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# Laboratory of Tissue Culture and Stem Cells

## RESEARCH TOPICS

- Characterization of adult and embryonic stem cells *in vitro*;
- development of nanoparticles for cell labeling suitable for *in vivo* cell tracking;
- cultivation and differentiation of human embryonic stem cells into a neuronal phenotype;
- phenotyping of stem cells by means of flow cytometry;
- regeneration and repair of stroke lesions using human embryonic stem cells;
- regeneration and repair of injured spinal cord using stem cells and biomaterials;
- analysis of the growth factors and cytokines released from injured and tumor tissue and their role in the homing of MSCs to the lesions;
- cell-polymer constructs designed to bridge lesions of the central nervous tissue;

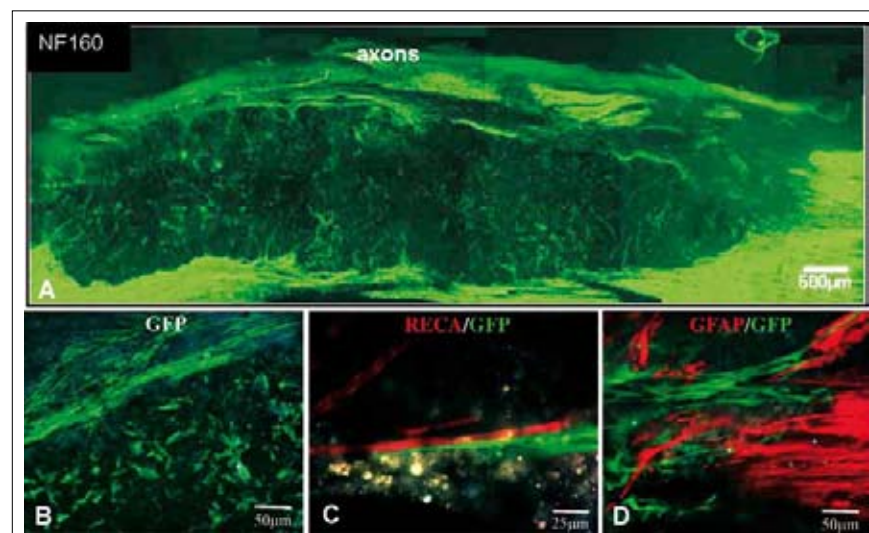
- nanofiber scaffolds for two- and three-dimensional cell cultivation.

## REGENERATION OF BRAIN AND SPINAL CORD INJURY USING STEM CELLS

Injury of the adult CNS, such as spinal cord trauma or stroke, invariably results in the loss of neurons and the loss of axonal processes involved in the lesion. This often results in severe functional impairment, due to the formation of complex scar tissue within the cavity as the result of cell death, inflammation and tissue degradation. Stem and progenitor cells from various sources are currently being investigated for their potential to treat CNS injury and numerous neurodegenerative diseases. Transplanted stem cells can either REPAIR damaged tissue by replacing missing populations of cells or RESCUE cells in the injured brain or spinal cord by the production of cytokines (interleukins) and/or neurotrophic factors that facilitate regeneration and/or revascularization.

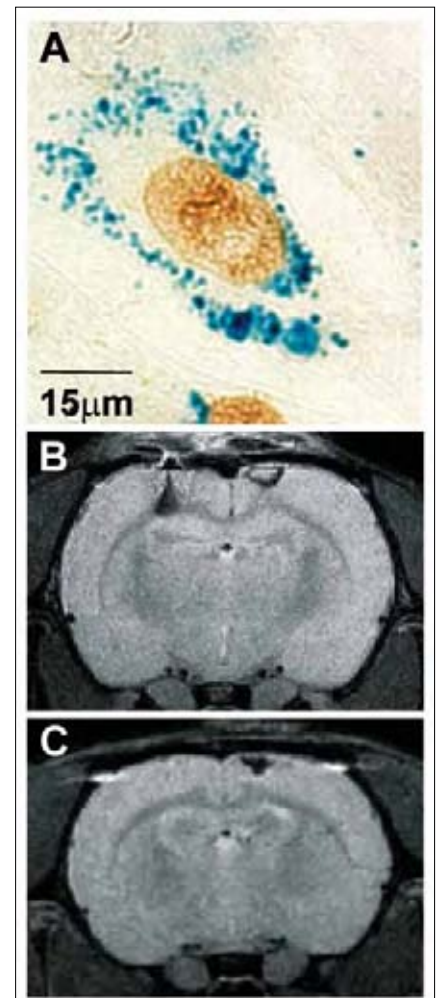
In our projects we study adult stem cells (isolated from bone marrow, peripheral blood or fat tissue) as well as human embryonic stem cells and

immortalized fetal spinal cord cells for the treatment of stroke and spinal cord injury. We use photochemical lesion and middle cerebral artery occlusion (MCAO) models to investigate stroke, while hemisection and balloon-induced compression lesions are employed as acute and chronic models of spinal cord injury, respectively. We evaluate the rescue



### Bridging a chronic spinal cord lesion with biomaterials.

- (A) Ingrowth of axons (staining for neurofilaments NF160) into a hydrogel implant that completely filled the post-traumatic cavity left after SCI.  
 (B) Cell/hydrogel implant 2 months after implantation. Mesenchymal stem cells survived in the implanted hydrogel and migrated towards the spinal cord stump.  
 (C) One month after implantation, MSCs facilitate the ingrowth of astrocytes into the implant by forming guiding strands towards the hydrogel.  
 (D) Similarly, blood vessels grow in close contact with MSCs.



### Labeling of stem cells with iron-oxide nanoparticles.

- (A) A cell labeled with iron-oxide nanoparticles undergoing cell division (staining for BrdU), confirming that the incorporation of nanoparticles does not adversely affect cell viability.  
 (B) T-2 weighted image of a cortical photochemical lesion and mouse embryonic stem cells implanted into the contralateral hemisphere two weeks after implantation. The cell implant in the hemisphere contralateral to the lesion as well as the lesion itself are visible as hypointense areas.  
 (C) A hypointense signal in the lesion observed thirty days after the intravenous injection of MSCs labeled with nanoparticles.

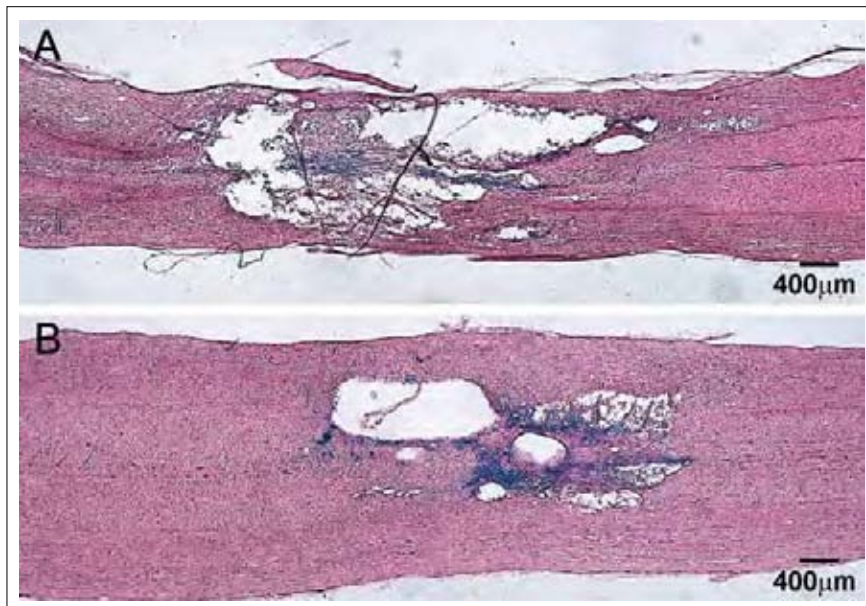


as well as the repair effect of the cells used in the treatment by means of behavioral tests, histology and immunohistochemistry.

### CELL LABELING

For the success of cell therapy it is important to monitor the fate of transplanted cells *in vivo*. One such approach involves the use of superparamagnetic iron oxide nanoparticles as labels for cell tracking.

In collaboration with the Institute of Macromolecular Chemistry ASCR, we have developed and patented several types of iron oxide nanoparticles with modified coatings that can be used for cell labeling and *in vivo* tracking by MR imaging. Cells labeled with these nanoparticles exhibit better viability and improved labeling efficiency in combination with a lower concentration of iron within the cells when compared with commercial contrast agents, such as Endorem, (Guerbet, France).



#### **MSCs labeled with nanoparticles implanted into rats with a spinal cord compression lesion.**

(A) Prussian blue staining of a spinal cord compression lesion. Only a few weakly stained Prussian blue-positive cells are found in the area of a spinal cord lesion without cell implantation. (B) Prussian blue staining of a spinal cord lesion with intravenously injected nanoparticle-labeled MSCs. The lesion is populated with Prussian blue-positive cells. Note the smaller lesion size in implanted animals than in controls.

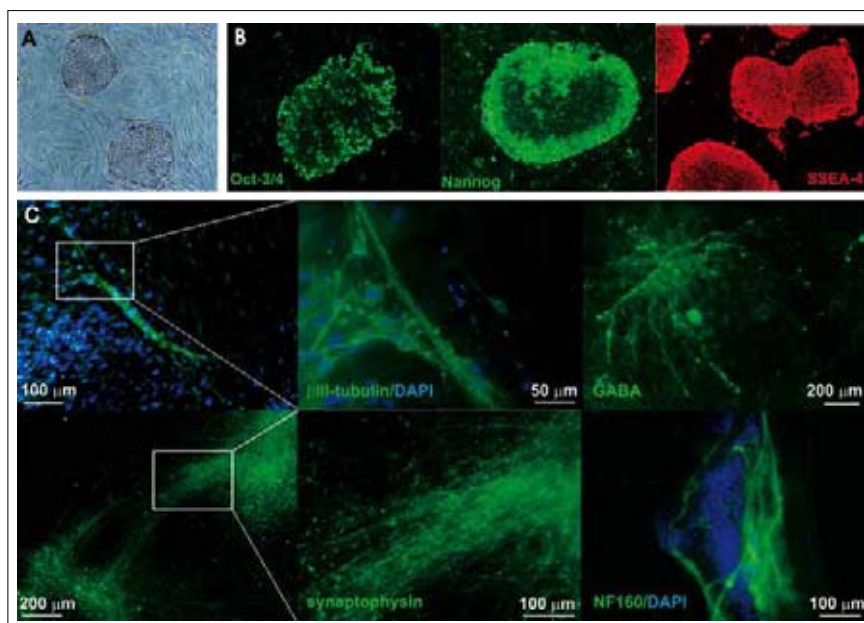
### CELL MIGRATION

Though mesenchymal stem cells (MSCs) have a positive effect on functional outcome after spinal cord injury (SCI), it is still not clear what is the mechanism of action of MSCs in the lesion, what mechanisms are

involved in attracting the MSCs into the site of SCI and why the cells migrate towards the lesion. Therefore, we study the mechanisms underlying the migration and engraftment of MSCs into a spinal cord injury from the point of view of chemotactic migration and cytokine expression. In collaboration with the University of Bergen, we also investigate the ability of MSCs to migrate to tumor tissue and the possibilities for their use in anti-cancer therapy.

### SCAFFOLDS AND POLYMER CONSTRUCTS

Poly(2-hydroxyethyl methacrylate) (pHEMA) and poly N-(2-hydroxypropyl)-methacrylamide hydrogels (pHPMA) belong to a group of synthetic, highly biocompatible polymers. In SCI repair they serve as a bridge for axonal growth across the lesion cavities. They also prevent scarring and thus create a permissive environment for tissue regeneration. In our Laboratory we investigate these hydrogels in combination with stem cells and/or scar-degrading enzymes and/or growth factors as



#### **In vitro differentiation of human embryonic stem cells (hESCs).**

(A) Colony of undifferentiated hESCs growing on a feeder layer. (B) Set of surface markers typical of undifferentiated hESCs. (C) Two to four weeks after the induction of neuroectodermal differentiation *in vitro*, the cells express markers of differentiated neurons.

bridges and cell carriers that support and facilitate regeneration after SCI. Another type of scaffold consists of electrospun nanofibers that can be used for cell culturing and for the transfer of cells into the host organism.

### CLINICAL STUDIES

Based on recent experimental studies, autologous bone marrow cell (BMC) implantation is used in our Phase I/II clinical trial in patients (n = 33) with a traumatic spinal cord lesion at Motol Hospital in Prague.

Another clinical study involves the use of BMCs and MSCs in the treatment of patients with a lower limb ischemic disease. The study is performed in collaboration with the Institute for Clinical and Experimental Medicine in Prague.

### CURRENT GRANT SUPPORT

GA CR, 203/09/1242, Surface-modified magnetic nanoparticles for cell labeling and in vivo and in vitro diagnostics, 2009–2011.

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Ministry of Education, 1M0538, Center for cell therapy and tissue repair, 2005–2009.

GA AS CR, KAN,201110651, Combined contrast agents for molecular MR imaging, 2006–2010.

GA AS CR, KAN,200520804, Biocompatible nanofibers for application of biologically and pharmacologically active substances, 2008–2012.

GA CR, 304/07/1129, Polarised cultures of hepatocytes and mesenchymal cells on nanofiber membranes in an experimental bioreactor, 2007–2011.

EU 6th FP, LSHC-CT-2004-504743, Targeting-Tumour-Vascular/Matrix Interactions, ANGIOTARGETING, 2004–2009.

EU 6th FP, CA LSHB-CT-2005-518233, From stem cell technology to functional restoration after spinal cord injury, RESCUE, 2005–2009.

EU 6th FP, LSHB-CT-2006-037328, STREP, Pre-clinical evaluation of stem cell therapy in stroke, STEMS, 2006–2010.

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EU 6th FP, MSCF-CT-2006-046102, Spring School on Regenerative Medicine – how to use neuronal stem cells for science and business, RegMedTeach, 2006–2009.

EU 6th FP, MEST-CT-2005-019729, EST: Cooperation in research and training for European excellence in neuroscience, CORTEX, 2006–2009.

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5. Syková E, Jendelová P. (2007) Migration, fate and *in vivo* imaging of adult stem cells in the CNS. *Cell Death Differ* 14(7): 1336–1342.
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## Laboratory of Diffusion Studies and Imaging Methods

### RESEARCH TOPICS

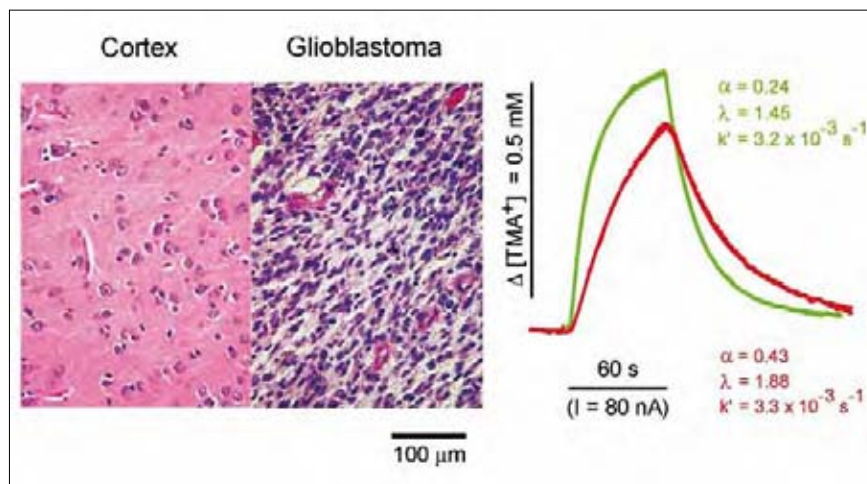
The Laboratory of Diffusion Studies and Imaging Methods studies the changes in the extracellular space diffusion parameters and extrasynaptic (volume) transmission that occur during physiological and pathological states.

Several animal models of pathological states and diseases attacking the CNS are used, e. g., models of chronic pain, ischemia and ischemic lesions, perinatal and early postnatal anoxia, brain edema, hydrocephalus, multiple sclerosis, Parkinson's disease, Alzheimer's disease, tumors, epilepsy, developmental disorders, aging, and brain and spinal cord injury, as well as models of CNS damage evoked by chemical or physical factors such as neurotoxins or X-irradiation. The research aims are the improvement of therapy and diagnostic methods for CNS diseases and the prevention of CNS damage.

### THE CURRENT RESEARCH FOCUSES ON:

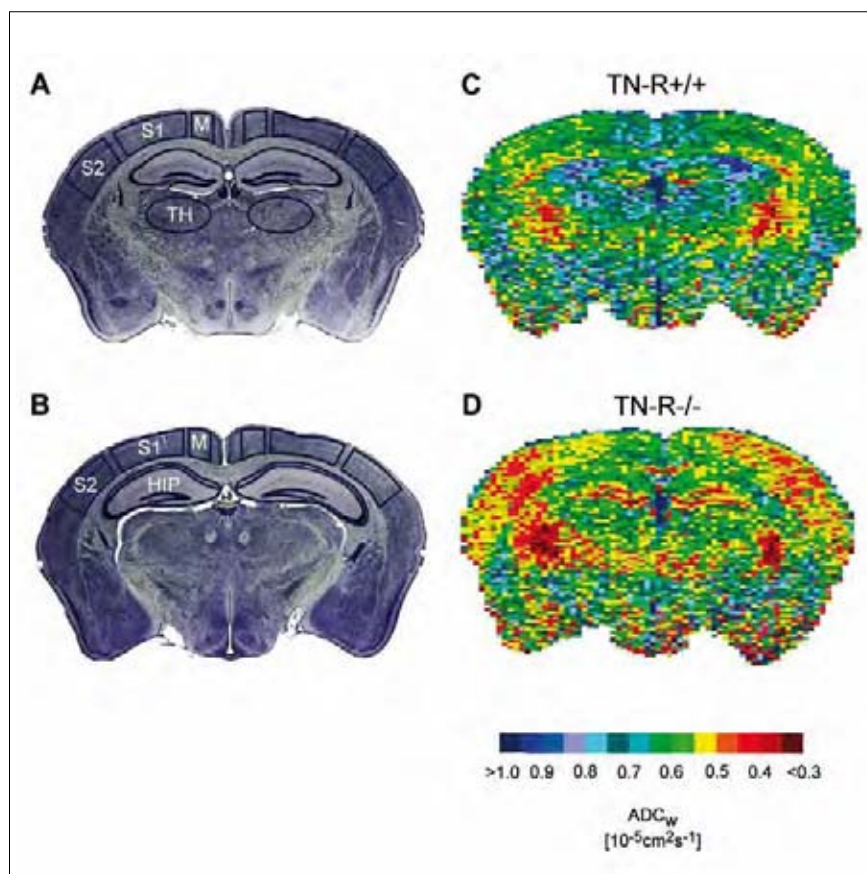
- The origin, mechanisms and pathophysiological significance of ionic changes in the extracellular space;
- diffusion in the extracellular space: the underlying mechanism of extrasynaptic („volume“) transmission;
- diffusion studies using the real-time TMA<sup>+</sup> iontophoretic method;
- diffusion studies using diffusion-weighted MR to measure the apparent diffusion coefficient of water;
- extracellular space volume and geometry – factors affecting diffusion in the CNS in health and disease;
- studies using models of pathological states, including transgenic animals;





**Diffusion parameters in a glioblastoma.**

Hematoxylin-Eosin staining of the human brain cortex and a glioblastoma (WHO grade IV) and representative TMA<sup>+</sup> diffusion curves with the corresponding values of the ECS diffusion parameters  $\alpha$ ,  $\lambda$  and  $k'$ . In comparison with healthy tissue, the ECS volume fraction ( $\alpha$ ) is almost doubled and the tortuosity ( $\lambda$ ) is significantly increased in a highly malignant glioblastoma.



**Typical apparent diffusion coefficient of water ( $ADC_w$ ) maps in tenascin TN-R<sup>+/+</sup> and TN-R<sup>-/-</sup> mice.**

$ADC_w$  was calculated in five selected areas: the motor cortex (M), the primary somatosensory cortex (S1), the secondary somatosensory cortex (S2), the hippocampus (HIP) and the thalamus (TH). (A and B) The areas are outlined in the microphotographs of Cresyl Violet-stained slices. (C and D) The images show  $ADC_w$  maps of TN-R<sup>+/+</sup> and TN-R<sup>-/-</sup> mice; both images are from the same coronal plane as shown in (B). The scale at the bottom of the figure shows the relation between the intervals of  $ADC_w$  values and the colors used for visualization. Note the lower  $ADC_w$  throughout the whole slice from the TN-R<sup>-/-</sup> mouse when compared with the TN-R<sup>+/+</sup> control.

– magnetic resonance imaging and spectroscopy.

Studies at the Laboratory are aimed at understanding the maintenance of ionic and volume homeostasis in the CNS, the extracellular space as a communication channel, the diffusion parameters of the extracellular space, extrasynaptic „volume“ transmission and the role of glia in signal transmission, behavior and regeneration.

**CURRENT GRANT SUPPORT**

AS CR, AV0Z50390512, Research project: Molecular, cellular and systems mechanisms of serious diseases of the human organism, their diagnosis, therapy and pharmacotherapy, 2005–2010.

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Ministry of Education, LC554, Research center: Center of Neuroscience, 2005–2009.

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EU 6th FP, LSHC-CT-2004-504743, “Targeting-Tumour-Vascular/Matrix Interactions, ANGIOTARGETING, 2004–2009.

EU 6th FP, LSHB-CT-2005-512146, Diagnostic Molecular Imaging: A Network of Excellence for Identification of NEW Molecular Imaging Markers for Diagnostic Purposes, DiMI, 2005–2010.

EU 7th FP, Programme PITN-GA-2008-214003, Axonal regeneration, plasticity & stem cells, AXREGEN, 2008–2012.

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parameters of the extracellular space. *Neurochem Int* 52(1–2): 5–13.

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## Laboratory of Eye Histochemistry and Pharmacology

Research in the Laboratory of Eye Histochemistry and Pharmacology is focused on the metabolic profile of the anterior eye segment and alterations evoked by various diseases or ocular injuries, such as the irradiation of the eye with UV rays and thermal or chemical burns. These severe disorders may result in corneal epithelial limbal stem cell deficiency leading to corneal conjunctivalization (ingrowth of the conjunctival epithelium) and permanent loss of vision. Recently, attempts at corneal regeneration have been started in an animal model (rabbit eye) using mesenchymal stem cell and/or corneal epithelial limbal stem cell transplantation with the aim of vision rehabilitation. In corneal healing processes, attention is devoted to conditions leading to the development of extensive intracorneal or intraocular inflammation. To affect these processes and achieve positive healing, various drugs are employed, particularly specific inhibitors of destructive proteases and scavengers of toxic oxygen products.

Great effort has been devoted to the possibilities of protecting the eye against the damaging effect of UVB rays, known to induce the generation

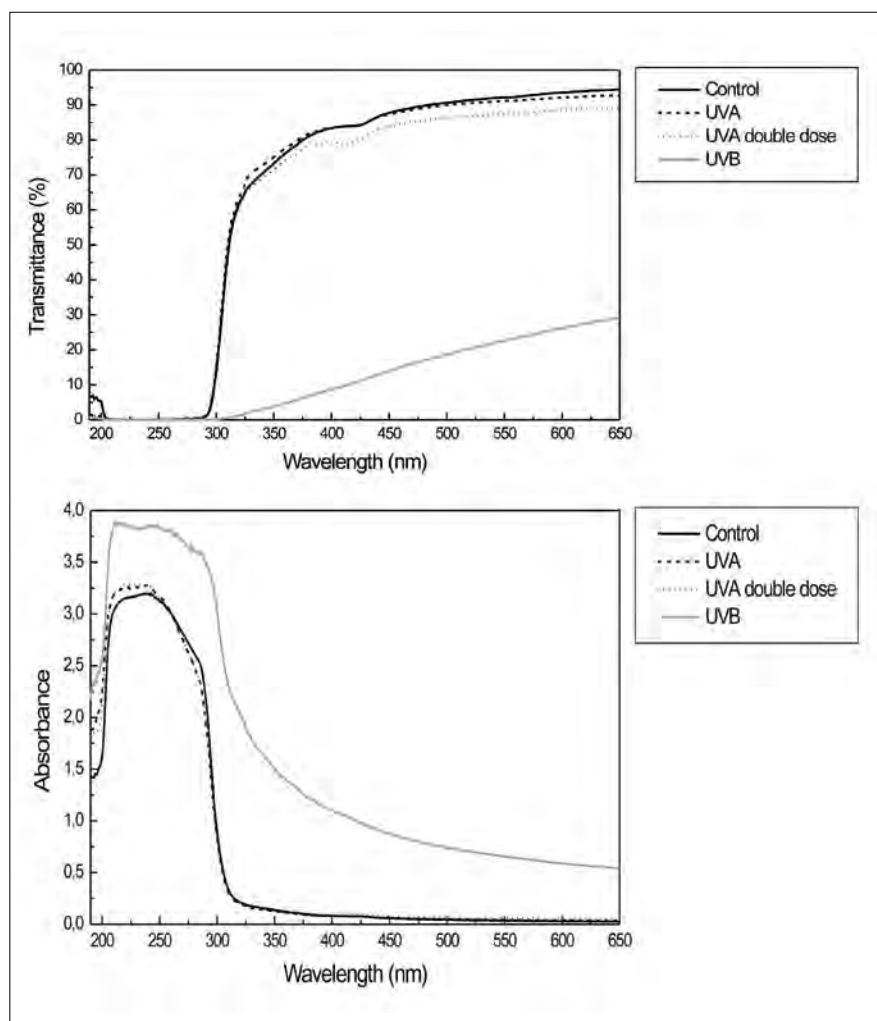
of reactive oxygen species, using UV filters (in cooperation with Laboratoires Thea, Clermont-Ferrand, France).

For evaluating the local toxicity of various drugs, a special method has been developed using the rabbit cornea, and a patent application based on this approach has been submitted (PV 2009–190).

Differences between UVB and UVA rays in terms of corneal light absorption have been distinguished.

The same doses of UVB or UVA rays were compared (1. 01 J/cm<sup>2</sup> and also UVA at a two-fold larger dose, 2. 02 J/cm<sup>2</sup>). The results showed that UVB rays are strongly absorbed by the cornea, whereas UVA rays are absorbed by the cornea only in small amounts (Čejka et al., 2007, 2008).

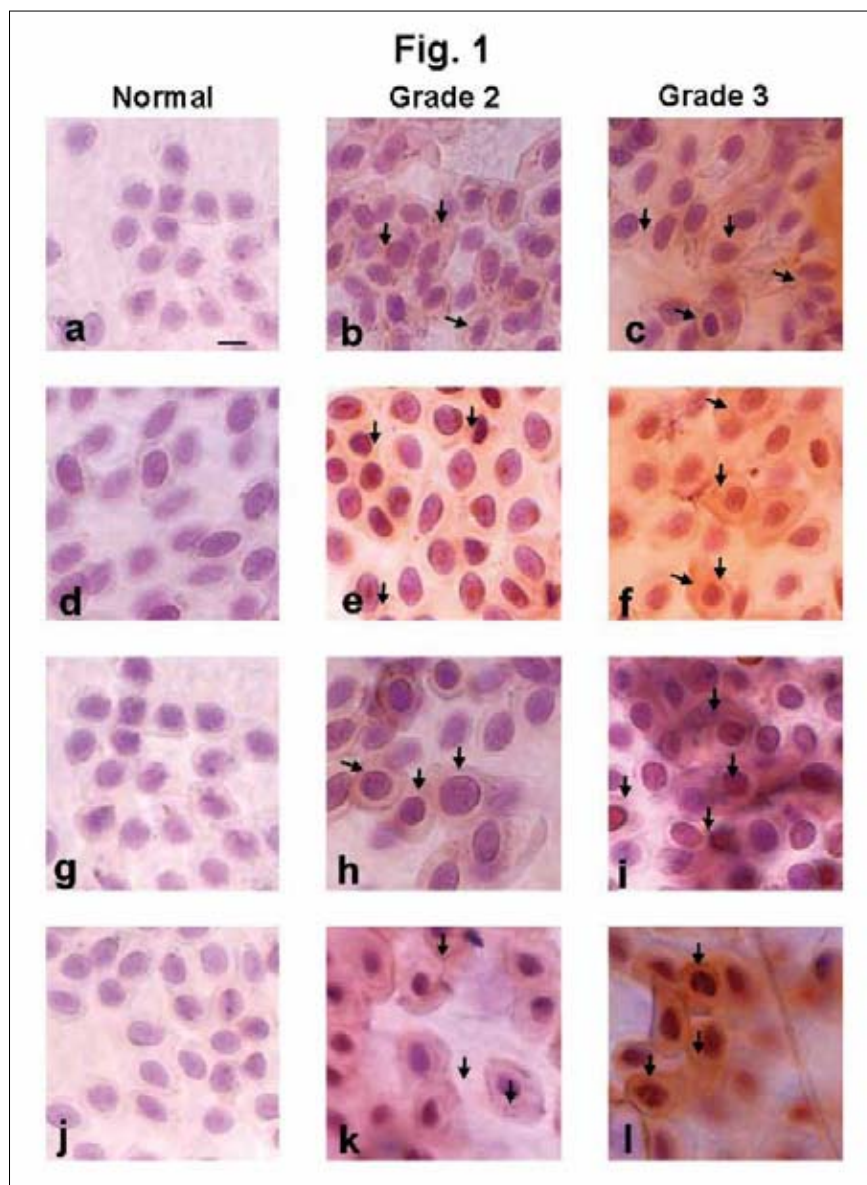
Our recent findings show that in some diseases of the ocular surface (particularly of an autoimmune character), oxidative injuries of the ocular surface appear in parallel with clinically observed



**Spectrophotometry results** of the of the corneal center, expressed either as the spectrum of transmittance  $T = T(\lambda)$  (A) or absorbance  $A = A(\lambda)$  (B). The spectral curves are means from measurements of 14 normal corneas, 7 irradiated with UVA rays (1. 1 J/cm<sup>2</sup>, once a day for 5 days), 6 irradiated with a double dose of UVA (2. 2 J/cm<sup>2</sup>, once a day for 5 days), and 7 irradiated with UVB (1. 1 J/cm<sup>2</sup>, once a day for 5 days). Note that for wavelengths shorter than about 300 nm, the spectra show the instrumental stray light error rather than the corneal optical properties.

The corneas repeatedly irradiated with UVB rays (daily dose of 1. 01 J/cm<sup>2</sup> for five days) absorb more light throughout the whole measurable spectral range than do normal corneas. In contrast, no significant differences between normal corneas and corneas irradiated with UVA rays (daily dose of 1. 01 J/cm<sup>2</sup> or a double dose, for five days) were found (tested at 320, 380, and 550 nm by one-way ANOVA with Dunnett's post-test).





**Immunohistochemical staining of pro-inflammatory cytokines (IL-1, IL-6, IL-8, TNF- $\alpha$ ) in the human conjunctival epithelium of autoimmune dry eye disease (Sjögren's syndrome, SS). Scale bar: 10  $\mu$ m. The severity of pro-inflammatory cytokine expression parallels the severity of the symptoms of dryness and the slit-lamp findings. Normal conjunctival cytology samples revealed no or very weak cytokine staining (mature interleukin-1 $\beta$  (IL-1 $\beta$ ), Fig. 1 a; interleukin 6 (IL-6), Fig. 1 d; interleukin 8 (IL-8), Fig. 1 g; tumor necrosis factor alpha (TNF  $\alpha$ ), Fig. 1 j). Only nuclei were stained with haematoxylin. However, all cytokines studied were already expressed in the conjunctival epithelium of dry eye (SS) grade 2, moderate symptoms of dryness with reversible slit-lamp findings (IL-1 $\beta$ , Fig. 1 b; IL-6, Fig. 1 e; IL-8, Fig. 1 h; TNF- $\alpha$  Fig. 1 k), and their expression increased in the conjunctival epithelium of dry eye (SS) grade 3, severe symptoms of dryness with irreversible slit lamp findings (IL-1  $\beta$  Fig. 1 c; IL-6, Fig. 1 f; IL-8, Fig. 1 i; TNF- $\alpha$ , Fig. 1 l). Arrows point to cytokine expression.**

slit lamp findings. The majority of injuries is evoked by the elevated expression of pro-inflammatory cytokines, which induce the increased expression as well as activity of enzymatic systems that generate reactive oxidative and nitrosative species. In contrast, enzymatic scavengers of toxic oxygen products are decreased (Čejková et al.,

Histol Histopathol. 22,997–1003, 2007; Čejková et al., Nitric Oxide 17, 10–7, 2007; Čejková et al., Histol Histopathol 23,1477–83, 2008, Čejková et al., Histol Histopathol 2009, *in press*).

### CURRENT GRANT SUPPORT

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Ministry of Health, NR/8828–3, New methods for the improvement of diagnostic as well as therapeutic purposes of the human eye with dry eye syndrome, 2006–2008.

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