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HIGHLIGHTS FROM THE ANNUAL MEETING OF THE ASSOCIATION FOR RESEARCH IN VISION AND OPHTHALMOLOGY (ARVO) 2009

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ABSTRACT

The city of Fort Lauderdale hosted the 2009 Annual Meeting of the Association for Research in Vision and Ophthalmology (ARVO). Over 10,000 vision researchers, clinicians and scientists from around the world gathered in the sunshine state to discuss cutting-edge research aiming to ameliorate the treatment of ocular diseases. In this report, we highlight presentations on novel therapeutic approaches for various ophthalmological conditions, giving special attention to novel drugs showing promise for the pharmacological management of glaucoma and macular degeneration.

INTRODUCTION

The 2009 Annual Meeting of the Association for Research in Vision and Ophthalmology (ARVO) took place in the city of Fort Lauderdale, Florida, also known as the "*Venice of America*". In Fort Lauderdale, the water offers more than just amusement for boating aficionados; it is also a means of transportation that facilitates the flow of goods and people throughout the Intracoastal Waterway. Similarly, the ARVO meeting provides the perfect medium every year for the flow of information among academic scientists, clinicians and health industry representatives, facilitating the successful development of much-needed therapies for a variety of eye diseases. ARVO is the largest and most respected vision research organization in the world, comprising more that 12,000 vision and ophthalmology researchers from 73 countries. During the 2009 meeting, a plethora of experts in ocular research from around the world gathered in the sunshine state to discuss cutting-edge research aimed at improving the treatment of eye diseases. In addition to presentations on novel therapeutic approaches and agents for uveitis, ocular malignancies, dry eye, glaucoma, retinopathies and on other areas of ophthalmological research, relevant data on stem cells and biomarkers were also disclosed. Here we highlight some of the most important presentations that took place during the meeting.

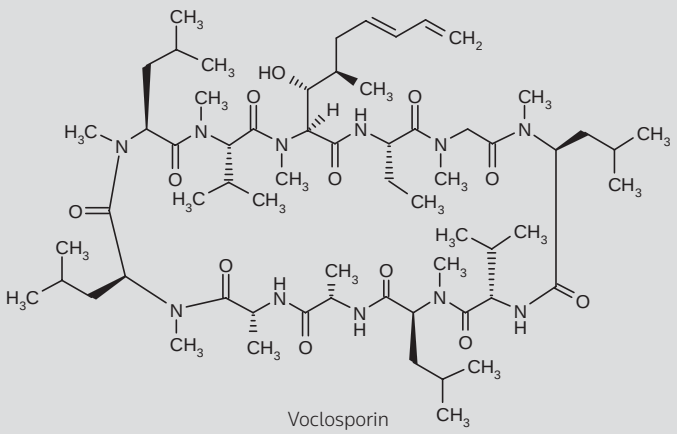
HIGHLIGHTED PRESENTATIONS

Stem cells

A group of Japanese researchers, who had previously demonstrated the generation of putative photoreceptors and retinal pigment epithelium (RPE) cells from primate embryonic stem (ES) cells using stepwise induction with defined factors, tested whether human induced pluripotent stem (hiPS) cells can be differentiated into retinal progenitors, RPE cells and photoreceptors with the same procedure used for ES cell differentiation. They presented evidence for the induction of retinal progenitor cells from hiPS cells by serum-free embryoid body-like culture added with Wnt and Nodal inhibitors. A prolonged culture period generated mature RPE cells and the addition of retinoic acid and taurine to the culture promoted differentiation of photoreceptors. Their results indicate that iPS cells can be differentiated into retinal cells by the same method as used for ES cells and may become a useful tool for cell transplantation therapy (1).

Biomarkers

Members of the Clinical Genomic and Proteomic Age-related Macular Degeneration Study Group presented the results of a study aiming to find plasma biomarkers for age-related macular degeneration (AMD). Quantitative analyses of plasma from 60 AMD patients and normal control donors showed that mean plasma protein carboxymethyllysine (CML) and pentosidine levels were elevated in AMD subjects by ~60% and ~80%, respectively. In these samples, carboxyethylpyrrole (CEP) adducts were 2-fold higher in the AMD group than in controls. The odds ratio for both CML and pentosidine being elevated was 15-fold greater in AMD than in control patients. For these plasma samples, C-statistics and ROC curves indicated that CML discriminated between AMD and control donors with 79% accuracy, CEP adducts with 81% accuracy and pentosidine with 92% accuracy. In combination with CEP adduct levels, CML provided 89% accuracy and pentosidine provided ~96% discrimination accuracy. The research team concluded that CML and pentosidine levels are elevated in AMD plasma and may prove useful for predicting AMD



Uveitis

susceptibility, as well as for monitoring therapeutic efficacy, especially in combination with CEP biomarkers (2).

Uveitis

Results from LUMINATE, a phase III trial assessing the ability of LX-211 (**voclosporin**) to improve uveitis, were released by Dr. Rosenbaum, representing the LUMINATE Steering Committee. LX-211 is a novel calcineurin inhibitor being developed by Lux Biosciences for ophthalmic indications. Of the three doses studied, the dose of 0.4 mg/kg b.i.d. demonstrated a clinically relevant benefit and also had the most acceptable safety profile. It also showed a 50% reduction (versus placebo) in the rate of recurrence of inflammation at 6 months. Moderate but manageable adverse effects were observed on glomerular filtration rate and blood pressure (3).

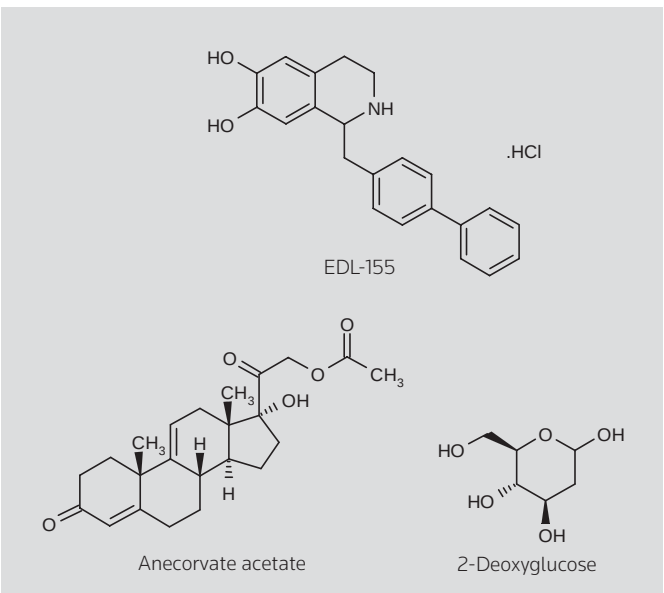
Retinoblastoma

Within the past few decades, retinoblastoma has evolved from a deadly cancer to a largely curable malignancy when diagnosed early. In developed countries, current treatments aim to salvage the eye and provide the best visual outcome possible. A study conducted at the University of Tennessee Health Science Center showed that periocular delivery of **EDL-155** depletes retinoblastoma tumor growth in rats. In vitro, EDL-155 was able to deplete cultured retinoblastoma Y79 cells (EC_{50} = 12.5 μM), without affecting normal brain astrocytes when applied at the same concentration. In an animal model of retinoblastoma, four doses of EDL-155 (20 mg/kg/day) delivered over 4 days caused a significant reduction (P = 0.01) in the size of viable intraocular tumors which developed following injection of Y79 cells into the vitreous cavity of the eye of newborn rat pups. No detectable living tumor was seen in 7 of 25 rats treated with EDL-155. Electron microscopic analysis of EDL-155-treated Y79 cells suggests that the compound may eliminate cells by destroying their mitochondria and inducing autophagic cell death. The researchers proposed that EDL-155 may synergize with other chemotherapeutic agents and could possibly be used in combination therapy (4).

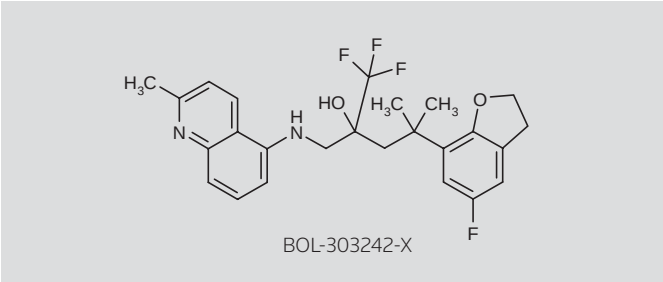
Another experimental study carried out at the Bascom Palmer Eye Institute (Miami, Florida) revealed that transgenic retinoblastoma tumors decrease following the administration of a combination of the vessel-targeting agent **anecortave acetate** and the glycolytic inhibitor **2-deoxyglucose**, suggesting a novel therapeutic approach (5).

Scarring

The selective glucocorticoid receptor agonist **BOL-303242-X** was assessed for its ability to decrease the levels of factors that promote scarring of the filtering bleb following stimulation with transforming growth factor-β (TGF-β), such as collagen type I (COL), α-smooth muscle actin (α-SMA) and tissue transglutaminase (tTGase), in human Tenon's capsule fibroblasts (HTF). Scarring of the filtering



Retinoblastoma



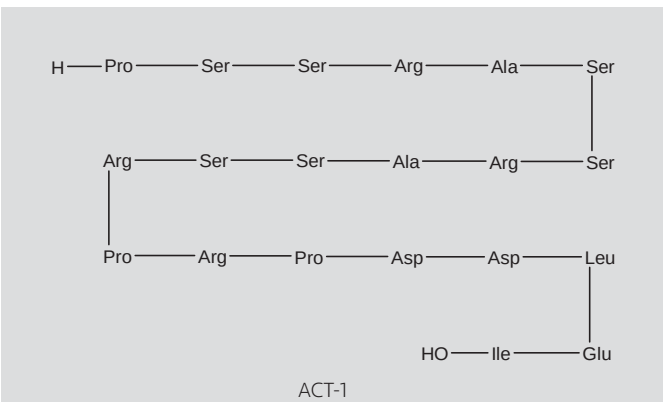
Scarring

bleb represents an important cause of failure following glaucoma surgery. This study found that TGF-β (5 ng/mL)-induced increases in COL, tTGase and α-SMA protein levels in HTF following 5-day incubation were decreased in a dose-dependent manner (8-, 4- and 29-fold, respectively) following BOL-303242-X administration. These findings indicate that the anti-inflammatory ocular drug BOL-303242-X may potentially be developed for the prevention of scar formation following trabeculectomy surgery (6).

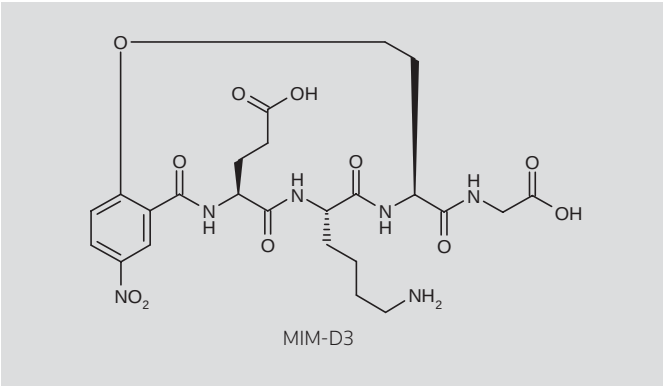
Corneal wounds

ACT-1, a synthetic peptide developed as a wound-healing agent by the Medical University of South Carolina, was found to enhance corneal epithelial wound healing in a rat burn model. Sprague-Dawley rats received either vehicle, ACT-1 (100 µM in 2 drops, approximately 100 µL) or control peptide (60 µM in 2 drops, approximately 100 µL) per eye at 0 and 24 h following corneal wound induction. At 24 h post-treatment, corneal wound areas in ACT-1-treated rats represented less than 13% of the initial wound dimensions, whereas in the control and vehicle-treated animals wound areas represented 32-34% of the initial damaged area. Near complete closure of the corneal wound was seen at 48 and 72 h in all treatment groups, with no significant differences between groups being detected at this stage. The enhancing effects of ACT-1 in wound healing over the first 24 h following corneal epithelial cell damage may lead to the development of therapies aiming to achieve faster visual recovery (7).

Gabison et al. investigated the therapeutic potential of mesenchymal stem cell (MSC) subconjunctival injection in a rat ocular surface



Corneal wounds



Dry eye

alkali burn model. The rats receiving subconjunctival injection of MSCs showed improved transparency and displayed decreased neovascularization, which suggests that MSC therapy may be useful in the management of ocular chemical burns (8).

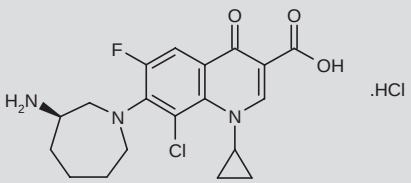
Dry eye

Mimetogen Pharmaceuticals tested a nerve growth factor (NGF) peptidomimetic and Trk receptor tyrosine kinase agonist (**MIM-D3**) for its effects in a rat model of scopolamine-induced dry eye, as well as in studies of mucin secretion in vitro. In the latter experiments, MIM-D3 concentration-dependently stimulated goblet cell mucin secretion without stimulating the proliferation of goblet cells. In goblet cell cultures, MIM-D3 significantly increased mitogen-activated protein kinase (MAPK) activation and it dose-dependently increased mucin production in tear fluid washings from rats (9). In the rat model of dry eye, chronic dosing of MIM-D3 ophthalmic solutions on days 5-21, followed by no dosing for 7 days, did not affect the Schirmer test of tear production or fluorescein clearance, but significantly reduced corneal staining, increased tear break-up time and increased mucin production at the 1% dose. The research team concluded that a higher dose (2.5%) may have desensitized the NGF receptors, while a lower dose (0.4%) may have been suboptimal (10).

Dr. Koffler from the LAC-07-01 Study Group presented data from a multicenter, two-visit, open label, 4-week study determining the acceptability and ease of use of **Lacrisert**® (hydroxypropyl cellulose ophthalmic insert) in adult patients with a history of dry eye syndrome. The use of this insert resulted in significant improvements in dry eye symptoms, activities of daily living and patient quality of life, with a > 25% improvement in mean Ocular Surface Disease Index (OSDI) total score (11).

Conjunctivitis

Besifloxacin hydrochloride, a novel fluoroquinolone under development by Bausch & Lomb for the treatment of bacterial conjunctivitis, displayed a consistently high microbiological eradication rate and potent in vitro activity in three separate clinical trials. At the end of 2008, an FDA advisory committee recommended approval of besifloxacin for the treatment of bacterial conjunctivitis. Topical administration of a 0.6% ophthalmic suspension of besifloxacin three times a day for 5 days across three randomized, double-masked,



Besifloxacin hydrochloride

Conjunctivitis

parallel-group studies in patients with culture-confirmed bacterial conjunctivitis resulted in MIC_{90} values of 0.03, 0.06, 0.5 and 0.5 μg/mL, respectively, against clinical isolates of *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Staphylococcus aureus* (13.6% methicillin-resistant and *Staphylococcus epidermidis* (45.9% methicillin-resistant). There was no evidence for the development of resistance to besifloxacin during treatment (12).

Visual function

New data on the development of the visual cycle modulator **ACU-4429**, designed to prevent or inhibit the accumulation of visual cycle by-products that could lead to the onset of degenerative ocular conditions, were disclosed by scientists from Acucela. ACU-4429 is a small-molecule inhibitor of the enzymatic isomerization of *all-trans*-retinol to 11-*cis*-retinol in the visual cycle. Assessment of ACU-4429 in a series of preclinical studies revealed potent inhibition of recombinant human isomerohydrolase activity in vitro (IC_{50} = 4.4 nM) and demonstrated no significant toxicity in dogs following oral doses up to 30 mg/kg/day (13). Additional in vivo studies presented at the meeting suggested that ACU-4429 may protect photoreceptors from acute light damage and reduce the accumulation of A2E/lipofuscin in the ABCA4 animal model of AMD, findings which have supported further clinical development of the compound (14). Clinical evaluation of ACU-4429 in a single-center, randomized, double-masked, placebo-controlled, dose-escalation phase I study in healthy volunteers demonstrated that the compound is safe and well tolerated. Oral administration of ACU-4429 (single oral dose) was tolerated up to 60 mg with no significant or unexpected adverse events. Pharmacokinetic profiling revealed a half-life of approximately 4-6 h. Approximately dose-proportional increases were seen in AUC and peak serum concentration (C_{max}) values in the higher-dose cohorts (C_{max}: 1.42 and 4.54 ng/mL, respectively, at 7 and 20 mg ACU-4429). Although dark-adapted electroretinographic (ERG) measurements were not affected by the treatment, most subjects exhibited a prolonged course of recovery (24-48 h postdose) following exposure to a bleaching light, a result indicative of a potential role for ACU-4429 in rod-mediated retinal activity (15).

Systemic administration of the novel calpain inhibitor **Neurodur** (Ceptor) was found to confer significant neuroprotection of the retina in a rodent model of transient retinal ischemia–reperfusion. Intraperitoneal injections of Neurodur (7.5-30 mg/kg) to Sprague-Dawley rats either prior to or just after the onset of ischemia induced by high intraocular pressure (IOP) resulted in significant preservation of retinal function, as observed on ERG performed 7 days after the induction of ischemia. Treatment with Neurodur (15 and 30 mg/kg) as early as 3 h following the onset of ischemia caused significant preservation of retinal function (43% and 35%, respectively). Rosenbaum et al. concluded that the inhibition of calcium-dependent proteases such as calpain may provide scope for the development of clinically relevant treatments for retinal disorders involving ischemia (16).

Researchers from Eos Neurosciences, along with other academic institutions, showed that targeting the expression of channelrhodopsin-2 (ChR2), a light-sensitive protein responsible for neuronal depolarization, activates specific neural circuits to restore behavioral and physiological visual function in adult rd1 mice. Wild-type and capsid-mutated adeno-associated virus (AAV) serotypes delivering *ChR2* and *GFP* genes under the control of the GRM6 or CBA promoter were injected in 2-month-old rd1 mice either subretinally or intravitreally. Transduction efficiency of retinal bipolar cells and visual function were assessed 2 weeks after treatment. Capsid-mutated serotypes were able to increase bipolar cell transduction by as much as 20-fold, even with an intravitreal injection. In the Morris water maze task, the ChR2-treated mice learned the task nearly as well as the wild-type mice, while the untreated rd1 mice did not learn the task. Retinal patch clamp recordings of bipolar and ganglion cells showed that depolarization can be mediated by ChR2 activation. Collectively, these results warrant additional studies evaluating the perceptual threshold and visual acuity in these animals (17).

An attempt to identify novel nonretinoid small molecules that bind to mutant opsin and act as pharmacological chaperones for the potential treatment of adult dominant retinitis pigmentosa led to the discovery of **BIK-381** by scientists at Bikam Pharmaceuticals. In vitro treatment of HeLa cells expressing the P23H mutant form of opsin with BIK-381 (40 μM) was able to rescue the misfolded mutant protein and resulted in enhancement of the amount of rhodopsin produced in these cells, while promoting opsin localization to the cell surface. BIK-381 also caused a reduction in the association of misfolded mutant opsin with the endoplasmic reticulum (ER) molecular chaperone calnexin, which contributes to ER retention of the misfolded form of opsin. Aggregation of misfolded proteins in the ER induces a proapoptotic response, leading to photoreceptor cell death and eventual blindness due to retinal degeneration. In vivo, oral administration of BIK-381 at 5 and 25 mg/kg to mice displayed a good pharmacokinetic profile (peak serum concentrations of 368 and 1707 ng/mL and oral bioavailability of 109% and 93%, respectively). Therefore, the use of pharmacological chaperones may prove beneficial for the treatment of ocular conditions associated with mutations in the photoreceptor cell protein opsin (18).

Glaucoma

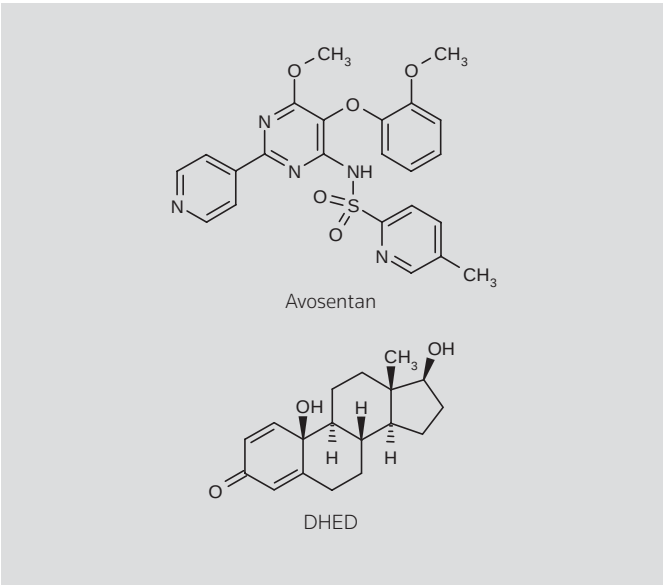
The ocular hypotensive compound **PF-04475270** (Pfizer), a prodrug of CP-734432, is a prostanoid EP_4 receptor agonist that is rapidly hydrolyzed to CP-734432 in rabbit corneal homogenates and exhibits good permeability in a human corneal epithelial cell (cHCE) model. PF-04475270 is a candidate for clinical development for the treatment of glaucoma and ocular hypertension. Prasanna et al. presented results showing that topical dosing (single and multiple doses) of PF-04475270 to normotensive beagle dogs is more effective than latanoprost at lowering IOP; maximum decreases in IOP

of 30-45% and 20%, respectively, were achieved by PF-04475270 at 24 h postdose and by latanoprost at 12-18 h postdose (19). In monkeys with unilateral laser-induced glaucoma, PF-04475270 (0.0025%) displayed similar efficacy to latanoprost in causing a significant decrease in IOP at 6 h postdosing ($P < 0.05$), an effect which persisted for up to 24 h after a single dose (20).

Scientists from the Mount Sinai School of Medicine and Speedel showed that topical application of **avosentan** (SPP-301), a new endothelin ET_A receptor antagonist, to the eyes of monkeys with laser-induced unilateral glaucoma reduced IOP dose-dependently. Administration of SPP-301 at three different concentrations (0.003, 0.03 and 0.3%) twice daily for 5 consecutive days resulted in a significant reduction in IOP; the maximum IOP reduction (21%) was seen at 2-3 h following morning dosing of 0.3% and lasted for at least 6 h. The 0.3% SPP-301 dose also produced a significant reduction in IOP (11%) following morning dosing in untreated normal eyes. One in eight eyes treated with 0.3% SPP-301 exhibited mild conjunctival discharge or a closed eye. The study suggests that endothelin receptor antagonists may represent good candidates for the development of antiglaucoma treatments (21).

It is known that topical administration of a 17β-estradiol (E2) prodrug confers retinal protection in rat glaucoma models. Koulen et al. elegantly reported that 10β,17β-dihydroxyestra-1,4-dien-3-one (**DHED**), a novel prodrug of E2 with no systemic effects, induces significant protection of retinal ganglion cells in ovariectomized rats with surgically elevated IOP. In experiments conducted by University of North Texas Health Sciences Center and University of Missouri researchers, treatments were administered topically as eyedrops and animals were sacrificed 19-30 days after IOP elevation. The in vitro transcorneal permeability of DHED was 10 times higher than that of E2, and the DHED to E2 conversion rate in the rat retina was the highest among all ocular and nonocular tissues tested. In vivo, significant protection of the ganglion cell layer (as measured by reduction in apoptotic cell numbers by a TUNEL assay) was observed in the DHED group, although IOP remained unchanged when compared to vehicle. Visual function assessed by contrast sensitivity at a given spatial frequency was significantly preserved with DHED treatment. The neuroprotective effects of DHED exceeded those of existing or experimental ophthalmic drugs. DHED, by selectively converting in vivo to E2 inside the eye, provides significant retinal ganglion cell protection while overcoming the setbacks of topical or systemic steroid administration (22).

Aerie Pharmaceuticals reported on novel Rho kinase (ROCK) inhibitors identified in a screen of 6-aminoisoquinoline amides. Structure–activity relationship (SAR) analysis and modification led to **AR-12286** (ROCK2 K_i = 1.5 nM). This agent and others identified were found to reversibly affect cell shape and cytoskeletal structure in porcine and human trabecular meshwork (PTM and HTM) cell lines, and AR-12286 was chosen for further development (23). In Dutch belted rabbits and cynomolgus monkeys, once-daily dosing with AR-12286 significantly reduced IOP and demonstrated a longer-lasting effect than the ROCK inhibitor Y-39983. In a study of ocular tolerability in New Zealand white rabbits, dosing 8 times daily for 7 days resulted in mild conjunctival and iridial hyperemia (24). A further study in monkeys indicated that the reduction in IOP was due to an increase in tonographic outflow facility, which increased 39% 4 h after administration of a single dose of 0.6% AR-12286 in drug-



Glaucoma

treated eyes compared to contralateral vehicle-treated eyes. Aqueous humor flow rates did not change, and pupil size increased in drug-treated eyes compared to baseline but not compared to vehicle-treated contralateral control eyes (25).

Retinopathies – macular degeneration

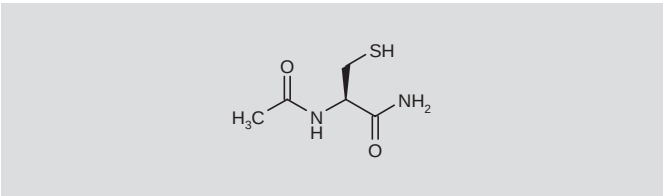
Alcon researchers presented data on **AL-8309A**, a selective serotonin 5-HT_{1A} receptor agonist (IC_{50} = 25 nM) that may be useful for the treatment of AMD by protecting against retinal oxidative stress. The drug protected RPE cells from oxidative damage induced by the cytotoxin 7-ketocholesterol. A significant concentration-dependent increase in the survival of RPE cells exposed to oxidative damage was seen following treatment with AL-8309A (0.01-100 μM) for 12 h (EC_{50} = 4.8 nM). The protective effects of AL-8309A correlated with increases in MEK1/2 and ERK-1/2 phosphorylation and subsequent upregulation of antiapoptotic and antioxidant proteins such as SOD1, SOD2, Bcl-2 and Bcl-XL (26). AL-8309A was also evaluated in vivo for its ability to protect the rat retina from light-induced injury, a commonly used model for AMD. Retinal damage caused by exposure to blue light for 6 h was completely ameliorated following topical ocular dosing with AL-8309A (1.75%). The protective effects of a single dose of AL-8309A were found to persist for 48 h (27). In addition, Wang et al. reported that s.c. administration of AL-8309A (10 mg/kg) to albino rats with photic-induced retinopathy due to a 6-h exposure to blue light resulted in prevention of RPE and photoreceptor damage and was correlated with a decrease in complement C1q, C3, factor B, factor H and membrane attack complex deposition in the outer retina. AL-8309A may be potentially useful for the development of a treatment for AMD (28). Evaluation of a topical formulation (AL-8309B) as an ophthalmic solution is under way for the treatment of geographic atrophy secondary to AMD in a phase III trial that is currently recruiting patients.

A study communicated by TransMolecular showed that **TM-601** (chlorotoxin), a synthetic polypeptide with a scorpion venom-derived

sequence, selectively binds to vascular cells in choroidal neovascularization (CNV) lesions and causes CNV regression. Intraocular injection of TM-601 (50 µg) in mice with laser-induced CNV at the time of or 1 week following rupture of Bruch's membrane caused a 50.4% reduction in CNV area compared to vehicle-treated eyes. Daily periocular injections of the compound (10 µg) did not significantly reduce CNV size; however, reductions in CNV size of 65-70% were seen following injections of 50, 250 or 1000 µg. Selective localization of TM-601 to new vessels was observed by immunohistochemistry of ocular sections following intraocular or periocular injections. Apoptosis of endothelial cells induced by TM-601 (50 µg) could account for a 62.4% regression in CNV size compared to a CNV reduction of 9.6% without apoptosis in vehicle-injected eyes. The proapoptotic activity of TM-601 in CNV lesions and its demonstrated selectivity for vascular cells within CNV lesions make this compound a good candidate for future development (29).

The novel antioxidant ***N*-acetylcysteine amide** (NACA), with a previously demonstrated ability to protect human RPE cells against oxidative cell death, was found to inhibit oxidative stress-induced injury to the RPE in vitro and prevent retinal degeneration in vivo. In a study conducted by Washington University and Missouri University researchers, NACA preincubation of ARPE-19 cells caused a complete inhibition of *tert*-butylhydroperoxide-induced RPE lipid peroxidation ($P < 0.0001$). In addition, NACA pretreatment significantly enhanced the activity of glutathione peroxidase, a key enzyme involved in cell detoxification, and caused a restoration of catalase concentrations to unstressed control levels. The functional deterioration of cell monolayer health as a result of exposure to *tert*-butylhydroperoxide and oxidative stress was also prevented by NACA pretreatment. In vivo, early testing in mice revealed good tolerance of the highest concentration tested (550 mg/kg/day), with promising potential for the prevention of outer nuclear layer cell death. These results indicate that NACA may be potentially useful for the delay or prevention of retinal degenerative conditions (30).

Ranibizumab (Genentech), an anti-vascular endothelial growth factor (anti-VEGF) humanized monoclonal antibody fragment, was launched in the U.S. in 2006 for the treatment of neovascular wet AMD. Several studies showing promise for the efficacy of ranibizumab combinations in various retinopathies were presented during the meeting. Boyer et al. reported that treatment of patients with subfoveal neovascular AMD with a combination regimen of the platelet-derived growth factor (PDGF) inhibitor **E-10030** and ranibizumab was well tolerated in a phase I trial. This dose-escalating, uncontrolled, single- and multiple-dose, multicenter study involved the administration of E-10030 either as a single injection of 0.03 mg/eye followed by three monthly injections of ranibizumab (0.5 mg/eye) or as repeated (three monthly) injections of one of four different doses of E-10030 (0.03, 0.3, 1.5 and 3.0 mg/eye) with ranibizumab (0.5 mg/eye). Combined analysis of all subjects to date revealed a gain of at least 15 letters in 32%, 45% and 60% of patients, respectively, at weeks 4, 8 and 12, at which time points standardized ETDRS visual acuity displayed a mean change of +11.1, +13.4 and +15.7, respectively. Fluorescein angiography assessment revealed neovascular regression in 12.85% of lesions. Despite limitations associated with the lack of control and the small sample size (n = 3-8 patients per dose group), the study suggests the potential bioactivity of the combination therapy, manifested as regression of the neovascular membrane (31).



N-Acetylcysteine amide

Similarly, preliminary results from a phase I study of intravitreal **ARC-1905** (Ophthotech), a complement factor 5 inhibitor, in combination with ranibizumab for the treatment of neovascular AMD, revealed no signs of acute toxicity. In the study, intravitreal administration of ARC-1905 as three monthly doses (four cohorts receiving 0.03, 0.3, 1 or 3 mg/eye) in combination with monthly ranibizumab (0.5 mg/eye) correlated with a mean change in visual acuity of +9.5 letters and a mean change in center point thickness of –104 µm at week 4 following combination treatment (32).

Finally, intravitreal administration of ranibizumab alone was found to be safe and effective in reducing retinal thickness and improving visual acuity in patients (N = 20 eyes) with polypoidal choroidal vasculopathy (PCV) in a small, prospective phase I/II trial. This open-label, single-center, nonrandomized, uncontrolled study assessed the effects of intravitreal ranibizumab (three consecutive monthly injections of 0.5 mg or 0.3 mg/0.05 cc) in patients with exudative, active PCV, defined as choroidal neovascularization which displayed occult characteristics on fluorescein angiography and polypoidal interconnecting vascular channels with saccular dilatations on indocyanine green angiography and/or fluorescein angiography. Best corrected visual acuity (BCVA) displayed an improvement from baseline (BCVA = 20/127) after the first three ranibizumab injections and at the last follow-up visit (BCVA values = 20/116 and 20/79, respectively). Optical coherence tomography (OCT) central subfield thickness was found to be reduced at the same time points compared to baseline (233 µm vs. 302 µm). Treatment-related adverse events included the development of a macular hole in one eye, which exhibited vitreous and subretinal hemorrhage at enrollment, posterior vitreous detachment with mild hemorrhage in one eye, and two patients experienced cataract progression which required cataract extraction (33). Evaluation of intravitreal ranibizumab in 10 patients with PCV using spectral domain OCT analysis to assess changes in the outer retinal layers revealed a marked improvement as a result of a significant decrease in retinal thickness (> 25% decrease and > 100 µm in size) in 80% of cases. A regression in inflammatory signs and exudative reaction was observed in 90% of patients; frequent exudative recurrences (90%) were efficiently overcome by subsequent intravitreal injections of ranibizumab. The development of a fibrotic reaction was observed in 60% of cases, which was either minimal or extensive (30% of patients) and included polyps that persisted following treatment. The occurrence of inflammatory changes near the polyps was taken as an indication to continue treatment (34).

Research conducted at Neurotech suggested that the intraocular polymer implant **NT-501** may be used for the treatment of dry atrophic macular degeneration, a condition leading to degeneration

of cone photoreceptors, for which no effective treatment is currently available. An ongoing phase II study was designed to evaluate the safety and efficacy of NT-501, an encapsulated ciliary neurotrophic factor (CNTF)-secreting cell implant, in 48 patients with vision loss associated with atrophic macular degeneration. Preliminary results revealed that a high dose of NT-501 resulted in stabilization of BCVA at 12 months; treated patients (96.3%) lost fewer than 3 lines of vision (or 15 letters) compared to patients in the sham-operated group (75%). OCT demonstrated statistically significant and dose-dependent increases in retinal thickness following NT-501 as early as 4 months postimplantation (high and low NT-501 dose). There were no changes in a and b waves by electroretinography in treated or sham-operated subjects and the progression of atrophic lesion size remained equivalent in these groups. Over the course of the implant period there were no detectable serum antibodies to either the NT-501 implant or the CNTF protein, which supports the safety and tolerability of the procedure. Full results from this study will be presented upon completion of the 12-month follow-up period and are expected to permit the design of future phase III studies to further evaluate NT-501 in dry atrophic macular degeneration (35).

Safety and efficacy results for **IBI-20089** (Icon Bioscience), a triamcinolone acetonide (TA) intravitreal injection formulated using the Verisome technology, have been evaluated in a phase I trial in patients with cystoid macular edema (CME). Patients (N = 10) with CME as a result of retinal vein occlusion received one of two doses (6.9 mg/25 µL TA or 13.8 µg/50 µL TA) and were subsequently followed for up to a period of 12 months. Preliminary results from this study showed IBI-20089 administration to be safe, with only one severe adverse event occurring in the high-dose cohort. There was also evidence of controlled-release efficacy for TA, with the 13.8-mg dose displaying more evidence of efficacy compared to the 6.9-mg dose; a significant reduction from baseline in mean central subfield OCT thickness was seen at day 30 in the 13.8-mg cohort compared to the 6.9-mg cohort. The preliminary evidence for IBI-20089 efficacy presented in this study would support further evaluation of the compound in larger patient cohorts (36).

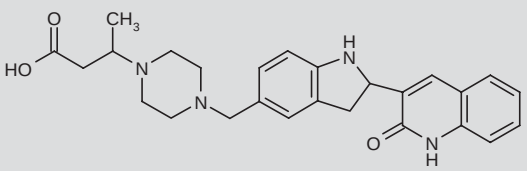
A screen for the identification of VEGFR-2 kinase inhibitors with suitability for local ocular delivery conducted by Merck & Co. led to the selection of **KDR-4**, a compound that displayed high in vitro potency (IC_{50} = 79 and 18 nM, respectively, in enzyme and cell culture assays). VEGFR and its receptors have been described as mediators of the angiogenic component of wet AMD, and as such represent targets for the development of treatment modalities. Preliminary efficacy evaluation of KDR-4 revealed an in vivo IC_{50} of 30 nM, while the compound had a half-life of 4.9 h in pharmacokinetic profiling. The compound yielded no treatment-related adverse events following intraocular injection in rabbit eyes, with only a few histopathological alterations such as occasional mononuclear inflammatory cells in the posterior vitreous following administration of the highest doses (100 and 250 µg). KDR-4 has been selected for further formulation development and is believed to be suitable for intravitreal delivery via a sustained-release formulation (37).

Heier et al. reported on a subgroup analysis of results from the CLEAR-IT 2 study, a randomized, double-blind phase II trial of VEGF Trap-Eye (**aflibercept**) in patients with neovascular AMD. This study allowed the identification of patient groups more likely to respond. Study subjects were treated with aflibercept 0.5 or 2.0 mg monthly or 0.5, 2.0 or 4.0 mg quarterly, with monthly reassessment and PRN dosing to 1 year. In the overall study group (N = 157), BCVA significantly improved over 1 year, with a mean increase of 5.3 letters. The mean gain was 8.26 letters in patients aged 75 or less, compared to 3.73 letters for those over 75. The mean gain in patients with a BCVA at baseline of 54 letters or less was 7.54 letters, compared to 3.65 letters in those with a baseline BCVA of over 54 letters. Baseline lesion size and whether patients were treatment-naïve did not affect treatment responses (38). Aflibercept is being investigated (phase III) by Bayer and Regeneron for macular degeneration and is also in phase III trials for various cancers.

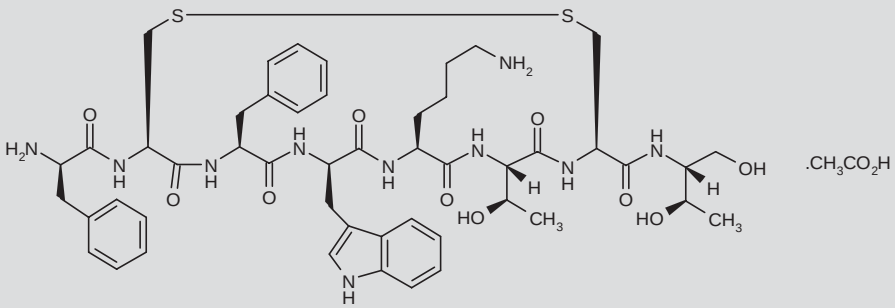
In a study in patients with retinitis pigmentosa and cystoid maculopathy, BCVA improved in 18 (10 patients) of 34 eyes (17 patients) after treatment with **octreotide** long-acting repeatable (LAR). Patients included in the study had failed treatment with acetazolamide and received octreotide LAR 20 mg in monthly i.m. injections for a mean of 17.7 months. No positive effect on BCVA was seen in 16 eyes (9 patients), and 4 patients were still being treated at the time of reporting. Long-lasting stable improvement led to discontinuation of treatment in three patients, another five discontinued due to absence of improvement and three discontinued due to adverse events. It was concluded that further work is required to determine which patient characteristics might be predictive of response to octreotide (39).

Early findings of the EMPOLS study, which is evaluating the preventative potential of oral supplementation with **lutein** in patients with early signs of AMD (N = 60), were reported at the meeting. Study subjects served as controls (n = 20) or were given nonester lutein 10 mg for 6 months. Over 6 months, macular pigment density at the fovea increased significantly with lutein supplementation, but not in the untreated group. BCVA remained stable in both groups over the course of the study, while Pelli-Robson contrast sensitivity significantly increased in the supplementation group. It was also found that the response to supplementation could not be predicted from serum carotenoid levels. Further investigation of the study data is under way (40).

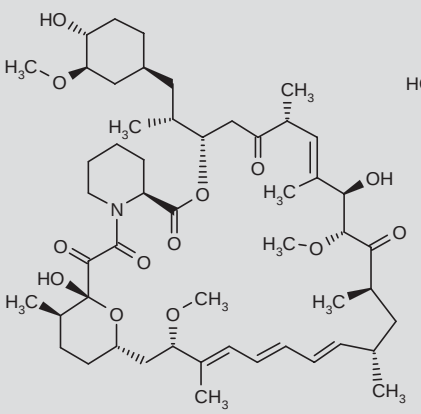
Data from a clinical study in patients with CNV due to AMD and from an evaluation of effects on CNV in a monkey model were also reported for **KH-902**, a humanized fusion protein of key domains from VEGFR-1 and VEGFR-2. KH-902 reduced the incidence of laser-induced CNV formation in monkeys, and the leakage of CNV in the control animals which were crossed over to KH-902 40 days after laser exposure was reduced notably. In the clinical study, 28 patients were enrolled and treated with intravitreal doses of 0.05, 0.15, 0.5, 1.0, 2.0 or 3.0 mg KH-902. Dose-limiting toxicities were not encountered and the maximum tolerated dose was 3.0 mg/0.05 mL/eye at each injection. No serious adverse events or drug-related systemic adverse events were seen and ocular adverse events were mild to moderate in severity. Transient intraocular pressure elevation after injection and injection-site subconjunctival hemorrhage were the most common ocular adverse events. Most patients (85.7%) gained visual acuity in the study and none lost acuity. Mean visual acuity increased 19.6 letters. After 42 days, the mean change in central retinal thickness was −77.19 microns and mean change in total macular volume was −0.62 mm^3. KH-902 treatment was also associated



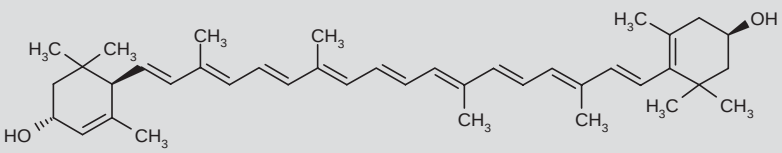
KDR-4



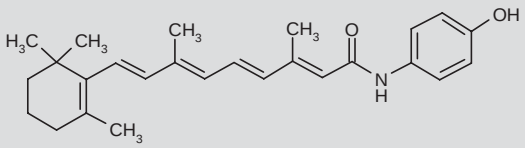
Octreotide acetate



Sirolimus



Lutein



Fenretinide

Retinopathies – macular degeneration

with reduced CNV leakage (41). KH-902 is being developed by Chengdu Kanghong Biotechnologies.

Sirolimus (rapamycin) is an immunosuppressive agent undergoing clinical evaluation for macular degeneration. Researchers at Macusight released pharmacokinetic data of a proprietary sirolimus depot-forming ocular formulation showing sustained dose-dependent delivery. In preclinical experiments with rabbits, a single subconjunctival injection of the formulation containing 66, 220 or 660 µg of sirolimus achieved substantial transscleral delivery. Detectable sirolimus levels in the sclera/conjunctiva, retina, choroid and vitreous humor lasted 60-90 days. Three days after injection of 660 µg of sirolimus per eye (1320 µg total), mean drug concentrations were 7518, 237 and 33 ng/g in the sclera/conjunctiva, retina/choroid and vitreous humor, respectively. The mean sirolimus concentration in peripheral blood was 11 ng/mL. Sirolimus levels declined exponentially over time, with a $t_{1/2}$ of 6-7 days. A strong correlation was found between the sirolimus concentration in peripheral blood and ocular tissues. The comparison of these preclinical results with systemic pharmacokinetic data in humans suggested similar ocular pharmacokinetics. In a prospective, randomized, open-label study, patients received a subconjunctival injection in one eye of 220, 440, 880, 1320 or 1760 µg of the proprietary sirolimus formulation. Peripheral blood sirolimus concentrations in these patients were also dose-related and followed a kinetic profile similar to that found in rabbits (42).

Capone et al. released data from a phase I dose-escalation study of single and repeated intravitreal doses of **JSM-6427**, a highly potent and specific small-molecule antagonist of $\alpha_5\beta_1$ that in animal models inhibits new CNV, regresses established CNV and inhibits ocular and systemic inflammation and fibrosis. All single-dose patients are in extended safety follow-up and show no signs of toxicity to date. Despite extensive treatment for wet AMD, prior treatments and long-standing disease, BCVA increased by a mean of +3.5 to +8.0 letters at day 15, depending on the dose group, and remained increased through day 43 in the two highest dose groups combined (mean +6.8 letters). Single intravitreal injections of JSM-6427 appear to be well tolerated in patients with neovascular AMD and may show early indications of biological activity. A sustained-release formulation is in development for the prevention and treatment of neovascular AMD (43).

Finally, preliminary results (1-year efficacy analysis) from a 2-year double-masked, placebo-controlled phase II trial of **fenretinide** for the treatment of geographic atrophy (GA) in patients with AMD were presented by Sirion Therapeutics. Fenretinide, a synthetic retinoid which binds to retinol-binding protein (RBP) and reduces retinol uptake by the pigment epithelium, was administered at a dose of 100 or 300 mg to subjects (N = 246) who had a total atrophic area of 2.54-20.32 mm^2, as assessed by the Digital Angiography Reading Center. The growth rate of the aggregate GA lesion area was the primary anatomical endpoint of the study, which also included the relationship between serum RBP and change in the GA area as a secondary endpoint. At baseline, the mean GA lesion area in the study eye and the mean serum RBP level were recorded at 9.72 mm^2 and 5.94 mg/mL, respectively. At month 12 of treatment, a dose-related decrease in mean serum RBP was observed: 2.92 and 1.91 mg/dL, respectively, with 100 and 300 mg fenretinide. Placebo-treated individuals displayed a mean serum RBP of 5.24 mg/dL. The mean GA lesion area at 18 months was recorded at 2.66, 2.84 and 1.80, respectively, following placebo, 100 and 300 mg fenretinide. Treatment with fenretinide in this study, which is the first trial to use lesion size and growth rates as anatomical endpoints, was found to be well tolerated (44). Preliminary demographic data from this study also presented at the meeting revealed a mean age of 78 years and a mean lesion size of 9.44 mm^2 (45).

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