Glaucoma Research Society *of* Canada

SPECIAL REPORT

2006 RESEARCH GRANTS

THANKS TO OUR DONORS RESEARCHERS RECEIVE MORE THAN $120,000

Dr. Graham Trope, founder of the Glaucoma Research Society and chair of its Scientific Advisory Committee, recently announced the Society's 2006/2007 research grants for:

- Determining important risk factors for falls and motor vehicle crashes in glaucoma patients
- Transplanting stem cells in the eye to discover new therapies for glaucoma patients
- Comparing Heidelberg Retina Tomography II to stereophotography in monitoring glaucoma
- Evaluating if a partial stroke to vision centres of the brain produces optic nerve damage without elevated eye pressure
- Using imaging technology to determine how ocular fluid moves in the eye.
- Constructing new lab equipment to continue experiments on intraocular pressure control mechanisms
- Improving patients' use of eye drops to treat glaucoma
- Developing a clinical application for flicker defined form
- Determining the effect on blood vessels in the eye from breathing safe amounts of carbon dioxide
- Studying the effect of Selective Laser Trabeculoplasty on intraocular pressure in patients with primary open angle glaucoma
- Developing a test to see if alterations in the newly proposed glaucoma gene cause glaucoma
- Showing how proteins interact to promote retinal nerve cell survival after optic nerve transection.

DETERMINING IMPORTANT RISK FACTORS FOR FALLS AND MOTOR VEHICLE CRASHES IN GLAUCOMA PATIENTS

Glaucoma affects mobility and driving. Previous studies have shown that glaucoma may be associated with an increased risk for falls and motor vehicle crashes causing injury, hospitalisation, reduced quality of life and considerable economic burden.

Our study will determine the most important risk factors for falls and motor vehicle crashes in patients with glaucoma so that prevention strategies may be developed and quality of life maintained.

In this ongoing study, we will ask patients to report falls, motor vehicle crashes and driving habits.Vision tests and questionnaires will be used to investigate underlying risk factors. For example, we will evaluate visual fields, letter acuity, contrast vision, depth perception, type of spectacles, type of glaucoma medication and optic nerve head damage. We will also take into account general health and independence in daily living.
– Dr. Balwantray Chauhan, Dr. Sharon Haymes, Halifax, NS

TRANSPLANTING STEM CELLS IN THE EYE TO DISCOVER NEW THERAPIES

One of the hallmarks of glaucoma is loss of function of some of the key cells in the visual system in the eye. This project uses a rodent model of experimental glaucoma to study the effect of transplanting rodent stem cells into the eye. It is important to study this transplantation in glaucomatous (as opposed to normal) eyes because stem cells implant and function better in tissues that have undergone damage.

The objective is to replace the non-functioning or absent cells with new active cells and to reverse some of the loss of ocular function that has occurred in glaucoma. Following transplantation, the presence and location of the stem cells will be localized in the eye using highly specific markers, and the function of the eye will be measured experimentally. We hope that this stem cell approach will lead to new therapies for glaucoma patients. ***– Dr. Mark Lesk, Montreal, QC***

Comparing Heidelberg Retina Tomography II to stereophotography in monitoring glaucoma

Glaucoma can cause changes to the optic nerve several years before changes in vision are noticed. Since changes to the optic nerve and other eye structures due to glaucoma are irreversible, it is important to develop tools for detecting changes as early as possible.

The Heidelberg Retina Tomograph (HRT) is a device used to produce a 3D map of the optic nerve and retina. It can be used to detect changes in the optic nerve and retina over time. Previous studies have shown it to be useful for detecting changes due to glaucoma. However, HRT only somewhat agrees with other techniques to evaluate the optic nerve such as stereophotography .

Our study will compare HRT to stereophotography to determine how good each one is at seeing and documenting changes in the optic nerve over time due to glaucoma. We need to know how well HRT predicts visual loss in order to start eye drops early or to change medication management.

The results of this study will lead to better follow-up of people with changes in the optic nerve and retina, and to early and more appropriate and individualized treatments. Early treatment is crucial for preventing further visual loss in patients with glaucoma or ocular hypertension (high pressure inside the eye).

– Dr. Yvonne Buys, Dr. Dimitrios Kourkoutas, Toronto, ON

Evaluating if a partial stroke to vision centres of the brain produces optic nerve damage without elevated eye pressure

Reduced blood supply to vision centres in the brain may cause nerve damage that spreads backward to connected retinal nerve cells in the eye, mimicking low tension glaucoma.

Glaucoma is often associated with elevated eye pressure and damage to the eye and optic nerve. However in one sixth of all cases, pressure in the eye is normal. The cause of cell injury in low tension glaucoma is currently unknown. We suspect that poor blood supply leads to episodes of stroke in the vision centres of the brain. This in turn damages the connected fibres of the nerve cells in the eye. This may be one cause for glaucoma without elevated eye pressure, or low tension glaucoma.

In our study, we will evaluate whether partial stroke to vision centres of the brain produces optic nerve damage without elevated eye pressure, as a model of low tension glaucoma. This study will help clarify mechanisms responsible for injury to nerve cells following partial stroke to vision centres of the brain. This rodent model may help shape future treatment strategies to prevent blindness in patients with low tension glaucoma.

– Dr. Yeni Yücel, Toronto, ON

Using imaging technology to determine how ocular fluid moves in the eye

Advanced mathematics, especially computational fluid dynamics (CFD), has enjoyed an increasingly important role in medicine as computers have become more affordable over recent years. Although most work has focused on blood flow in the heart, brain, and other key parts of the body's plumbing where disease is likely to strike, there is growing excitement among scientists to model fluid flow in the human eye. The eye makes and drains liquids continuously, has its own system of dams and currents, and of course, has its own set of diseases where the flow of fluid is important.

Since there are few medical problems as closely related to fluid flow as glaucoma, researchers who study this disease are particularly enthusiastic about the role that computer modeling can play in their work. Our research team will use the latest in imaging technology to gain what may be one of the most accurate characterizations to date of fluid flow in the eye.

The data we gather will be used to create accurate and flexible computer simulations of how ocular fluid moves and model drug delivery. This work can easily grow to encompass possible mechanisms by which glaucoma occurs and to suggest novel interventions.

We think in the future every patient will have advanced fluid dynamics modeling of their eyes so doctors can optimize care. Both medication and surgery will be integrated with mathematical precision to produce the best outcome possible for vision.

Our team is fortunate in having expertise from medicine and surgery, engineering and mathematics, as well as genetics and biology. All of these different skill sets are integrated into the modeling of what is a very complicated disease.

– Dr. Cindy Hutnik, London, ON

Constructing new lab equipment to continue experiments on intraocular pressure control mechanisms

In many patients with glaucoma, the intraocular pressure (IOP) is elevated above its normal value of 15 mmHg. In all glaucoma patients, the therapeutic goal is to lower IOP to a "safe" level (i.e. one at which vision is preserved). But what controls the pressure in the eye, and why is it elevated in many glaucoma patients? We know that elevated pressure occurs when the normal drainage of the aqueous humor out of the eye is impaired, but further details are elusive despite many years of research.

To unlock the secrets of how the eye controls pressure, and to screen novel pressure control medications, we need to be able to accurately measure IOP. For some types of studies, the best way to do this is to use isolated eyes, obtained either at autopsy or from animals. In these cases, the eye is "perfused" by infusing a substitute aqueous humor fluid into the eye and measuring the resulting pressure. In fact, this technique has been a mainstay of glaucoma research for more than 50 years.

It turns out that "perfusing" is hard to do: the flow rates are miniscule and the pressures are not easy to measure. This technique therefore requires specialized equipment, available in only a few labs worldwide. One such piece of equipment has been in use in my lab for almost 20 years, and is now at the end of its useful life. GRSC funding has enabled construction of a newer piece of equipment, so that experiments designed to better understand IOP control mechanisms in human eyes can continue. ***– Dr. C. Ross Ethier, Toronto, ON***

Improving patients' use of eye drops to treat glaucoma

Effective medication administration and compliance with treatment are vital and often overlooked factors in the delivery of glaucoma medications and the prevention of vision loss. But patients continue to have problems with managing their glaucoma. Our research will estimate the prevalence of, and risk factors associated with, non-compliance and ineffective medication administration in the treatment of glaucoma.

116 subjects on chronic glaucoma therapy without recent surgery were enrolled in the first stage of this study:

- 3.5% of subjects missed their eye completely when attempting to instill medication;
- 52% touched the bottle tip to their eye or eye lids while administering medication;
- 24% reported having been shown how to administer drops by their pharmacist; and
- 30% reported non-compliance.

Age, severity of visual field loss, disease stability and number of medications taken were not predictive of non-compliance or bottle contamination. We will continue to explore new avenues for addressing these problems. ***– Dr. Yvonne Buys, Dr. Robert J. Campbell, Toronto, ON***

Developing a clinical application for flicker defined form

There are two major pathways involved in processing visual information in humans: the magnocellular and the parvocellular processing streams. The magnocellular stream is primarily involved in processing low contrast and flicker information that dominates our peripheral vision. The parvocellular stream is mainly concerned with the fine detail and colour processing that dominates in central vision. There are about 0.15 million magnocellular projecting visual neurones in the eye compared to 1.2 million parvocellular projecting neurons.

Flicker Defined Form (FDF) is a visual stimulus generated using illusory contours. It has been shown to possess characteristics of the magnocellular visual pathway. These characteristics include:

- resistance to blur;
- improved visibility in peripheral vision; and
- being processed primarily in the temporal (or flicker) domain.

Research is underway to determine whether this stimulus can be useful in the early detection of visual damage caused by glaucoma.

Perimetry, or visual field testing, is used to examine visual function. It uses a simple target to which most of the visual system responds. FDF is believed to preferentially test the magnocellular system and may therefore detect damage earlier than standard techniques. It is easier to detect 100 dysfunctional cells in a population of 1,000 compared to detecting 100 dysfunctional cells in a population of 100,000.

The need for this type of test is highlighted by knowing that as many as 40% of the visual neurones can be lost before standard visual field tests detect a defect.
– Dr. John G. Flanagan, Dr. Patrick Quaid, Waterloo, ON

Determining the effect on blood vessels in the eye from breathing safe amounts of carbon dioxide

Some glaucoma patients may have an unstable, or inadequate, blood supply to the nerves at the back of the eye (i.e. the retina) that carry the signals that mediate vision. Assessing blood flow in the retina of human volunteers requires the use of non-invasive, laser-based optical instruments. In the past, the response of the blood vessels at the back of the eye was assessed using various stimuli to induce retinal vessel narrowing or widening.

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 flow of blood to the retina.

Our study will determine the effect of breathing safe amounts of 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 of glaucoma patients is distinctly different to that of age-matched subjects without glaucoma.
– Dr. Chris Hudson, Dr. John Flanagan, Waterloo, ON

Studying the effect of Selective Laser Trabeculoplasty (SLT) on intraocular pressure (IOP) in patients with primary open angle glaucoma

A number of studies have shown that SLT lowers IOP effectively in many patients with primary open angle glaucoma (POAG), but we don't know if SLT reduces IOP fluctuation. Fluctuation may adversely affect the health of the optic nerve in POAG patients.

We intend to study 24 patients with POAG who have not received glaucoma medical or laser treatment. We will measure the IOP before laser treatment at 8 am, 11 am, 2 pm and 5 pm on 2 separate visits one week apart. Patients will then receive SLT treatment and have the same IOP measurements repeated 3 and 6 months after treatment.

We hope to reduce daily IOP range, 6 months after treatment and show that SLT can reduce IOP fluctuation. ***– Dr. Karim Damji, Ottawa, ON***

Developing a test to see if alterations in the newly proposed glaucoma gene cause glaucoma

The WD40 repeat 36 (WDR36) gene has recently been proposed as a new primary open angle glaucoma locus. The function of WDR36 and its role in glaucoma are unknown. While a number of possible mutations of the gene have been found, proof that these alterations actually impair WDR36 function awaits demonstration.

Our recent efforts have revealed that WDR36 is similar in its 3D shape to a yeast gene UTP21. We will use this information to develop a test in yeast cells to determine if alterations of WDR36 are mutations or rare, non-disease-associated polymorphisms.

These experiments will result in a test for WDR36 mutations to determine:

- if sequence alterations found in patients are likely to cause glaucoma;
- if WDR36 functions like UTP21; and
- if disruption of the rRNA pathway could lead to glaucoma.

This information would make other proteins in the pathway potential glaucoma genes and would indicate a new cellular pathway to investigate to develop new glaucoma therapies.***– Dr. Michael A. Walter, Edmonton, AB***

Showing how proteins interact to promote retinal nerve cell survival after optic nerve transection

Glaucoma can be viewed as a neurodegenerative disease in which retina nerve cells die. These nerve cells carry signals from the retina to the brain, and their loss results in blindness.

A therapeutic approach to treat glaucoma would be to promote the survival of retinal nerve cells. We identified a new protein, RGMa, that promotes retinal cell survival when the connection to the brain has been damaged.

In our study, we will demonstrate that RGMa promotes retinal cell survival by interacting with the protein Neogenin. We will also try to understand how the retinal cells process the RGMa signal and finally survive better. ***– Dr. Phillippe P. Monnier, Toronto, ON***