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Lay Report to Retina Australia

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During 2004, we pursued two projects related to retinal degenerations, both funded by the National Health and Medical Research Council. Funding provided by Retina Australia strengthened both projects, but particularly the project *Molecular mechanisms of photoreceptor protection in rat models of degenerative retinal disease,* which ran from 2002-4.

Our scientific results from this project were published in 10 papers and reviews. Some of our finding concerned the biology of the retina – how the retina protects itself by expression 'trophic' factors, where those factors act and which cells express them. We also studied how these factors affect the function of the retina, showing that although they protect retinal cells they also suppress their responsiveness to light. Also at the scientific level we showed the early involvement of metabolic mechanisms in the death of photoreceptors. Perhaps the most important of our findings in this period was evidence that the loss of vision caused by retinal degenerations results only partly from the death of retinal cells, which is irreversible. Much of the loss of vision results from damage to the surviving cells, and is reversible. For the first time, still using animal models, which showed that visual performance can be restored to the degenerating retina, simply by managing the overall exposure to light. These findings were reported to Retina Australia at its 2004 meeting and are now published or being prepared for publication. We are currently extending this work, exploring other ways of restoring function to the retina, by manipulation of light and by a quite new approach (not part of this project) using near-infrared radiation.

For many years it has been assumed that the loss of vision in RP is caused by the death of photoreceptor cells of the retina, and was therefore irreversible without a major intervention, like transplantation. Our work raises the possibility of partial restoration of vision loss, by management of the exposure of the retina/patient to light, and to oxygen and perhaps by other techniques, such as infra-red radiation.

Publications:

1. Valter K, Bisti S, Gargini C, Di Loreto S, Maccarone R, Cervetto L, Stone J. Timecourse Of Neurotrophic Factor Upregulation Following Unilateral Optic Nerve Section. *Invest Ophthal Vis Sci*. 2005;in press.
2. Stone J, Sandercoe TM, Provis J. Mechanisms of the Formation and Stability of Retinal Blood Vessels. In: Tombran-Tink J, Barnstable C, eds. *Ocular Angiogenesis: Diseases, Mechanisms and Therapeutics*. Totowa, NJ: Humana Press; 2005. In press
3. Yu DY, Cringle S, Valter K, Walsh N, Lee D, Stone J. Photoreceptor death, trophic factor expression, retinal oxygen status, and photoreceptor function in the P23H rat. *Invest Ophthalmol Vis Sci*. 2004;45:2013-2019.
4. Walsh N, Van Driel D, Lee D, Stone J. Multiple vulnerability of photoreceptors to mesopic ambient light in the P23H transgenic rat. *Brain Res*. 2004;1013:194-203.
5. Stone J, Mervin K, Walsh N, Valter K, Provis J, Penfold P. Photoreceptor stability and degeneration in mammalian retina: lessons from the edge. In: Penfold P, Provis J, eds. *Macular Degeneration: Science and Medicine in Practice*: Springer Verlag; 2004:149-165.

6. Gargini C, Bisti S, Demontis G, Valter K, Stone J, Cervetto L. ERG changes associated with retinal upregulation of trophic factors: observations following optic nerve section. *Neuroscience*. 2004;126:775-783.
7. Bravo-Nuevo A, Walsh N, Stone J. Photoreceptor degeneration and loss of retinal function in the C57BL/6-C(2J) mouse. *Invest Ophthalmol Vis Sci*. 2004;45:2005-12.
8. Geller SF, Stone J. Quantitative PCR analysis of FosB mRNA expression after short duration oxygen and light stress. *Adv Exp Med Biol*. 2003;533:249-57.
9. Bravo-Nuevo A, Williams N, Geller S, Stone J. Mitochondrial deletions in normal and degenerating rat retina. *Adv Exp Med Biol*. 2003;533:241-8.
10. Valter K, Driel DV, Bisti S, Stone JS. FGFR1 Expression and FGFR1-FGF-2 Colocalisation in Rat Retina: Sites of FGF-2 on Rat Photoreceptors. *Growth Factors*. 2002;20:177-188.

In a second project *Oxygen toxicity as a factor in retinal degenerations: genetic and environmental mechanisms* (CI J. Stone), which runs from 2004 to 2006, we are studying the role of oxygen in the retinal degenerations. In 3 papers published so far we have shown that oxygen can be specifically toxic to photoreceptors, raising the possibility that oxygen management can slow degenerations. Many follow-up studies are now underway.

Published so far:

11. Lee D, Valter K, **Stone** J. Photoreceptors in the rat retina are specifically vulnerable to both hypoxia and hyperoxia. *Visual Neuroscience*. 2005; In press.
12. Geller S, Krowka R, Valter K, **Stone** J. Toxicity of hyperoxia to the retina: evidence from the mouse. *RD 2004*. 2005; In press.
13. Walsh N, Bravo-Nuevo A, Geller S, **Stone** J. Resistance of photoreceptors in the C57BL/6-c2J, C57BL/6J, and BALBB/cj mouse strains to oxygen stress: Evidence of an oxygen phenotype. *Current Eye Research*. 2004;29:441-448

We are very excited about the basic scientific findings concerning the retina, but particularly about the clinical possibilities of the use of light restriction in extending the functioning life of the degenerating retina, and to restore function partially to the retina suffering degeneration. These findings have been made in rat models, and will now be developed to a stage where they can be tested in humans.

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Support from Retina Australia enabled us to begin our work with retinal degenerations last decade, to gain the NHMRC grants on retinal degenerations we have maintained for nearly a decade, and to make the progress reported above.