Investigational Drugs
weekly highlights
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cells. Although Jenner demonstrated immunological memory and the concept of cross-reacting antigens to stimulate immunity, he did not know how this occurred, and even today some questions regarding immunization remain unanswered. Significant progress continues to be made in identifying putative protective antigens using bio-informatics. One of the key areas still impeding effective vaccine production is formulation and delivery and a great deal of research is focusing on these aspects. In the next decade progress in these areas will hopefully be significant, with effective and safer vaccines the result.

The anti-vaccines lobby has the positive effect of ensuring continued, even increased, vigilance by vaccine producers and regulators to ensure safety. An important negative effect, however, is that vaccines capable of saving thousands of lives may be delayed or never be licensed due to a few minor adverse reactions. For example, using a less-than-perfect smallpox vaccine, 2 million lives per year were saved and eventually the disease was eradicated. The question that must now be addressed is what is an acceptable balance between risk and benefit. There will be many different answers, but as a society this issue must be addressed. It must also be recognized that the disease burden in some countries may be greater than in others and, therefore, the risk-benefit associated with vaccination there will be different than in non-endemic countries.

The website for this meeting can be found at http://www.nfid.org/conferences [Ref IDdb].

Retinal Cell Rescue - Sixth Annual Vision Research Conference (Part II)

Stem cells, Remodelling, Neuroprotection, Apoptosis, and Replacement of Retinal Neurons

3-4 May 2002, Fort Lauderdale, FL, USA

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Attendance at the Vision Research conference prior to the Association for Research in Vision and Ophthalmology (ARVO) meeting (5-10 May 2002) has become essential for international researchers in the field of retinal degeneration. The meeting was chaired by Eberhart Zrenner (University Eye Hospital Tubingen, Germany) and the 2002 theme was retinal cell rescue focused on emerging strategies for vision restoration in retinal disease, including gene-based, cell-based and prosthetic implant approaches. Most presentations addressed shorter-term goals, such as retarding photoreceptor cell death in general, mapping multicellular remodeling of the neural retina following photoreceptor loss, and seeking common principles for regulation of retinal development, regeneration and stem cell behavior. The sixth Vision Research conference was cosponsored by Elsevier Science (Oxford, UK) and ARVO (Rockville, USA).

Introduction

Once a small gathering of specialists, the Vision Research conference (VRC) has emerged as a major annual summary of progress in rapidly changing arenas within retinal biology, attended by 500 plus researchers from academia, medicine and industry. Last year's electrifying presentation of gene-based rescue in an animal model of Leber's Congenital Amaurosis (LCA), an aggressive blinding disease of infancy, was followed in 2002 by incremental developments on many fronts. Inherited defects in rod photoreceptor gene expressions form a complex of diseases known collectively as retinitis pigmentosas (RPs), and allied diseases arise from gene defects in the retinal pigmented epithelium (RPE) and the cone photoreceptors. The loss of cones, often secondary to primary rod degeneration, creates major personal and societal burdens even if visual impairment is far short of blindness. Retinal impairment from trauma and multiple vasculopathies, compound the burden. Treatment schemes for many inherited and acquired defects converge on maintaining cone survival, a point emphasized by Gerald Chader (Foundation Fighting Blindness, USA) in his overview. The conference largely addressed key stages in disease progressions where molecular or cellular interventions might be feasible. The 31 invited presentations were divided into eight topical sessions, but there was much overlap as many explored delivery strategies for a range of growth factors (GFs), neurotrophins (NTs), cytokines, anti-apoptotic factors or anti-angiogenic factors, acting downstream of the primary gene defects. Most agent deliveries continued to employ ocular injections of factor genes carried by adeno-associated virus (AAV) or direct intravitreal or subretinal space (SRS) injections of proteins, but a compelling case was made for systemic and even topical protection by classic beta-blockers. A larger framework for these efforts emerged in sessions on the regulators shaping

proliferation and differentiation of the major types of retinal neurons, the attributes of stem cells in the eye, cell replacement schemes, and the systematic negative remodeling experienced by the neural retina in response to photoreceptor loss.

Injecting rescue agents

The session on gene-based therapies began with an overview by Alberto Auricchio (University of Pennsylvania, USA) on attempts to: i) better target AAV vectors by exchanging capsids (AAV2 with AAV1, 2, or 5 capsids); ii) better control expression by using pharmacological triggers of promoters (rapamycin); and, iii) gauge the benefits, risks or efficacy of intravitreal versus SRS delivery routes. Clear biases in cell preferences and transduction efficiencies emerge based on capsid serotype (eg, AAV2 and AAV2/5 for RPE), but much room remains for improvement. SRS delivery predominates among successful examples of AAV gene transduction in photoreceptors. The session presaged the bulk of the conference, however, by focusing primarily on delivery of survival, anti-apoptotic or anti-angiogenic factors to the retina.

Ciliary neurotrophic factor and Axokine

A presentation by Gregory Acland (Cornell University, USA) explored the use of ciliary neurotrophic factor (CNTF) and Axokine (CNTF-AX15; Regeneron Pharmaceuticals Inc) via intravitreal injection or encapsulated cell therapy (ECT) in *rcd1* dogs. The *rcd1* defect is a phosphodiesterase beta-subunit (PDEB) loss-of-function defect that rapidly kills developing rods. While both routes achieved transient rescues from cell death, ECT avoided cataracts and uveitis that attend intravitreal routes.

AAV delivery of fibroblast growth factor genes

An alternative rescue employing AAV delivery of fibroblast growth factor (FGF-2 or FGF-18) genes led to substantially improved survival of rods, especially via the SRS route, but also triggered undesired remodeling and proliferative neovascularization. Disappointingly, survival factors delayed rod death but did not restore function, a harbinger of findings throughout the sixth VRC. PDEB mutant rods are phototransduction-incompetent and prolonging survival was not expected to restore function, but slowing rod death did not prevent cone loss.

Rescue of the RPE65 defect in beagle-Briard dogs

In the final presentation of the session, Jean Bennet (University of Pennsylvania, USA) summarized the work from her lab that led to last year's stunning rescue of the RPE65 (an RPE visual cycle protein) defect in beagle-Briard dogs using SRS AAV-*RPE65* injections at 3 months of age (Aclund *et al Nature Genetics* (2001) **28**:92 [Ref IDdb]). This early intervention in an otherwise blinding disease has achieved persistent rescue of vision in these animals. Dr Bennet reviewed human loss-of-function diseases that might be approached using gene therapy: LCA (the RPE65 defect accounts for 10 to 20% of cases), choroideremia (rab escort protein-1 defect) and autosomal recessive RP (PDEB defect). In the latter, absence of functional PDE beta subunits triggers early rod death through unregulated rises in outer segment cGMP, demanding an early, perhaps even *in utero* rescue.

Survival factor and anti-apoptosis rescues

Later sessions revisited the theme of survival factor and anti-apoptosis rescues. Downstream of the primary defect, therapeutic windows of opportunity are arguably longer, offering broader treatment options by acting closer to the convergence of cell death pathways.

Rong Wen (University of Pennsylvania, USA) discussed the JAK-STAT gp130 signaling cytokines, showing that periodic intraocular cardiotropin-1 injections rescued fast postnatal rod degeneration in the S334ter rhodopsin mutant rat (line 3, produced by Matthew LaVail, University of California San Francisco, USA). Rescue of inner segments early in disease with 3-day injection intervals did not lead to outer segment restoration and prospects that the rods were functional were poor.

AAV-GF and AAV-NT survival factors

John Flannery (University of California at Berkeley, USA) presented summary data from a large screen of AAV-*GF* and AAV-*NT* survival factors via the SRS route in S334ter, P23H (rhodopsin N-terminal mutant, also from Dr LaVail), RCS (Royal College of Surgeons, tyrosine kinase MERTK mutant) and light-damaged rats. AAV2 delivery effected good FGF-2 and FGF-5 expression in rods, rescuing a large fraction of rods at postnatal day 60 in the rhodopsin mutants, but only delayed the inevitable. Rod numbers were improved in RCS rats, indicating partial rescue, but the accumulation of debris in the SRS continued unabated since the RCS RPE remains incompetent at shedding outer segments. Light damage was attenuated if the retina was allowed to express FGF prior to induction of damage, but neither the ERG nor outer segment production recovered. The immature appearance of the surviving rods was

noted. Single survival factors clearly cannot sustain a complete rod phenotype. Consistent with prior work, FGF expression was also pro-angiogenic. On the contrary, glial-derived neutrophic factor (GDNF) delivered via AAV constructs with the chicken beta-actin promoter (AAV-CBA) achieved good rescue without evidence of angiogenic effects.

Rescue of cones in retinal degenerations

A technical strategy was described by Jose-Alain Sahel (Centre Hospitalier National, France). Since the major emergent defect in most retinal degeneration is the death of cones, do they require survival factors produced by rods? Putative survival factor rdCFV1, identified through expression cloning and assay with a chicken cone culture system, appears restricted to the retina and is expressed by rods. The nature of rdCFV1 and its mechanism are unknown and it is possible that it triggers survival via pathways similar to GFs and cytokines.

Protection of photoreceptors against light-induced apoptosis

Alternative molecular-rescue designs emerged. Hypoxic challenge had previously been effective in reducing pathologies accompanying retinal detachment (Lewis *et al Am J Ophthalmol* (1999) **128**:165 [Ref IDdb]). Christian Grimm (University of Zurich, Switzerland) demonstrated that similar protection was obtained in LD apoptosis models through hypoxia inducible factor-1alpha oxygen-sensing triggering of endogenous erythropoietin (Epo) production. Epo receptors were shown to be expressed by rod inner segments and rescue was interpreted as interruption of caspase-1 activation. However, hypoxic challenge yielded only transient Epo levels and longer durations were achieved with intraperitoneal delivery of recombinant human Epo, with Epo entering the retina through the choroidal/RPE route. In this regard, there is increasing interest in the direct uptake of proteins by target cells, as opposed to receptor-mediated signaling.

Heat-shock protein responses

Based on evidence that some effective neuroprotectants (eg, lens epithelium-derived growth factor) evoke heat-shock protein (HSP) responses, Ronald Bush and colleagues (National Eye Institute, USA) examined direct intravitreal delivery of HSP25 to RCS, P23H and LD rats. The P23H rats proved refractory, but both LD and RCS rats displayed significant retention of rods and, importantly, significant preservation of ERG b-waves. Mitochondrial release of cytochrome C (triggered by LD or cytotoxic processes arising in SRS debris) could have been buffered by HSP25 binding, preventing caspase-9 activation.

Glaucoma

Perhaps the most promising example of anti-apoptotic therapy was presented by Stuart McKinnon (University of Texas San Antonio, USA). Ganglion cell apoptosis in glaucoma is slow and cumulative and apoptosis blockade may provide therapies for glaucomas unresponsive to standard pressure-regulation agents. Baculoviral IAP repeat containing protein-4 (BIRC4) is an inhibitor of caspase-3, the key agent of cytosolic and nuclear proteolytic degradation. A popular rat glaucoma model, based on quick scarring of aqueous outflow channels following limbal hypertonic saline injections, was shown to receive as much as 50% ganglion cell protection from intravitreal AAV-CBA-BIRC4.

Levobetaxolol

A novel approach to retarding the effects of retinal degeneration on photoreceptors was outlined by Robert Collier (Alcon Laboratories Inc, USA). Using P23H rhodopsin mutant rats and variant of the LD model, systemic, oral and even topical doses of the beta-blocker levobetaxolol provided significant protection gauged by histology and ERGs. As levobetaxolol triggered increases in endogenous mRNA for both CNTF and bFGF, the same penultimate mechanisms of rescue may be at work, activated by a significantly less expensive and more tolerable route. There is clearly more to the mechanism as cytokines and GFs alone appear to effect only partial rescues.

Calcium permeability

Using the *rd* mouse model (PDEB defect, common to many species), Serge Picaud (University of Strasbourg, France) provided detailed evidence that excessive calcium permeability in outer segments due to elevated cGMP levels is likely the distal insult triggering apoptosis. The classic cardiac anti-hypertensive calcium-channel blocker diltiazem, known to cause a channel-occluding block of photoreceptor cGMP-gated channels, rescued rods effectively *in vitro* and *in vivo*. This rescue is clearly upstream from survival factor target sites, since the ERG is partly rescued, implying successful cone maintenance. Other laboratories have had difficulty reproducing the finding, but data from the rat retinal explant model using zaprinast to block PDE and raise cGMP levels clearly showed diltiazem effective in reducing the number of TUNEL-positive cells (a marker for DNA cleavage in cell death) and the level of caspase-3 immunoreactivity.

Development, regeneration and transdifferentiation

In a departure from 'inject-and-count' studies, two sessions addressed the processes involved in making retinas in the first place and how some species continue to do so throughout life. The power of development/regeneration might be harnessed to rebuild retinas, but the details remain elusive. It has long been known that different retinal cell types emerge from the proliferating neuroprogenitor pool in an overlapping but ordered sequence.

bHLH function and retinal cell fate

A beautiful presentation by Monica Vetter (University of Utah, USA) provided evidence that specific proneural proteins of the basic helix-loop-helix (bHLH) DNA binding family (eg, Ath5 and NeuroD) are not immutable cell-specific gates, but rather context-dependent regulators. Xenopus Ath5 (Xath5) is required for the production of retinal ganglion cells and Xath5 over-expression yields a superabundance of ganglion cells, whereas xenopus NeuroD (XNeuroD) is biased for emergence of amacrine cell phenotypes. The function of XNeuroD in early retinal development is inhibited by glycogen synthase kinase 3-beta but if its target motif is inactivated by mutagenesis, ganglion cell over-expression is favored. Alternatively, if Xath5 over-expression is delayed, increases in bipolar cells and rods are obtained. Retinal progenitor cells thus change competence over time and poorly understood networks regulating the timing of bHLH function are key arbiters of cell specification.

A similarly exceptional presentation by Nadean Brown (Northwestern University, USA) followed detailing bHLH protein roles in the mouse retina correlating overlapping protein expression regimes with cell types: mouse Ath5 (Math5) with ganglion cells, Neurogenin-2 with photoreceptors and bipolar cells, NeuroD, Math3 with amacrine cells, Mash1, Math3 with bipolar cells. Consistent with the key role of Math5, its deletion leads to mice with no ganglion cells but a superabundance of cones.

Genomics approaches

Connie Cepko (Harvard Medical School, USA) provided an overview of her laboratory's serial analysis of gene expression (SAGE) profiling of developing and mature retinal neurons, which has resulted in a remarkable catalogue of retinal genes, including some 900 *in situ* hybridization patterns, many available at the lab's website. Profiling gene expressions by competency requires identification of progenitor cells. Isolating DNA-enriched 4N (ie, tetraploid) cells yielded populations that were 95% nestin-positive, definitive for neuronal progenitors. By comparing expression profiles of 4N with 2N cells, adult retina and other neural populations, a core set of 568 genes shared across neural progenitors was defined, and annotation revealed enrichments in cell cycle components, transcription factors, protein turnover, cytoskeleton, metabolic regulation and plasma membrane components. Finally, efforts are underway to develop profiles of single neurons, potentially leading to identification of signature proteins for each neuronal class.

The final presentation of the development session by Claire Russell (University College London, UK) covered the global roles of FGF and hedgehog signaling pathways in patterning the optic outflow and axon guidance to the optic nerve.

Retinal regeneration and retinal stem cells in fish

Many non-mammalian retinas (fish, amphibians, birds) harbor circumferential marginal zones (CMZs) enriched in retinal progenitor cells that give rise to mature neurons as the retina grows throughout life. The temporal progression of progenitor cell competence in early development must somehow be embedded in the spatial map of the CMZ, though little is known of the cycling of progenitor production there. Fish and urodele amphibians possess remarkable powers of retinal regeneration, a feat denied to mammalian retinas. Peter Hitchcock (University of Michigan, USA) described the ability of goldfish and zebrafish retinas to recreate intact, patterned and physiologically functional arrays of neurons after excisions of small patches. This is all the more impressive as fishes likely manufacture some 120 distinct neuronal classes, compared with 55 to 60 for simpler mammalian retinas. In the normal adult retina, this production is restricted to the CMZ, except for rod progenitors distributed through the outer and inner nuclear layers across the retina. Damage triggers an injury response resulting in the formation of differentiation-competent margins around the wound; the margins may arise from rod progenitors. Molecular triggers for the response are unknown but normal growth is regulated by the growth hormone (GH) and insulin-like GF-1 (IGF) signaling. Retinal GH is capable of activating IGF synthesis in the brain and retina and activates CMZ proliferation, gauged by the increase in BrdU-positive (Bromodeoxyuridine labeling in S-phase) cells in the adult retina.

Progenitor cells in endotherms

Thomas Reh (University of Washington, USA) described the search for progenitor cells in endotherms,

phenotype changes begin very early in the *rd* mouse, with rod bipolar cells failing to form proper dendrites and decreasing expression of mGluR6, the signature glutamate receptor of ON-center bipolar cells. Rod bipolar cell terminals (their synaptic output) were shown to be anomalous, with immature synaptic ribbons. Extensive remodeling of horizontal cells into nematode-like cells with few processes also occurred. These are profound wiring, but subtle histological changes, detectable only with advanced visualization reagents and tools.

Extreme neural remodeling in adult mouse photoreceptor degeneration models

Results from the laboratory of Robert Marc (University of Utah, USA) summarized slow, progressive changes in retinal architecture after rod loss in multiple rodent-degeneration models mimicking those of advanced human RP. In a large screen of molecular signatures of all cell types, the investigators found that most moderate-to-fast retinal degeneration triggers extensive remodeling: including formation of multilaminar glial seals at the proximal and distal margins of the retina; anomalous migrations of amacrine, bipolar and ganglion cells on glial columns; variable, sometimes extensive loss of neurons; and abundant ectopic microneuromas and neurite sprouting where retinal neurons engage in new circuitry. All of these changes are likely to corrupt outcomes of transplantation and implant schemes.

Remodeling processes that follow experimental rhegmatogenous detachment

Finally, Steven Fisher and Geoffrey Lewis (University of California Santa Barbara, USA) presented a summary of remodeling processes that follow experimental rhegmatogenous detachment (feline model). The issue is critical because some reattachment surgeries fail to restore proper vision. Detachment triggers Muller cell proliferation and, if reattachment is not timely, glial seals appear. Expressions of many Muller cell signature proteins change, and cell adhesion protein CD-44 signals at the external limiting membrane are lost early in detachment; they recover later but are distributed anomalously. Consistent with earlier presentations, cones lose expression of characteristic proteins (opsin, calbindin). Significant remodeling of neurons ensues, with rods first retracting, then extending neurites through the retina, and postsynaptic cells, such as rod bipolar cells, initially attempt to follow their synaptic partners. Overall, these data suggest that most retinas are susceptible to significant, stereotypic remodeling after photoreceptor loss, regardless of the primary defect.

Cell-replacement therapy by stem cells or cultured cell lines

One strategy for dealing with cell loss in various diseases is cell-replacement therapy by stem cells or cultured cell lines from adult sources. The RPE might be the simplest place to start in diseases such as AMD, where the RPE is damaged in excision of choroidal neovascularizations. Prior efforts to repair RPE wounds with explants failed because the cells did not adhere. Marco Zarbin (University of Medicine and Dentistry of New Jersey, USA) reported use of freshly isolated or cultured RPE cells from adult and fetal donors coupled to resurfacing methods in an explant system. Culture-aged RPE cells successfully survived and resurfaced model wounds, where fresh cells did not, and fetal cells were superior to all. The basal faces of normal RPE cells attach to a multilaminar ECM known as Bruch's membrane and the initial attachment of cultured RPE cells was clearly favored by access to the outer RPE basement membrane rather than the superficial or deep inner collagenous layer. Once attached RPE resurfacing was less discriminating, but deeper damage of the collagenous layer slowed or blocked resurfacing. RPE cell integrin expression may underlie these specificities, but treating the surgically damaged surface of Bruch's membrane with ECM components may bypass the need to control integrin expression.

Characterization and transplantation of ocular stem cells or progenitors

Replacing the photoreceptors in the intact eye remains out of reach, though successes with iris transdifferentiation are encouraging. Extending this exploration of epithelial precursors, Iqbal Ahmad (University of Nebraska Medical Center, USA) showed that stem cells of the RPE, ciliary margin cells and the corneal limbus, seem to harbor capacity for producing neural progenitor cells and form renewing sources. Transplantation of such progenitors into the SRS evokes some cells to survive and even express rhodopsin. How these cells acquire signals to partially activate the rod phenotype remains unknown; might it be by *Crx* activation? However, a significant amount of focal trauma is required for stem cells to invade the retina, which is sensible as there is otherwise no place to migrate.

A similar result has been obtained in degenerating rat retinas, where transplanted green fluorescent protein (GFP)-expressing human neural stem cells appear to intercalate into the retina (channels likely formed by remodeling), and begin to develop neuronal morphologies, extending neurites, and expressing rod

signature molecules. Michael Young (Harvard University, USA) described how the cells do not invade well unless surrounding tissue is damaged, but appear to survive. What is the signal in retina that enables these cells to activate partial rod phenotype gene expression? Given the recent interest in retinal cell protein uptake and the possibility of direct DNA incorporation, is it possible that macromolecules from damaged host photoreceptors are scavenged by adjacent stem cells?

MHC expression by various neural stem cell lines

Henry Klassen (Childrens Hospital of Orange County, USA) presented analysis of major histocompatibility complex (MHC) expression by various neural stem cell lines, concluding that they neither express MHC II nor trigger immune reactions, reducing the need for autologous cell transplant schemes or immunosuppression.

True visual outcomes in retinal rescue

Four presentations addressed true visual outcomes in retinal rescue. Ray Lund (University of Utah, USA) summarized successful rescue of defective RPE function in RCS rats with both transplanted adult human cultured RPE and Schwann cell lines. With basal cyclosporin immunosuppression, both effected good medium-term rescue of photoreceptors. The gold-standard for any study is spatial vision, and high-quality single unit data from V1 cortex argued for good preservation of receptive field tuning in transplanted animals. Recent behavioral data further support the functional nature of the rescue. The Schwann cell approach is particularly powerful as modified cell lines can express survival factors. GDNF Schwann cell transplantation improves anatomical rescue and preserves head-tracking. As the oldest animals analyzed were aged 8 months, however, remodeling of the neural retina had not yet progressed significantly and outcomes for older animals (and patients with more advanced disease) may not be as good. Fast, high-quality evaluations of visual performance have become more critical as screening of strategies becomes more complex.

Noninvasive tracking of outcomes in animal models is now possible using confocal scanning laser ophthalmoscopy even in the eyes of mice, and longitudinal studies of vasculature and GFP reporters can be performed. Mathias Seeliger (Universitat Tubingen, Germany) described how Ganzfield ERG methods have been implemented in many laboratories, but more precise mapping of retinal function requires multifocal ERGs. Even so, high quality visual behavior remains the best index and in this regard, rodents remain less tractable subjects than carnivores and primates.

Bionic cortical and retinal implants

Bionic cortical and retinal implants (prosthetics) remain the most speculative of treatments for the many patients whose retinal disease lacks a viable gene therapy, whose window of opportunity is small, or where damage is due to vascular disease or trauma. Two retinal implant designs were featured in remarkably different presentations. Eugene de Juan (University of Southern California, USA) is one of several investigators exploring the use of vitreal surface stimulation via epiretinal electrode arrays driven by an external sensor or camera, similar to cochlear implant designs. Using digital video, he presented a case-study of a simple array tacked to the retinal vitreal surface in a severely impaired patient that led to distinct but obviously coarse percepts. These preliminary results appeared similar to those of other laboratories reporting phosphene-like effects in acute stimulation of the retina with epiretinal electrodes.

A more sophisticated engineering approach was detailed by Eberhart Zrenner (University Eye Hospital Tubingen, Germany), summarizing the efforts of a large team to design subretinal microphotodiode implants for driving remnant retinal circuitry in a spatially proper manner, to validate biocompatibility, test resolution, and to solve the power supply problem. Microphotodiodes simply cannot generate enough focal current to drive tissue signals and an external power coupling is necessary, perhaps through an IR link. The SRS seems to tolerate encapsulated implants well, though implants do not tolerate the retinal environs indefinitely. Tests of the electrode design to drive central signals in animal models using electrically evoked cortical potentials yielded an impressive one degree of visual arc resolution. Even higher resolutions seem possible via on-chip preprocessing. To the extent that a window of opportunity exists, the subretinal prosthesis appears to offer the best spatial vision. The epiretinal prosthesis may be the preferred scheme when remodeling is advanced (which obliterates the SRS) but ganglion cell survival is still adequate. Severe remodeling, however, thwarts both efforts.

Summary

Though no great breakthroughs emerged, the sixth VRC was marked by solid progression in rescue schemes, basic science and technique. Research is rapidly converging on a restricted set of survival

factors targeting rods and cones that may stave off apoptosis in retinal degeneration, albeit for limited duration. The slower progression of glaucoma suggests that AAV-based transduction of anti-apoptotic proteins in ganglion cells may be of benefit clinically. Consistently, however, anatomic rescue of photoreceptors by survival factors falls far short of phenotype rescue and, taken together, many presentations repeated the consistent theme of down-regulation of protein expression by cones in retinal degeneration. More complete understanding of the transcriptional control of mature neurons and transcription networks in retinal development is essential for devising functional photoreceptor rescue strategies. Attempts to shape progenitor or stem cell fates in non-mammalian retinal regeneration and damage responses in birds may offer insight into how mammalian retinas might be coaxed into similar actions. Stem cell transplantation research is moving slowly and proper phenotyping of stem cells is quite limited, though alien stem cells seem well tolerated. At the other end of the transplantation spectrum, cultured, mature RPE and Schwann cells have been proven to maintain functional photoreceptors for long periods and, more importantly, maintain functional vision. Where photoreceptors have already failed, it may be possible to re-engineer such cells from autologous iris cells, which can be virally transduced to express key phenotype proteins. The full complement of rod- or cone-specific proteins is likely to be large, however, and recapitulating photoreceptor structure seems well beyond the reach of current knowledge. For most retinal degeneration patients, and certainly those suffering from vasculopathies, bionic tools remain the last hope and even these must rely on the survival of the neural retina. The hope that neural retina remains essentially unchanged after photoreceptor degeneration has proven untrue for most human and animal model retinal degeneration. Therapeutic strategies must define proper windows of opportunity. Prosthetic vision is going to be very hard to deliver, whether or not the neural retina remodels. Some surviving ganglion cells may support photic percepts from an implant, but will that ever be adequate? The theoretical superiority of the well-designed subretinal implant appears to be emerging, but the epiretinal implant is already in testing, and its implementation is far simpler. Finally, small molecules were a tiny but bright spot in the proceedings. If beta-blockers already in use for glaucoma management truly have the additional benefit of reducing the rate of photoreceptor cell death in human RP, that small study may be a watershed.

The website for this meeting can be found at http://www.visres-interactivemeeting.com [Ref IDdb].

Skeletal Complications of Malignancy - Third North American Symposium

25-27 April 2002, Bethesda, MD, USA

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Interest in the skeletal complications of malignancy continues to increase rapidly. There are several reasons for this growing trend including an aging population and higher incidence of cancer, improved diagnostic tools, and effective anticancer therapy. In addition, life expectancy is prolonged, in particular those patients suffering from breast and prostate cancer. Bone metastases are a frequent event in a variety of cancer types. Dissemination of the carcinomas of the breast and prostate to the skeleton is particularly prevalent and also a notable feature of malignancy originating in the lungs, thyroid and kidneys. Multiple myeloma is a unique neoplastic disorder associated with extensive bone involvement. Important clinical problems that arise from cancer metastases to bone include humoral hypercalcemia of malignancy, cancer-associated osteoporosis and significant implications on the quality of life of cancer patients including bone pain. The major topic of the conference was treatment modalities targeting the prevention of skeletal disease. One particular focus was given to stromal derived cytokines and growth factors due to evidence which indicates the critical role that bone marrow and stroma play in homing of tumors to the bone and development of bone metastases.

Prostate cancer

Abbott's atrasentan

Endothelin-1 in osteoblastic bone metastases was described by Teresa Guise (University of Texas Health Science Center, USA), who reported that osteoblastic bone metastases could be found in both breast and prostate cancers. There is clinical evidence that men with prostatic bone lesions have elevated serum levels of endothelin-1. This 21-amino acid peptide has vasoconstriction potential and can stimulate osteoblast cell proliferation. Interestingly, osteoblastic effects can be inhibited with an endothelin A receptor antagonist. Dr Guise's group tested atrasentan (Abbott Laboratories) in nude mice injected ic with ZR-75-1, a human breast tumor cell line known to secrete endothelin-1 and induce bone