Glaucoma Research Society *of* Canada

SPECIAL REPORT

2007 RESEARCH GRANTS

THANKS TO OUR DONORS RESEARCHERS RECEIVE MORE THAN $130,000

Dr. Graham Trope, founder of the Glaucoma Research Society and chair of its Scientific Advisory Committee, recently announced the Society's 2007/2008 research grants for the following projects:

- Inhaling Carbon Dioxide and Its Effect on Blood Vessels in the Eye
- Studying The Role of Immune Cells in Retinal Cell Survival
- Using A Molecular Approach to Understand the Cause Of Glaucoma
- Determining the Effect of Anti-Inflammatory Eye Drops following Selective Laser Trabeculosplasty
- Determining if a Vaccine for Multiple Sclerosis Can Prevent Glaucoma Injury to Central Vision
- Comparing Trabeculectomy Techniques
- Studying the Role of CREB in Retinal Ganglion Cell Survival in Glaucoma
- Purchasing a New Microscope to Support Research
- Using Drugs to Neutralize Negative Stress on the Eye
- Investigating the Connection Between a Gene and Glaucoma
- Developing a New Model for Studying Nerve Cell Death after RGMa Treatment
- Discovering Mechanisms that Contribute to Cell Death in Glaucoma
- Studying a Clinical Application for Flicker Defined Form
- Studying the Response of Human Optic Nerve Cells to Different Modes of Mechanical Strain

INHALING CARBON DIOXIDE AND ITS EFFECT ON BLOOD VESSELS IN THE EYE

Some glaucoma patients have unstable or inadequate blood supply to the nerves at the back of the eye. Non-invasive, laser-based optical instruments are used with various stimuli to assess blood flow in the eye.

One of the ways to assess the response of the retinal blood vessels is by inhaling safe amounts of carbon dioxide. Carbon dioxide normally results in widening the blood vessels, increasing blood flow to the eye.

Our study will determine the effect of inhaling carbon dioxide on blood vessels of patients with glaucoma and of age-matched subjects without glaucoma. Preliminary results suggest that the response of the retinal blood vessels in the two groups is distinctly different.
– Dr. Chris Hudson, Dr. John Flanagan, Waterloo, ON

STUDYING THE ROLE OF IMMUNE CELLS IN RETINAL CELL SURVIVAL

Immune cells in the retina protect retinal cells from infection and disease. In animal models of glaucoma, immune cells become activated when retinal cells are lost and it is widely believed that the immune cells secrete toxic substances that worsen the disease.

Our recent research shows that immune cell activation is an early event in the animal model of glaucoma, and that retinal cell death continues even after the immune cells return to their resting state. We hypothesize that immune cells may become activated in an effort to increase retinal cell survival by removing cellular debris and by secreting survival factors.

Our research will determine if immune cell activation is beneficial, or detrimental, to retinal cell survival in glaucoma. We will use drugs to selectively inhibit or activate immune cells in animal models of glaucoma, and measure retinal cell death. Our studies will lead to new glaucoma therapies aimed at controlling the activation of immune cells.
– Dr. Alexander K. Ball, Hamilton ON

Using A Molecular Approach to Understand the Cause of Glaucoma

Mutations in one of the genes associated with glaucoma has been implicated as a risk factor for glaucoma. This mutation in the protein *optineurin* is associated with cellular pathways that are known to be essential for retinal cell survival.

Our recent research used a new molecular approach to decrease *optineurin* levels in retinal cells. Continued research will determine why retinal cells are dependent on this protein for survival. We will reduce *optineurin* levels in retinal ganglion cells and then measure cell survival under stressful conditions that contribute to cell death in glaucoma.

Revealing the role that *optineurin* plays in retinal ganglion cell survival will lead to a better understanding of the cause of primary open angle glaucoma, and new therapies for its treatment.
– Dr. Alexander K. Ball, Hamilton, ON

Determining the Effect of Anti-Inflammatory Eye Drops following Selective Laser Trabeculosplasty

Although the degree of inflammation following laser treatment is often minimal, a short course of anti-inflammatory eye drops is used to decrease side effects of laser-induced intraocular inflammation. However, low-level inflammation may be important to the IOP lowering effect of the laser. This is because the mechanism by which IOP is lowered may involve an inflammatory reaction induced by the laser treatment.

We have designed a multi-surgeon, randomized clinical trial in which patients undergoing laser treatment receive anti-inflammatory drops or a placebo to use following treatment. Comparing the groups will help us understand if anti-inflammatory therapy enhances, or detracts from, the IOP lowering effect of laser treatment.
– Dr. Robert Campbell, Kingston, ON

Determining if a Vaccine for Multiple Sclerosis Can Prevent Glaucoma Injury to Central Vision

Good vision depends on healthy eyes and strong connections to vision centres in the brain. In glaucoma, injured nerve cells in the eye are connected to major vision centres in the brain that can suffer injury too. So protecting nerve cells in both the eye and brain may be more important than previously believed in glaucoma.

A nerve protectant (Cop-1) in the form of a vaccine is used to treat a variety of diseases, including multiple sclerosis. In a glaucoma model, COP-1 helps protect neurons in the eye.

We are looking to see whether vision centres in the brain are also protected by COP-1 in the same glaucoma model. If COP-1 also protects the brain in glaucoma, there may be greater opportunities for potential immune system-based treatments in glaucoma.
– Dr. Neeru Gupta, Dr. Yeni Yücel, Toronto, ON

Comparing Trabeculectomy Techniques

Trabeculectomy is the most common glaucoma operation performed in Canada. This operation involves creating a new drainage system for the eye that allows the fluid in the eye to flow out with less resistance, thereby lowering eye pressure.

Standard trabeculectomy surgery often results in early post-operative eye pressure levels that are too high or too low. Many successful operations stop working as scar tissue forms and stops the flow of fluid out of the eye. Infusing fluid into the eye during surgery may increase safety and provide better outcomes.

We have designed a randomized clinical study to compare trabeculectomy using an infusion system to standard trabeculectomy. We will compare the safety profile of the two techniques, as well as early and long-term surgical success.
– Dr. Robert Campbell, Kingston, ON

Studying the Role of CREB in Retinal Ganglion Cell Survival in Glaucoma

The characteristic visual field changes and loss of vision in glaucoma are caused by the death of retinal ganglion cells (RGCs). Although the primary mechanism of optic nerve damage in glaucoma is not well understood, there is convincing evidence that RGC loss occurs as part of normal growth and development.

The goal of our research is to characterize the role of cyclic AMP response element binding protein (CREB) in a rat model of optic nerve damage induced by chronic elevation of intraocular pressure. We will use a gene therapy approach to selectively activate CREB in RGCs.

Our hypothesis is that selective activation of CREB in RGCs will protect these neurons from ocular hypertension damage. This study will provide insight into the role of CREB in adult RGC survival, and may have implications for the design of neuroprotective strategies involving stable transfer of survival genes to prevent vision loss in glaucoma.

– Dr. Adriana Di Polo, Montreal, QC

Purchasing a New Microscope to Support Research

Our long-standing research program using donor eyes requires extensive use of light and fluorescence microscopy to better understand:

- how the trabecular meshwork functions,
- what goes wrong with this tissue to elevate intraocular pressure, and
- how to treat this tissue to lower intraocular pressure (IOP).

We will use the new microscope to:

- screen trabecular meshwork samples to identify specific components thought to influence IOP. (A dedicated microscope will save significant time and allow more samples to be studied.), and
- determine how substances that could eventually be developed into drugs affect the structure of trabecular meshwork tissue.

– Dr. C. Ross Ethier, Toronto, ON

Using Drugs to Neutralize Negative Stress on the Eye

The eye takes in light and converts it into images. Doing so generates by-products that can be harmful if they are not cleared in healthy ways.

Our study proposes that targeting and neutralizing these by-products may be a way of protecting and rescuing nerve tissue when negative influences overwhelm the eye.

The focus of our research is to examine the ability of a specific drug to prevent, slow and/or reverse the genetically programmed natural history of eye degeneration in mice. The drug, *memantine*, has been used to treat other human degenerative diseases such as Parkinson's Disease and Huntington's Disease. In fact, a major pharmaceutical company has sponsored a large clinical trial looking at the ability of *memantine* to preserve peripheral vision in patients with glaucoma. The results have not yet been released.

Our research may provide further insight into the types of therapies that may be of greatest benefit to patients suffering from progressive, degenerative diseases such as glaucoma.

– Dr. Cindy M.L. Hutnik, London, ON

Investigating the Connection Between a Gene and Glaucoma

Frequently, in glaucoma, the optic nerve degenerates, showing a link between the health of the optic nerve and the disease.

We have recently identified a novel gene that is important for the formation of the retina. Preliminary experiments show that this gene is also important for optic nerve maintenance and that it may represent a significant cause of glaucoma.

Our study will investigate the connection between this gene and glaucoma.

– Dr. Andrew Waskiewicz, Dr. Ordan J. Lehmann, Edmonton, AB

Developing a New Model for Studying Nerve Cell Death after RGMa Treatment

Nerve cells connect the eye to the brain allowing us to see. In glaucoma, these nerve cells progressively die leading to loss of vision.

Our goal is to develop drugs that stop nerve cell death in glaucoma. To do so, we follow two approaches. First, we study the newly discovered protein *RGMa*, which has the potential to prevent nerve cell death and may offer a means to stop vision loss in glaucoma.

Second, we develop an in vitro model that will allow us to study the effect of various drugs on nerve cell death. This model will be a keystone for the discovery of drugs that protect against vision loss.

– Dr. Philippe P. Monnier, Toronto, ON

Discovering Mechanisms that Contribute to Cell Death in Glaucoma

The risk for glaucoma increases with age. Over a lifetime, many tissues are exposed to many sources of cellular and environmental stress. Cells and tissues can effectively survive these challenges. But over time, a lessened ability to respond to the accumulation of cellular damage, contributes to the development of age-related disorders such as glaucoma.

Our research aims to uncover mechanisms that contribute to cell death in glaucoma. We have determined that changes in genes involved in the eyes' responses to stress underlie a genetic form of glaucoma. This suggests that the inability to adequately respond to stress is important in developing glaucoma.

We plan to stimulate stress response pathways in eye-derived cells to prevent their degeneration. Understanding how to control these stress response pathways in the eye may prove to be an important therapeutic intervention point for glaucoma

– Dr. Michael A. Walter and Dr. Fred B. Berry, Edmonton, AB

Studying a Clinical Application for Flicker Defined Form

Flicker defined form (FDF) has been shown to be useful for detecting early glaucoma. Preliminary results show test-retest characteristics that are superior to existing perimetry tests. This suggests that the approach may be useful for monitoring disease progression.

Our research aims to:

- continue investigating the mechanisms responsible for the FDF illusion,
- identify the cortical regions responsible for the FDF illusion using functional MRI,
- instigate a prospective clinical trial of FDF perimetry in patients with glaucoma, and
- continue investigating manipulations of FDF stimulus configurations to optimize monitoring of moderate to late stage glaucomatous visual function loss.

– Dr. John G. Flanagan, Waterloo, ON

Studying the Response of Human Optic Nerve Cells to Different Modes of Mechanical Strain

Mechanisms proposed to explain the development of optic nerve damage in glaucoma, include the effects of mechanical stress at the level of the lamina cribrosa (LC) and insufficient vascular perfusion of the LC.

We have developed a unique system, using post-mortem human eyes, that allows us to measure IOP-induced changes in optic nerve head (ONH) topography, and to then morphometrically analyze the underlying LC. We have used this system to investigate the biomechanical properties of the ONH using finite element modelling, in order to better understand the mechanical environment experienced by astrocytes and nerve fibres at the level of the LC.

The specific aims of our research are focussed towards developing models that will improve the understanding of how biomechanical factors affect the initiation and progression of glaucomatous optic neuropathy.

– Dr. John Flanagan , Waterloo, ON