Annual report prepared for Retina Australia

For the Retina Australia Grant received in 2006
Project: "***Photoreceptor degeneration in retinitis pigmentosa***"

Investigators: Professor Michael Kalloniatis[1] Dr Monica Acosta[1], Dr Keely Bumsted O'Brien[1], Dr Brendan O'Brien[1] and Dr Erica Fletcher[2]

[1]*Department of Optometry and Vision Science, University of Auckland, Auckland, New Zealand*
[2]*Department of Anatomy and Cell Biology, University of Melbourne, Parkville 3010, Australia*

The grant from Retina Australia was in support of our Health Research Council of New Zealand grant. The grant has several aims focusing on understanding cell death in normal and an animal model of Retinitis Pigmentosa (P23H) rat. The generous support from Retina Australia for this work is greatly appreciated.

Our second year of this grant was very productive in that a number of studies characterising cell death in normal and an animal model of retinal degeneration (RD) were completed. We have also completed the pharmacological studies on normal and retinal degeneration rats and are finalizing our neurochemical results in preparation for publication. The major theme and findings are as follows:

- In order to understand the changes that occur in both normal and animal models of RD, we have mapped out both the neurochemical and functional architecture in normal and RD models. This is important not only for understanding normal neuronal development but to understand the changes in retinal disease.
    - In the normal developing mouse retina, we have identified the ages when cells communicate with each other using a range of chemicals (neurotransmitters). This work has laid the foundations to understanding the changes in the anomalous retina and was published early 2007 (Acosta et al., 2007).
- In RD retinas, the degeneration causes structural (anatomical) and chemical (neurochemical) remodeling. These changes mean that in adult or advanced retinal degeneration, the retina is reshaped both in terms of its anatomical structure but also by its chemical composition making intervention using cell transplants or implants difficult. Although the anatomical changes have been well characterized, we have now characterized the chemical changes (neurochemical communication between cells). In other words, we have mapped out the way cells in the RD retinas communicate by identifying the unique neurotransmitter receptors in different subpopulations of retinal cells. If the appropriate receptors are not expressed, it would be impossible for cells to communicate with each other, particularly if intervention measures are undertaken such as cell transplant or gene therapy.
    - We have found that the retina in an animal model of retinal degeneration (rd/rd mouse) that cells display unique loss of cell types and neurochemical development and neurochemical receptor expression early in degeneration

(Chua et al. submitted). This finding has major implications to potential intervention measures. We have discovered a 'critical' period where intervention is possible, ie, during which cell receptor expression is still pliable and can be modified. After this period, ie, in advanced RD, the changes in anatomy and also in chemical communication may render the retina difficult to modify.

- One of the ways retinal degeneration can be accelerated is via excessive light damage. We have investigated this in normal and an animal model of RD, the P23H rat with the focus being to characterize the mechanism of cell death (Yu et al., 2007).
    - We have found that photoreceptor cell death occurs via two mechanisms: one involving excessive entry of ions into the cells (unregulated ion flow) and the second through the process of 'programmed cell death' or 'apoptosis'. This finding suggests that therapeutic strategies directed towards slowing down cell death have to be directed to both controlling ion flow into the cells and also through the control of the apoptotic pathway.
- Finally, in collaboration with Dr Fletcher (Uni of Melb), we have pharmacologically intervened in our RD model and delayed the degeneration. We are still analyzing these results and more will be reported next year when our analysis is complete.

In summary, we have identified the time course over which intervention is viable in retinal degeneration and have also modified the progression of the degeneration by light exposure (accelerating photoreceptor death) or slowed photoreceptor death (pharmacological intervention).

Articles (peer reviewed journal)

YU TY, ACOSTA ML, READY S, CHEONG YL, KALLONIATIS M. 2007 Light exposure causes functional changes in the retina: increased photoreceptors cation channel permeability, photoreceptor apoptosis and altered retinal metabolic function.. JOURNAL OF NEUROCHEMISTRY. 103: 714–724 Impact factor = 4.6500

ACOSTA ML, CHUA J, KALLONIATIS M. 2007 Functional activation of glutamate ionotropic receptors in the developing mouse retina. JOURNAL OF COMPARATIVE NEUROLOGY. 500(5) : 923-941 Impact factor = 3.4700

CHUA J, FLETCHER EL, KALLONIATIS M. 2008. Functional remodeling of glutamate receptors by inner retinal neurons occurs from an early stage of retinal degeneration. JOURNAL OF COMPARATIVE NEUROLOGY. (SUBMITTED) Impact factor = 3.4700

Michael Kalloniatis (on behalf of all the investigators)