RECENT DEVELOPMENTS IN RETINAL DEGENERATION.

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There have been considerable advances in our knowledge of the pathogenesis of inherited retinal degenerations over the last five years that have lead to the development of some very promising treatments. Below, we have summarized some of our own findings examining new animal models of inherited retinal degeneration, ways to slow photoreceptor death and also novel ways of replacing lost photoreceptors.

i) New animal models: Most research into the mechanisms of photoreceptor death have utilized animal models that carry mutations in rod associated proteins (e.g., rhdopsin). Whilst this work has been very important, it has little relevance to some of the rarer forms of retinal degeneration such as Leber Congenital Amaurosis. Recently, we have identified a novel mouse that replicates many of the features of one form of Leber Congenital Amaurosis. This mouse called the Histidine decarboxylase null mouse develops severe changes in the outer retina because the support cells of the retina lack proteins that maintain the correct position of the rods and cones. These mice will be used by us now to study some of the rarer forms of retinal degeneration.

ii) Slowing photoreceptor death: much of our work over the last few years has been directed at examining whether dying rods release a toxic factor that effects neighbouring photoreceptors. Our work has shown that the energy molecule, ATP is released in large amounts from dying rods and accelerates the death of neighbouring cells. We have tested two drugs known to block the action of ATP, and shown them to slow photoreceptor death in a mouse model of retinal degeneration. In addition, we have found that the rate of photoreceptor death is slowed in transgenic mice that lack the expression of the receptor to ATP. Agents that block the action of ATP are under development by large pharmaceutical companies because of their potential role in controlling some forms of pain. We hope our work expands the possible uses of these compounds into the ophthalmic area.

iii) Novel ways of replacing lost photoreceptors: The two most exciting developments to restore vision in those who have few photoreceptors remaining are the development of electronic implants, and the use of gene therapy to target visual pigments to the remaining neurons of the inner retina. There are currently two large groups in Australia developing electronic implants to restore vision. One group is designing retinal implants: a wide-field device that sits underneath the retina, and another high visual acuity device that is designed to target the output neurons of the retina. It is hoped that trials for the wide view device in patients will begin in the next year. The high visual acuity device is currently undergoing preclinical testing. A second group, based at Monash University is designing an implant to be inserted into the visual area of the brain. This device, is intended to restore vision in those who have no remaining ganglion cells or an intact optic nerve. Currently this device is undergoing extensive preclinical development.

Gene therapy has been used to target visual pigment to inner retinal neurons. The inner retina of those with inherited retinal degeneration is usually intact. By using gene therapy, inner retinal neurons can become light sensitive, performing the duties of photoreceptors. These studies are very exciting because the technology can be used in most patients with inherited retinal degeneration irrespective of the specific genetic cause of the disease.

In summary, over the last few years our knowledge of inherited retinal degeneration has increased dramatically, to the point where treatments are now being tested in patients, with exciting results.