: “Rd1 photoreceptor cell survival depends on the in vitro calpain inhibition paradigm employed”

Markus Thiersch: “Conditional knock out of HIF-1a and the consequences for hypoxia induced neuroprotection in a model of light induced retinal degeneration”

12.30h Closing remarks

13.00h Start of the ProRetina 2007 meeting

A QTL on mouse Chromosome 19 controls variation in the light adapted ERG

Alison Reynolds

Trinity College Dublin, Ocular Genetics Unit,
Dublin, Ireland

It has previously been shown that a quantitative trait locus (QTL) located within 10cM of a marker on proximal chromosome 19 controls variation in timing and amplitude traits of the light-adapted electroretinogram between two strains of inbred mouse commonly used in vision research, particularly in the generation of transgenics: C57BL/6JOlaHsd and 129S2/SvHsd (Harlan, UK). The observed strain-specific differences in the light-adapted ERG b-wave are likely to be caused by a gene or gene(s) involved in modulating retinal neurotransmission. At present, a backcrossing experiment is being performed so the QTL may be refined and the gene(s) involved in such variation identified. Studying phenotypic variation between strains of inbred mouse is a valuable resource for the identification of novel genes, modifying, for example, retinal function.

Studies on Transcriptional Regulation in the Human Retina

Ronald Carpio

University Eye Hospital Tuebingen, Germany

One of the most important goals of the post-genomic era is the identification of tissue-specific gene regulatory networks. The retina, a highly differentiated neuronal tissue, expresses a considerable number of genes involved in specific processes like phototransduction. The aim of our study is the identification of transcription start sites of retinal expressed genes for further exploration of the promoter and other cis-regulatory sequences at the 5´end of the genes. We used available public database information, namely EST sequence and cross-species comparisons to perform *in silico* assembly and analysis of 5´transcript termini. In addition, RNA from human retina is used for Cap Finder RACE experiments to study and characterize the ultimate 5´ termini of the genes of interest. So far, we have mapped the TSS of 54 genes expressed in the retina and we are employing the generated information for analyzing the promoter regions of some of those genes.

Identification of GDNF-induced retinal Müller glial cell-derived neuroprotective factors

Patricia del Rio Medina

Institute of Human Genetics, GSF-Research Center for Environment and Health, Ingolstaedter Landstr. 1, D-85764 Neuherberg, Germany

Purpose: Inherited retinal degenerations involve death of either light-receptive photoreceptors (PR) or neurons of the inner retina that eventually leads to blindness. Glial cell line-derived neurotrophic factor (GDNF) was found to rescue PR function during inherited retinal degeneration in rd1 mice. Recent evidence has proposed that the GDNF-induced neurotrophic rescue of PR is indirect, mediated by interaction of GDNF with retinal Mueller glial cells (RMG) (Hauck et al., 2006). RMG are proposed to release as of yet unidentified factors in response to stimulation with GDNF. These factors are good candidates for directly supporting PR rescue during retinal degenerations.
Methods: The strategy is to obtain pure populations of primary RMG by using hGFAP::eGFP adult mice (2months) that express GFP exclusively in RMG in the retina. For obtaining pure populations of GFP-positive RMG, retinas were disrupted enzymatically and RMG were sorted and collected by FACS. Freshly sorted RMG populations were then stimulated with GDNF or left unstimulated. Verification of induced signal transduction in response to GDNF stimulation was performed by Western blot analysis with antibodies against phosphorylated ERK. For analysis of mRNA changes induced by GDNF stimulation, pure populations of RMG were stimulated for 24h with GDNF and total RNA was prepared.
Results: Retinal specimen of hGFAP::eGFP adult mice show expression of GFP exclusively in RMG as demonstrated by co-staining with RMG-specific marker glutamine synthetase (GS). The percentage of GFP-positive RMG can be estimated at 50%. FACS sorting of GFP-positive cells from the pool of total retinal cells after enzymatical trituration yielded on average 4.34 % GFP-positive cells. Direct GDNF stimulation of FACS-sorted GFP-positive cells resulted in increased phosphorylation of ERK.
Conclusions: The analysis of murine GFP-positive RMG from hGFAP::eGFP verifies that freshly sorted primary RMG are reactive to GDNF stimulation. With the aim to identify secreted candidate proteins that have survival promoting activity on PR, this experimental setting can be used to study GDNF-induced changes in the mRNA expression.

The complex (clinical and molecular genetic) examinations of patients with congenital achromatopsia – from a clinician's point of view

Balázs Varsányi

Department of Ophthalmology, Semmelweis University, Budapest, Hungary

Introduction: Congenital achromatopsia is an autosomal recessively inherited stationery retinal disorder. Symptoms are caused by the lack of functioning cone photoreceptors. There are complete and incomplete forms of the disorder. Because of the rarity of the disorder (1:50 000), the patients are often misdiagnosed. The clinical diagnosis is based on standard ophthalmologic examinations and electroretinography (ERG).
Aim: To confirm the clinical diagnosis of the patients by molecular genetic analysis, and thereby provide data for the families for genetic counselling. Our purpose was also to find an appropriate method to distinguish the complete and incomplete form of achromatopsia. We also tried to analyse the morphological changes and the possibly time course of the disorder, as these data could be quite important for a forthcoming gene therapy.
Patients and methods: There are 12 patients from 9 families at our department with the clinical diagnosis of achromatopsia. CNGA3 and CNGB3 genes were screened for mutations in patients and relatives. Spectral luminosity testing, relative brightness matching test and ERG with colour-stimuli was performed to distinguish the complete and incomplete forms. The retinal morphology was analysed by optical coherence tomography (OCT).
Results: Pathogenic mutations were found in all 12 patients either in CNGA3 or CNGB3 genes. 2 patients were found having incomplete form of achromatopsia, according to the special colour tests. Using OCT, the central retina was found significantly thinner in patients compared to control subjects. The thinning of the retina was more marked in older patients than in younger ones.
Conclusions: Molecular genetic analysis verified the clinical diagnosis of achromatopsia in all of our patients; this way helped them and their families to cope with this non-progressive retinal disorder. Patients with the incomplete form of the disorder may need different support (i.e. glasses) than those with the complete form. The morphological changes seen imply the need for early intervention, before the degeneration of cones and related structures.

Candidate gene analysis for RP25

Ciara O'Driscoll

Department of Molecular Genetics, Institute of Ophthalmology, UCL, London, United Kingdom

Retinitis pigmentosa (RP) is a clinically and genetically heterogeneous group of retinal degenerations. RP is one of the most debilitating hereditary retinal disorders and can be inherited as an autosomal dominant (ad), autosomal recessive (ar), X-linked or digenic. Autosomal recessive RP (arRP) is the most common form of RP worldwide. To date, 24 loci are known to be responsible for arRP, of which 4 causative genes still remain to be identified. One such locus is RP25, which has been mapped between microsatellite markers D6S257 and D6S1570 on chromosome 6q in 6 Spanish families. RP25 spans approximately 16.1 cM and contains 120 genes. Candidate genes within the interval are selected based on their function, tissue expression pattern and/or genetic data. So far approximately 50% of genes have been excluded. Methods used include polymerase chain reaction (PCR) amplification, direct sequence analysis, genotyping and restriction enzyme analysis. Analysis of novel SNPs have been undertaken in patients as well as control populations.

Conditional knock out of HIF-1a and the consequences for hypoxia induced retinal neuroprotection in a model of light induced retinal degeneration

Markus Thiersch

Lab of Retinal Cell Biology, Ophthalmology, University Hospital, Zurich, Switzerland

Purpose: Hypoxic preconditioning protects the retina from light induced photoreceptor apoptosis. During hypoxia the transcription factor hypoxia inducible factor-1a (HIF-1a) is stabilzed in the retina. This leads to the upregulation of several HIF-1 target genes like Epo and to neuroprotection. To elucidate the role of HIF-1a in neuroprotection, we generate and test a conditional HIF-1a knockout.
Methods: Tamoxifen (TAM) inducible Prp-Cre mice were intercrossed with HIF-1a$^{flox/ko}$ mice and ROSA26. TAM was injected twice a day for 5 days. Knock out efficiency was estimated by real time RT-PCR and Western Blot. Mice will be exposed hypoxia and afterwards to white fluorescent light to test for the efficacy of neuroprotection in the partial absence of HIF-1a.
Results: Cre expression was mainly detected in the photoreceptor layer. RT-PCR data revealed, that excision of HIF-1a in the retina occurred with an efficiency of almost 80%. The effect on HIF-1a ablation on hypoxic preconditioning and neuroprotection will be presented.
Conclusion: TAM inducible Prp-Cre;HIF-1a$^{flox/ko}$ mice are a very good tool to analyze the impact of lacking HIF-1a in the photoreceptor layer. These mice will be tested in our model of light damage to investigate whether the lack of HIF-1a in photoreceptor cells influences hypoxia induced neuroprotection.

Effects of bevacizumab on HUVEC´s proliferation and apoptosis

Manuel Falcão

Opthalmology Department of Hospital S. João – Porto, Portugal

Bevacizumab has been used intravitreally as an off-label therapy for age-related macular degeneration. Doubts on its safety have been raised due to the high intra-ocular concentrations reached in the vitreal cavity after injection.

Purpose: To evaluate short term in vitro effects of bevacizumab in human umbilical vein endothelial cells (HUVECs).

Methods: Cultures of HUVECs were established and treated during 24 h with bevacizumab (0.25 – 5mg/ml) diluted in culture medium. Controls were incubated with excipient solutions. Cell viability was evaluated by MTT and trypan blue exclusion assays. Proliferation was analyzed by 5'-bromo-2'deoxyuridine (Brdu) incorporation and morphologically assessed by microscopy. Apoptosis was assessed by TUNEL assay.

Results: Viability of HUVECs incubated with bevacizumab did not significantly differ from controls in any of the concentrations examined by the two methods. Despite an increase in cell apoptosis by increased concentrations of bevacizumab, these values were not statistically different from the controls. A tendency towards a significant decrease in cell proliferation was found when HUVECs were incubated with bevacizumab at 0.25, 0.5 and 1mg/ml.

Conclusions: These findings indicate that bevacizumab at concentrations identical to doses normally used in clinical practice neither inhibit endothelial cell viability and proliferation or induced significant apoptosis. Our results are in agreement with the established lack of toxicity in clinical use.

The role of PRPF31 in Retinitis Pigmentosa

Francesca Fiocco

Department of Molecular Genetics, Institute of Ophthalmology, UCL, London, United Kingdom

Pre-mRNA processing factor 31 (PRPF31) is a ubiquitous protein, needed for the assembly of the pre-mRNA splicing machinery. It has been shown that mutations in this gene cause autosomal dominant retinitis pigmentosa 11 (RP11), which is characterised by rod-cell degeneration. Interestingly, mutations in this ubiquitously expressed gene do not lead to phenotypes other than retinal malfunction. Furthermore, the dominant inheritance pattern has shown incomplete penetrance which poses interesting questions about the disease mechanism of RP11. In order to characterise the specificity of *PRPF31* function in the rod cells, an animal model has been generated. This is a knock-in (KI) mouse carrying a point mutation A216P, which has been previously identified in RP11 patients. Degeneration of the KI mouse retina was monitored by electroretinography (ERG) and histology. In this talk, RP11 background and undergoing functional characterisation will be presented.

Role of inflammation in photoreceptor cell degeneration

Javier Sancho Pelluz

Ophthalmology, Lund University, BMC-B13, Lund, Sweden

There is an increasing amount of evidence suggesting that the immflamatory and immune mechanisms play an important role in the photoreceptor cell degeneration in Retinitis Pigmentosa (RP), in the death of the rods and in the secondary loss of the cones.
In other chronic neurodegenerative diseases, such as Parkinson's or Alzheimer's disease, activated microglial cells have been observed. These cells are the macrophages of the CNS and they are employed in producing cytokines, chemokynes and other inflammatory factors.

Our purpose in this study is to get to know more about the implications of immflamation in this disease. So far, we have studied the distribution of microglia in different stages of the disease and in different animal models of RP. One purpose was to determine if there is an expression of sialoadhesin (Sn), a sialic acid binding receptor, in microglial cells in *rd1* retinae. Thus far, there is no evidence of Sn-expression in the tested samples. Nevertheless, we observe Sn-positive cells in connection with retinal transplantation.

Cell on the crossroads

Krzysztof Kucharz

Lund University, Experimental Brain Research, BMC-A13, Klinikgatan 26, 22185 Lund, SWEDEN

Cell exposed to negative environmental factors counteracts with cellular stress response. One of the mechanisms involved in cell protective measures is the ubiquitous process called "Unfolded Protein Response (UPR)". UPR results in almost complete protein translation shutdown limiting the accumulation of unfolded proteins in ER which would eventually lead to apoptosis. Only the genes involved in stress response are able to overcome this blockade. However, protein transcription blockade can not last forever and has to be restored. This is the time when cell holds its breath, standing on the crossroads where one way leads to apoptosis and other to survival…

Role of the ubiquitin proteasome system in retinal degeneration

Kirsten Wunderlich

Ophthalmology, Lund University, BMC-B13, Lund, Sweden,

Many neurodegenerative diseases are characterized not only by neuronal cell loss due to a primary insult (mutation, injury, ischemia etc.) but also by reactive changes that may eventually lead to secondary cell death which can sometimes have an even more severe effect.
Retinitis pigmentosa is a retinal degeneration disease in which rod photoreceptor cell death causes tunnel vision and night blindness. A delayed cone photoreceptor cell loss will eventually lead to total blindness.
One of my interests is to investigate the role of the ubiquitin proteasome system (UPS) in retinal degenerations. The UPS is a protein degrading machinery that has been found to play a role in the pathogenesis of many neurodegenerative disorders.
By using transgenic mice expressing GFP (green fluorescent protein) attached to ubiquitin, a signal protein leading to degradation, cells with an impaired UPS can easily be identified by green fluorescence as a result of accumulated GFP-ubiquitin.
Several mouse models for retinal degeneration, including models for inherited or induced Retinitis pigmentosa, will be investigated with respect to impaired UPS. This might lead to a better understanding of how the progress of retinal degeneration and UPS function are connected.

The PARP enzyme plays a role in the rd1 retinal degeneration

José Silva

Ophthalmology, Lund University, BMC-B13, Lund, Sweden

Purpose: The rd1 mouse represents a model for Retinitis Pigmentosa leading to the degeneration of rod photoreceptors. Poly(ADP-ribose) polymerase (PARP) is important for DNA repair. Overactivation of PARP is involved in cell death. The present study comparatively looked into the activity of PARP in the rd1 and WT retina.
Methods: Retinas were collected from rd1 or WT background C3H mice at various ages, fixed, cryo-sectioned and immunofluorescently labeled using primary antibodies towards PAR. In addition, an in situ enzymatic assay was used on unfixed histological sections to reveal PARP activity at the cellular level. Cell death was evaluated through the use of the TUNEL assay kit.
Results: Staining for PAR or PARP activity revealed a clear signal in many rd1 photoreceptor nuclei in the rd1 retina, but very little in the WT counterpart. PAR staining overlapped with PARP activity and TUNEL labeling of apoptotic nuclei in rd1 photoreceptors. These parameters remained stable and negligible throughout the study period.
Conclusions: PARP activity and PAR were colabeled with TUNEL positivity, in the rd1 photoreceptors. These results indicate that PARP activity does indeed play a role in rod cell death.

Rd1 photoreceptor cell survival depends on the in vitro calpain inhibition paradigm employed

Julianne McCall

Ophthalmology, Lund University, BMC-B13, Lund, Sweden

The rd1 mouse demonstrates an inherited retinal degeneration which allows for studies of the molecular mechanisms underlying the blinding disease retinitis pigmentosa (RP). Activation of the calcium-dependent protease calpain has been suggested to play an important role in cell death in various tissues; however, its employment in retinal degeneration has yet to be established. Previously, we have shown that calpain expression in rd1 mouse retina is unchanged when compared to the wt counterpart. Activity of calpain is, however, dramatically increased in rd1 photoreceptors and correlates with markers of cell death. This implied a causal connection between excessive calpain activity and cell death and further prompted us to study the effect of calpain specific inhibitors on photoreceptor viability in an in vitro retinal explant culture system. Our results suggest that the preservation of photoreceptors is dependent on the calpain inhibitor treatment paradigm, including substance concentration and duration of application. The data propose that calpain may be essential for both the promotion and prevention of cell death under changing circumstances. These ambiguous results may be due to calpain isoform specific effects and should be an important consideration as the use of calpain inhibitors to prevent or delay photoreceptor degeneration is further studied.

Congenital blindness, retinitis pigmentosa and cone-rod dystrophy: Identification of molecular causes and genotype-phenotype correlation.

Karin Littink

Department of Human Genetics, Radboud University Medical Centre, Nijmegen, the Netherlands

Congenital blindness (LCA), retinitis pigmentosa (RP) and cone-rod dystrophy (CRD) are clinically and genetically heterogeneous diseases. In recent years 9 genes have been identified that are involved in LCA, 32 genes that are involved in RP and 8 genes that are involved in CRD. It is estimated however that at least 50% of the genes involved in these diseases have not yet been identified. In this research project we will identify new genes involved in LCA, RP and CRD with a genome-wide approach.
Currently we are studying families with autosomal dominant RP. Patient DNAs are screened for known mutations in known disease genes using arrayed primer extension microarray analysis. Unsolved cases will then be further analysed to find new loci and new genes for RP. Patients who carry a mutation in a new gene will be clinically characterized to establish a genotype-phenotype correlation.