



RETINA SOUTH AFRICA
Fighting Blindness

RETINA E-News

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Seeking a cure for Retinitis Pigmentosa, Macular Degeneration and allied Retinal Dystrophies

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Reader's competition...

RETINA E-NEWS to YOU

WORLD RETINA WEEK- 21ST TO 27TH SEPTEMBER

Novartis South Africa is partnering with Retina South Africa to create awareness of Age Related Macular Degeneration (AMD) during this global event. Our theme is: **IMPROVING VISION - RETURNING HOPE**. We are highlighting the fact that conditions such as Wet AMD are Now Treatable [Lucentis] and that other treatments will soon follow. You can help to create awareness in your area by hanging posters and distributing pamphlets. Contact your Retina branch for supplies.

Retina South Africa, Novartis and the AMD alliance care about your vision. We want you to take this important eye test for macular degeneration and pass it on to family and friends. Remember that the **FIRST EFFECTIVE TREATMENT** for AMD is now available in South Africa but urgent intervention is necessary for successful treatment.

Click on the link below to begin.

<http://www.testyourvisionforamd.com/rpsa.php>

IntelliPen COMPETITION and SPECIAL OFFER



IntelliPen is a new and innovative way to improve communication for partially sighted people. The pen digitally captures handwriting, drawings and sketches on any type of paper. You can then store this on the USB Flash drive and upload the information onto your PC. Your notes can then be converted to text and then to a

Word document, and edited or e-mailed. The pen can be used anywhere - at meetings, in the classroom, in lectures. IntelliPen are giving Readers of the Retina E-News a special discount of 20% off the retail price of R1,599 and will also make a donation of R50 per unit sold to Retinal Research. They are also donating a free pen for the prize in a competition to celebrate World Retina Week.

Q: What conversion software does IntelliPen include in the purchase price? See www.intellipen.co.za for a clue. Orders and competition entries by email to: national@rpsa.org.za or fax to 011 622 6277.

Include your full name, contact number and eMail address.

They are also suppliers of LiveScribe which uses a special paper with inbuilt icons. See www.livescribe.co.za. A 15% discount on the purchase price of R2,499 [1GB] and R2,799 for the 2GB LiveScribe is also being offered. Discount is only available on orders via Retina South Africa.

UPDATE ON RETINAL RESEARCH

The 12TH Annual Vision Conference – ARVO, was held in Florida, USA in May 2009. This update was extracted from a report prepared for Retina International by Dr Elaine Richman. For a copy of Dr Richman's entire report please contact Retina South Africa (national@rpsa.org.za) - ED.

GENE REPLACEMENT CLINICAL TRIALS

LCA - RPE65 Gene Therapy – Dr. A. Cideciyan, University of Pennsylvania, Philadelphia, USA.

A Phase I clinical trial began in 2007 in LCA patients with the RPE65 gene mutation. The trial is led by Dr. Samuel Jacobson and vector virus to deliver the gene is made at the University of Florida under the leadership of Drs. William Hauswirth and Barry Bryne. The primary outcome of the trial is safety; secondary outcomes include changes in vision. The trial was initially planned for 3 groups of patients, each with three patients. The first group consisted of 3 young adults aged between 21 and 24 years. These patients received injections of the vector with the normal RPE65 gene underneath the retina in one eye. The results after the first 90 days post-treatment have been published and were encouraging. Safety: There were no vector-related Serious Adverse Events (SAEs) and no toxic effects. All patients said they had an increase in visual sensitivity in their treated study eye compared with their control eye. This was especially noticeable under reduced ambient light conditions. Using a full-field stimulus test under dark-adapted conditions, the study eye showed significant sensitivity increases. Specialized testing corroborated that there were significant improvements in sensitivity localized to the area of treatment in the injected eye. The gene therapy procedure improved both day vision [cone photoreceptors] as well as night vision [rod photoreceptors] of the LCA patients. Day vision could be improved up to 50-fold and night vision up to 63,000-fold compared to pretreatment levels.

NEWS FLASH – Here is an unexpected bonus result – ED.

An article just published in the New England Journal of Medicine describes the brain's ability to find new ways of processing visual information. A patient who received the gene therapy 12 months before was able to read a digital clock from the back seat of her parent's car- something she was never able to do before. Testing revealed that she was using 2 different centres of vision – depending on the brightness of the object. Her treated retina must have acquired

enough image processing strength to rival the retina's normal centre for visual perception- the fovea. The discovery suggests that even in adults with mature visual circuitry the brain can find new ways to process optical information.

CHOP Trial on LCA - RPE65 Gene Therapy – Dr. J. Bennett, University of Pennsylvania, Philadelphia, USA

Dr. Bennett reported that at the Children's Hospital of Philadelphia (CHOP) as well as in Naples, Italy and Ghent, Belgium, the trial to investigate the RPE65 gene replacement in LCA subjects continues.

The trial started in October of 2007 and 10 additional individuals have received injections. The first 3 patients enrolled in Naples, Italy are young adults (19-26 yrs) and are now 15 months post-injection. They continue to do well in both safety and efficacy. Individuals enrolled over the last year include 4 children. All have recovered visual function with improvement in their Nystagmus. *They are reading without assistive devices.* All the patients are happy with the results and are asking to have their second eye injected.

MORE CLUES TO ROD AND CONE SURVIVAL IN RP

In Retinitis Pigmentosa [RP] gene mutations cause the death of Rod photoreceptors. Later in the disease the cone photoreceptors are also affected. Here is a review of 3 groups investigating this process: Dr Connie Cepko from Harvard Medical College and her colleagues are studying a mouse model of RP. Their findings suggest that part of the answer might relate to a protein called HDAC4. Supplementation of this protein extends rod and cone cell survival. They also found a possible relationship between cone death and decreased activity of an insulin signaling pathway. These findings could lead to the development of therapies for RP.

Dr Claudio Punzo also from Harvard Medical School believes that Cone photoreceptor cell death in RP is caused by "starvation". They are studying various mice models with Rod photoreceptor cell death and also found that cone death was associated with the Insulin pathway. Insulin is used to transport the nutrient glucose into cells and additional insulin led to cone survival. They also suggest that the Retinal Pigment Epithelial [RPE] layer – the source of nutrients for the photoreceptors is involved in the process. The researchers DO NOT suggest extra insulin as a treatment for RP but hope that this study will lead to further exploration of the starvation theory.

Treating Oxidative Stress

Dr Jose-Alain Sahel of INSERM is investigating the protein RDCF that increases cone survival in rodent models of RP. This Rod Derived Cone Factor is a growth factor and appears to be involved in the defense against oxidative stress. When the protein was delivered by an injection into the retina of rodent models of RP the retinas showed improved cone survival and better amplitude in electrical activity. The growth factor could also be delivered via a protein producing gene delivered to the retina via an adeno - associated virus – the same system used for the gene replacement therapy described above.

OXIDATIVE DAMAGE IN ROD AND CONE DEATH IN RP

Rods in the retina use a lot of oxygen. When they die in RP, the amount of oxygen in other portions of the retina goes up and causes oxidative damage to cones. It would make sense, therefore, that treatment with anti-oxidants would spare the cones. The logic of this approach is what Dr Peter Campochiaro of Johns Hopkins University described in animal models of RP. The researchers are examining various drugs for reducing oxidative damage. They are also looking at gene therapies to improve patients' own anti-oxidant resources for prolonging cone survival.

RETINA COMPLEX- CLINICAL STUDY IN RP PATIENTS

Drs. Javier Romero and Theo van Veen, University CEU Cardenal Herrera and Mediterranean Ophthalmology Foundation, Valencia, Spain and University of Tuebingen, Tuebingen, Germany.

Anti-oxidants for RD DO work!

Previous work by Prof. van Veen established the efficacy of using a combination of antioxidants called Retina Complex in slowing the degeneration in animal models of RP. Professor van Veen reported on the current clinical patient study. This is a randomized double-blind study being performed in Spain. 23 Patients received Retina Complex and 21 patients received a placebo for 12 months. In the placebo group the Multi focal ERG readings taken at the beginning of the study showed a statistically significant difference to those taken at the end of the 12 month period. Patients receiving Retina Complex showed no statistically significant difference between the two sets of data. This confirms that there is a SLOWER progression of disease in the treated subjects compared with those getting only placebo. Plans to extend the study to 2 years are underway.

- Retina Plus, a comparable product is available in South Africa – ED.

Stem Cell Update...

RETINAL PROGENITOR CELLS TO REPLACE PR CELLS

Research continues into ways to replace photoreceptor [PR] cells using retinal progenitor cells in Retinal degeneration. It has been shown in animal studies that transplanted retinal progenitor cells (RPCs) from fetal, newborn, or adult animals are capable of migrating throughout the degenerating retina, becoming nerve cells, integrating into the retina and circuitry of the central nervous system, and even responding to light. The maturation and survival of RPCs appears to be dependent on numerous factors. Also important are the source of the donor cells, their stage of development, their exposure to and regulation by various cellular and extracellular agents including those of the immune system, and the way these cells are delivered to the retina (e.g. by injection into the vitreous or subretinal space; on a synthetic scaffolding placed subretinally). *Henry Klassen* of the University of California at Irvine stated that many other questions need answering before retinal cell transplants can become a viable therapy for replacing photoreceptor cells. This will require a multidisciplinary approach with experts from molecular biology, tissue engineering and other fields.

Usher Syndrome Update...

OVERRIDING A NONSENSE MUTATION IN USHER SYNDROME

Researchers from the Technion-Israel Institute of Technology and the University of Mainz in Germany described experimental compounds for treating the USH1C gene nonsense mutation that causes USH1, the most severe form of Usher syndrome. A nonsense mutation causes a halt to the production of the protein that a gene is normally programmed to make. The researchers investigated several compounds — commercial aminoglycosides, modified aminoglycosides and the novel compound PTC124 — that shows promise for treating other genetic disorders (e.g., cystic fibrosis and muscular dystrophy). The compounds work by inducing a read-through of the gene. In cultured cells and in the mouse retina with the Usher gene mutation, the researchers found that the commercial aminoglycosides and PTC124 successfully induced a read-through and restored protein expression and function in a dose dependent manner. Much more work is needed to understand the toxicity and efficacy of these compounds.

Dry AMD Treatment Trial...

FENRETINIDE TREATMENT FOR DRY AMD

Sirion Therapeutics, recently announced results from its Phase 2 clinical trial of their drug Fenretinide for the treatment of geographic atrophy (GA) associated with dry age-related macular degeneration. The positive results put the drug on a fast-track with the U.S. Food and Drug Administration. Fenretinide, provided in pill form, is a vitamin A binding protein antagonist and may work by reducing the formation or effect of Drusen under the RPE. Patients with lesions of all sizes who

received 300 milligrams of Fenretinide daily had slower rates of growth of their geographic atrophy than patients in control groups. A Phase 3 trial with more than the 245 subjects is being planned.

THE ARTIFICIAL RETINA

Although photoreceptors cells die in RP, other neuronal cells of the retina remain capable of transmitting signals that reach the brain to be interpreted as vision. These cells, mainly retinal ganglion cells, if stimulated with enough electrodes in a fashion that is coordinated with light and shapes in the visual field, can provide patients with functional vision, or so researchers are hoping. Work is being done by several groups to develop a retinal implant that will electrically control these cells..

One group at the Doheny Eye Institute under the leadership of Dr Mark Humayun is developing the Argus System. The stimulus in the visual field is captured by a tiny camera mounted on eyeglasses worn by the patient. The information is sent to a belt-worn microprocessor where it is converted to an electronic signal and transmitted to the retinal implant. The patterns of stimulation “seen” by the brain correspond to the spatial and temporal stimulation of the electrodes in the retinal implant. The researchers are testing a new 60-electrode unit and comparing the results to earlier tests of an implant consisting of 16 electrodes. Twenty-one people with advanced RP (little or no light perception), in the U.S., Mexico, Great Britain, France, and Switzerland, have been fitted with the newer unit. A just released report describing the outcome in a patient with the 16-electrode epiretinal implant showed that the device enabled him to detect patterns of stimulation (when rows of electrodes at right angles were stimulated one row at a time; patient drew lines indicating pattern). Furthermore, when he was shown high-contrast square-wave gratings on a video monitor, he could detect distances between lines that corresponded to the spacing between neighboring electrodes. All patients with the implants detected phosphenes when the electrodes are stimulated.

The group in Germany is led by Professor Eberhart Zrenner of University Eye Hospital, Tübingen. The sub-retinal implant called the Retinal Implant AG essentially replaces the photoreceptor cell layer with an implant having stimulus electrodes on its surface. There is no external camera or computer; all electronic components are placed under the retina in a 3 x 3 x 0.1 mm chip, except for a small power supply, connected by a thin cable, ending behind the ear. The researchers reported on an advanced technique for implanting their newest device, which consists of a 1500-electrode chip that is

stimulated by light and 4 x 4 electrodes for direct stimulation. Despite the complexity of implanting the subretinal microelectrode array, no damage appears to occur to retinal tissue even in patients implanted up to three months. When direct stimulation is presented in a pattern meant to represent a certain letter, some patients are able to correctly name the letter. By means of the light sensitive chip the most recent three patients were able to discern the direction of fine stripes. One patient was able to read letters 4 to 8 cm in size presented on a table in regular reading distance under dim illumination, and combine them into words. The patient was able to recognize and precisely localize unknown objects such as a banana or an apple.

Many questions concerning these electronic devices have yet to be answered with regard to device fabrication, packaging, and location, surgical technique for implantation, long-term tissue tolerance to the devices and to the unique electrical stimulation, characterization of ganglion cell activity, and much more. Basic, preclinical, and clinical studies continue in the hands of scientists involved with the Artificial Retina Project and Retinal Implant AG and also with others including Optobionics with its Artificial Silicon Retina (ASR) implant, IMI Intelligent Medical Implants AG with its Learning Retinal Implant System, and the EPI RET3 epiretinal array.

RP, PREGNANCY AND BREAST FEEDING

Italian researcher *Luca Lacobelli*, of the Italian Institute of Neurotrauma, and colleagues reported on the effect of pregnancy and breast-feeding on visual acuity in women with RP. The only statistically significant finding occurred when best corrected visual acuity at month one of pregnancy and at five months post-partum was compared. All the women were breast feeding and the researchers suggest a possible relationship between decreased visual acuity and depletion of vitamin A and docosahexaenoic acid (DHA) through the mother's milk. Post- partum vitamin supplementation is advised. NB. Vitamin A should NOT be taken during pregnancy, by Stargardt patients or Smokers – ED.

NANOPARTICLE DELIVERY OF GENES IN LCA

Researchers, including *Muna Naash*, from the University of Oklahoma recently demonstrated the successful use of RPE65 nanoparticles (plasmids expressing human RPE65 cDNA compacted into rod-like particles) for delivering a gene therapy for treatment of Leber's congenital amaurosis, [LCA]. The nanoparticle approach has the potential to overcome limitations of viral vectors including random integration into the host genome, inflammation, and more severe outcomes. It also demonstrates superiority over other non-viral gene delivery approaches in its transfection ability and duration of expression, say the researchers. The findings indicate that successful and sustained gene expression and functional improvement can be attained using the nanoparticle approach.

Changing nerve cells to light responsive cells?

ENGINEERED GANGLION CELLS RESPOND TO LIGHT

Changing the behavior of one type of neuron in the central nervous system to take over the function of another type of cell is a huge challenge. Each cell has its own innate regulatory system and responsibility, which was considered immutable until recently. But the potential for such a toggle therapy for retinal degenerative diseases is huge. *John Flannery* of University of California, Berkeley, and his colleagues have found that they can confer light sensitivity (the typical venue of rod and cone photoreceptor cells) on retinal ganglion cells in cell culture, zebrafish larvae, and now mice. Using a viral vector they delivered an engineered light sensitive protein (the glutamate receptor, LiGluR) by intravitreal injection to retinal ganglion cells in a mouse model of retinal degeneration (*rd-1* mice). They then stimulated the ganglion cells with light, studied the response in the brain's primary visual cortex (V1), and found a robust response and light-evoked responses at all post-injection time points. The researchers conclude that LiGluR is worthy of study as a possible therapy for restoring light sensitivity in patients who are blind because of photoreceptor loss.

- John Flannery and Elise Heon were our guest lecturers in 2006 – ED.

NEUROPROTECTION CLINICAL TRIALS

CNTF-ECT Trials – Dr Kathleen Dickinson – Neurotech, Lincoln, USA

CNTF is a natural compound found in the body that helps to protect neuronal cells from damage, hence it is a “neuron-survival” and “neurotrophic” agent. It has been shown to slow the course of retinal degeneration in a number of RD animal models. To overcome the problem of delivery of the therapy, Neurotech has devised a capsule that is implanted within the vitreous cavity of the eye that delivers a sustained and safe dose of CNTF to the retina. This is called “Encapsulated Cell Technology” or NT-501-ECT. Preclinical experiments were successful using this device, showing relative safety as well as efficacy. Phase I of an FDA-approved trial has been successfully completed and advanced-phase trials on subjects with RP and on those with Geographic Atrophy (GA) are underway. The trials are: CNTF2 for dry AMD; CNTF3 for late stage RP; CNTF4 for early stage RP. 51 Patients with dry AMD are being studied in the GA trial. To date in this ongoing work, the safety results are good and no significant treatment-related Serious Adverse Events (SAEs) have been observed. No serum antibodies have developed against CNTF or the ECT. OCT images have demonstrated that there is improved definition of the Outer Nuclear Layer (ONL) of the retina in treated

Award for Christina Fasser

subjects at 12 months, compared to baseline images. A significant increase in retinal thickness, measured as total macular volume was determined by OCT. This was a dose dependent effect and observed in all three CNTF protocols. These results are consistent with published reports from preclinical observations. Retinal thickness was determined not to be due to cystoid macular edema, epiretinal membrane formation, vitreoretinal traction or choroidal neovascularization. Thus, the results appear to be so encouraging that CNTF-ECT might be the first treatment generally available to both RP and dry AMD patients.

PRESTIGIOUS AWARD FOR RI PRESIDENT

Ms Christina Fasser, President of Retina International has been selected as a recipient of a SPECIAL RECOGNITION AWARD by the Association for Research in Vision and Ophthalmology and will be presented at ARVO 2010. We congratulate Ms Fasser on this award which is richly deserved and is a fitting international recognition of the years of dedicated service she has given to fighting retinal vision loss.



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was sponsored by Novartis**

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