Drugs of the Future 2007, 32(7): 643-654

CCC: 0377-8282/2007

**Meeting Report**

# Ophthalmic therapeutics: new basic research and clinical studies

## Highlights from the Annual Meeting of the Association for Research in Vision and Ophthalmology (ARVO) 2007: The Aging Eye

***E. Ferrer, P. Cole***
*Prous Science, P.O. Box 540, 08080 Barcelona, Spain*

**CONTENTS**



**Abstract**

The Annual Meeting of the Association for Research in Vision and Ophthalmology (ARVO) took place in Fort Lauderdale, U.S.A., on May 6-10, 2007. This meeting brought together an international panel of members from different disciplines within the ophthalmology field to discuss recent research developments in new ocular therapeutics. This article highlights selected work from this meeting.

### Introduction

Over 10,000 scientists from around the world gathered at the Annual Meeting of the Association for Research in Vision and Ophthalmology (ARVO) to discuss age-related eye diseases, their treatment and the latest research to find cures. Ocular disorders, including age-related macular degeneration (AMD), glaucoma, cataracts and diabetic eye disease, were at center stage at this year's conference. The meeting included over 6,000 paper and poster presentations covering a wide range of topics. Here, we highlight some of the most relevant discoveries on new drug targets and novel therapies, as well as the most recent clinical trial results.

### New drug targets

*Glaucoma*

1. TRP channels: TRPV1

The vanilloid receptor-1 (TRPV1 or VR1), a member of the transient receptor potential (TRP) family of ion channels, is a nonselective cation channel that is highly expressed in sensory neurons and upregulated during inflammation. In the eye, TRPV1 expression has been identified in the corneal nociceptive nerve terminals (1), which are able to respond to mechanical, chemical and thermal stimuli. Upon corneal injury, local inflammatory substances may activate the TRPV1 receptor in corneal nerve terminals, thus mediating inflammation and pain. Spanish researchers demonstrated that capsaicin-induced corneal irritation may be attenuated via TRPV1 gene silencing. Topical application of small interfering RNA (siRNA) targeting the TRPV1 receptor reduced the behavioral response to corneal irritation in guinea pigs treated with topical capsaicin. Thus, decreasing TRPV1 expression appears to reduce chemical sensitivity of corneal nociceptors (2).

In glaucoma, elevated intraocular pressure (IOP) may trigger the degeneration of retinal ganglion cells (RGCs) and their axons by different mechanisms, including intracellular calcium overload. Researchers at the Vanderbilt Eye Institute have investigated the role of the TRPV1 channel in RGC survival *in vitro*. Retinal expression of TRPV1 was found to be upregulated nearly 20-fold in hypertensive aged DBA2J mice compared to young normotensive animals. Also, TRPV1 overexpression in the RGC-5 cell line caused apoptosis in 50% of cells, which was prevented by ruthenium red, a nonspecific cation channel blocker. Antiapoptotic effects could also be mimicked by co-transfecting TRPV1 siRNA into RGC-5 cells. These findings suggested that TRPV1 channel overexpression may interfere with normal calcium regulation in RGCs, contributing to RGC death in glaucoma (3).

Further experiments revealed that TRPV1 channel expression increased by 16-fold in primary RGC cultures exposed to elevated hydrostatic pressure for 24 h, resulting in a 35% loss of RGCs. Treatment with the TRPV1 antagonist iodo-resinferatoxin (IDX) decreased pressure-induced RGC death, whereas capsaicin at ambient pressure mimicked high-pressure conditions, decreasing RGC density by 50%. Capsaicin also raised calcium accumulation in RGCs by 2.5-fold, which could be reduced by 62% with IDX treatment. Together, these results indicate that TRPV1 activation may contribute to pressure-induced RGC death via an increase in intracellular calcium (4).

In addition to TRPV1, other members of the TRP channel family have been identified in aqueous humor outflow pathway tissues —trabecular meshwork and ciliary body—, where they may play relevant roles in the regulation of aqueous humor outflow, therefore representing potential therapeutic targets in glaucoma. High expression of *TRPC4, TRPC6, TRPM4* and *TRPM7* genes was identified in porcine trabecular meshwork tissue. Most of these channels play a role in mechanotransduction and shear stress and membrane stretch-sensing in other cell types. Incubation of trabecular meshwork cells under chronic oxidative stress conditions caused over 5-fold upregulation of *TRPC6* (5).

2. The sodium pump ATPase

IOP is maintained by the balance between aqueous humor secretion (inflow) and outflow from the eye. The aqueous humor is formed mainly by transferring sodium chloride from stromal cells in the ciliary pigmented epithelium into the posterior chamber, together with water following the osmotic gradient. The final step of this process involves sodium ion release into the aqueous humor by the $Na^+/K^+$-ATPase. Researchers at the Universidad Complutense in Madrid, in collaboration with Sylentis, have investigated the effects of blocking $Na^+/K^+$-ATPase activity with specific siRNA against the $\alpha$ 1/2 and $\beta$ 1/2 subunits, on rabbit IOP. Topical instillation of siRNA targeting the $\alpha$ 1 and $\alpha$ 2 ATPase subunits caused 18.13% and 15.28% reductions in IOP that lasted for 96 and 75 h, respectively. Similarly, silencing the $\beta$ 1 ATPase subunit decreased IOP by 16% for 88 h, whereas targeting the $\beta$ 2 subunit had no effect. In general, IOP-lowering effects of siRNA ATPase sequences were more sustained than those elicited by latanoprost (23.4% IOP reduction for 5-6 h) and similar to those of other siRNAs targeting carbonic anhydrases and beta-adrenoceptors (6).

3. *GADD45B*

The growth arrest- and DNA damage-inducible 45$\beta$ (*GADD45B*) gene belongs to a family of genes that are rapidly induced in response to genotoxic stress. Researchers at the Northwestern University School of Medicine have discovered that *Gadd45b* expression is upregulated in the retinas of aged mice compared to young mice. The Gadd45b protein was localized specifically in the RGC layer, where it also increased NF-$\kappa$B activation (a *Gadd45b* gene transcription regulator). When RGCs were exposed to oxidative stress conditions, high levels of *Gadd45b* expression and NF-$\kappa$B activation were detected. These findings indicate that *GADD45B* signaling may be a specific stress response pathway with neuroprotective actions in aging RGCs and may reflect increased oxidative stress during aging. Modulation of *GADD45B* signaling pathways may be useful for preventing RGC loss in the aging retina (7).

*Age-related macular degeneration (AMD)*

1. Thioredoxin

The thioredoxin system controls cellular redox status by scavenging harmful intracellular reactive oxygen species. Increased expression of thioredoxin-1 (TRX-1) and its negative regulator thioredoxin-binding protein (TXNIP-1) was found in the retinas of aged and diabetic mice. In fact, hyperglycemia induced a time-dependent increase in both TRX-1 and TXNIP-1 protein expression. Thus, an altered TRX system correlates with decreased antioxidant capacity in the aged and diabetic retina (8). In addition, IOP elevation caused upregulation of TRX-2 expression in glaucomatous rat retinas (9). Thus, changes in the thioredoxin system may be associated with the retinal neurodegeneration process.

2. Cathepsin L

The protease cathepsin L has been shown to be important for endothelial progenitor cell-mediated neovascularization. Japanese researchers have demonstrated that cathepsin L inhibition significantly reduced retinal (49.6% *vs.* 26.0%) and choroidal neovascularization (CNV; 40.8% *vs.* 21.1%) in mice with oxygen-induced ischemic retinopathy and CNV, respectively, compared to vehicle-treated animals. These results indicate that cathepsin L may represent a new therapeutic target in ocular disease involving neovascularization (10).

3. CD59

CD59 belongs to the group of complement-regulatory proteins that protect host tissues from injury when complement is activated. A recent study highlighted that CD59a is downregulated during laser-induced CNV in mice. CD59-defective mice developed CNV early in the disease process and showed increased membrane attack complex (MAC) formation. Administration of a recombinant soluble CD59a-$IgG_{2a}$ fusion protein (rsCD59a-Fc) inhibited the development of CNV complex in the mouse model by blocking MAC formation and also inhibited the expression of angiogenic growth factors compared to control animals. Thus, inhibition of complement by rsCD59 may provide a novel therapeutic alternative to current treatments (11, 12).

*Allergic conjunctivitis*

1. CCR3 chemokine receptor

Researchers at Mitsubishi Pharma reported that prophylactic treatment with the CCR3 antagonist W-5 sup-

pressed allergen-induced inflammatory responses, including eosinophil, neutrophil and mast cell recruitment and mast cell degranulation, as well as clinical symptoms, in a mouse model of allergic conjunctivitis (13).

2. Protease-activated receptor 2 (PAR2)

Protease-activated receptor 2 (PAR2) is a potent mediator of tissue inflammation and is known to be activated by mast cell tryptase and cellular-derived trypsin in a number of inflammatory disorders. Researchers at the University of Colorado have identified trypsin and PAR2 expression in human conjunctival epithelial cells. Trypsin expression was upregulated by the inflammatory cytokines interleukin-1$\alpha$ (IL-1$\alpha$) and tumor necrosis factor-$\alpha$ (TNF-$\alpha$). Trypsin induced a rapid increase in the intracellular calcium concentration, NF-$\kappa$B nuclear translocation, IL-1$\alpha$, IL-1$\beta$, IL-6, IL-8 and TNF-$\alpha$ mRNA expression, and IL-6 and IL-8 protein secretion in a time- and concentration-dependent manner. All these effects were mediated via PAR2 activation, as anti-PAR2 antibodies blocked trypsin-stimulated responses (14).

## New experimental therapies

*Choroidal neovascularization (CNV)*

1. Sphingozumab

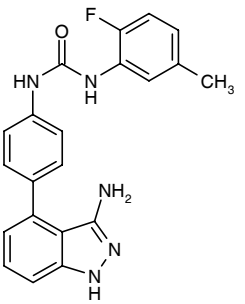
Researchers at Lpath have developed sphingozumab, a novel humanized monoclonal antibody against sphingosine-1-phosphate, a sphingolipid metabolite that has been shown to regulate cell growth, invasion and angiogenesis in cancer. In a mouse model of laser-induced CNV, intravitreal sphingozumab (5 $\mu$g/eye) inhibited CNV formation by 98.5% compared to vehicle. These results indicate that sphingosine-1-phosphate may play a role in CNV in this model and represents a novel therapeutic target for treating ocular diseases featuring pathological angiogenesis (15).

2. IMS-2186

Researchers at Immusol presented *in vivo* findings on a novel small nonsteroidal molecule, IMS-2186, which may have potential in treating CNV in eye conditions such as AMD. Due to its low water solubility, IMS-2186 is expected to slowly dissolve in the vitreous. IMS-2186 (2.5 mg/0.05 ml) was injected into the vitreous of rats with laser-induced CNV, with no toxic effects up to 36 weeks postinjection. Analysis of 175 CNV lesions revealed that IMS-2186 treatment reduced fluorescein angiographic leakage and caused a 26% reduction in neovascular lesions and a 40% decrease in endothelial cell proliferation compared to vehicle. These results indicate that IMS-2186 is a long-acting compound that could be used as add-on treatment to other antiangiogenic therapies (16).

3. AL-39324

Alcon researchers have investigated the antiangiogenic properties of AL-39324, a novel receptor tyrosine kinase (RTK) inhibitor, *in vitro* and *in vivo*. AL-39324 prevented vascular endothelial growth factor (VEGF)-induced increases in bovine retinal endothelial cell viability in a concentration-dependent fashion, with maximal effects at 100 nM. In a rat model of oxygen-induced retinopathy, AL-39324 was superior to other RTK inhibitors, namely PTK-787 (vatalanib; Novartis, Bayer Schering Pharma), in reducing retinal neovascularization. AL-39324 significantly decreased CNV lesion size by 70.6% compared to vehicle in a mouse model of laser-induced CNV. These results indicate that AL-39324 may be useful for the treatment of conditions featuring ocular neovascularization (17).




AL-39324

*Glaucoma*

1. MIM-D3

Nerve growth factor (NGF) exerts positive effects on neuronal survival, differentiation and repair via binding of the TrkA receptor tyrosine kinase. In glaucoma, elevated IOP and neurotrophin deprivation have been shown to cause RGC death. Researchers at Mimetogen tested the effects of a novel, highly potent and selective Trk receptor tyrosine kinase agonist, MIM-D3, on RGC death in a rat model of glaucomatous optic neuropathy. After glaucoma induction, animals were randomized to receive no treatment, MIM-D3, betaxolol 0.5% or a combination of the two agents. MIM-D3 was found to potentiate the neuroprotective effects of betaxolol, as combined treatment led to only an 8% RGC loss, compared to 21% and 29% loss with betaxolol and MIM-D3 treatment alone, respectively. Thus, the combination of an IOP-lowering agent with a neuroprotectant like MIM-D3 may be an effective strategy to prevent RGC loss in glaucoma (18).

*Uveal melanoma*

Uveal melanoma is the most common ocular malignancy and usually involves the development of metastatic disease, primarily in the liver, associated with poor prognosis.

1. MHC II vaccine

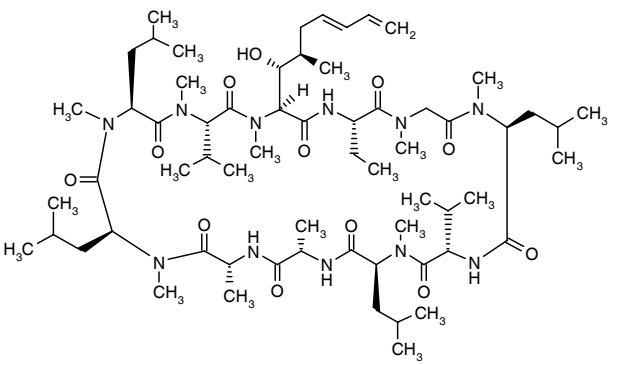
Researchers at the University of Maryland investigated the efficacy of a novel vaccine for the treatment of uveal melanoma consisting of uveal tumor cells geneti-

cally modified to express major histocompatibility complex II (MHC II). MHC II vaccines facilitate the presentation of MHC class II-restricted tumor peptides to responding CD4-positive T-cells. In fact, MHC II vaccines originated from primary uveal melanoma cells were able to activate CD4-positive T-lymphocytes from both healthy donors and uveal melanoma patients. These activated CD4-positive T-cells showed cross-reactivity with metastatic and primary uveal melanomas, but not with similar vaccines derived from breast and lung cancer cell lines. Uveal melanoma cell-based MHC II vaccines were also able to activate cytotoxic T-cells that killed primary and metastatic uveal melanoma cells (19).

*Uveitis*

Uveitis is a common ocular inflammatory condition that can be associated with systemic inflammatory conditions, autoimmune diseases or ocular infection, although the etiology is unknown in some cases. Uveitis is a serious eye condition that if left untreated can lead to vision loss.

1. Voclosporin

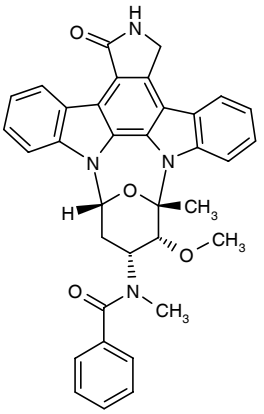


The efficacy of voclosporin (LX-211, ISA-247; Lux Biosciences), a novel calcineurin inhibitor, in experimental autoimmune uveoretinitis (EAU) in rats was investigated by researchers at Lux Biosciences and the National Eye Institute. Prophylactic and therapeutic use of voclosporin (40 mg/kg s.c.) prevented the development of EAU in a similar fashion to ciclosporin treatment. Therapeutic treatment with voclosporin at 10 mg/kg was already effective in reversing EAU (20).

2. Bevacizumab

University of Bern researchers have tested the antiinflammatory effects of bevacizumab (Avastin®; Genentech, Roche) in a murine model of endotoxin-induced uveitis (EIU). Intravitreal bevacizumab (100 mg/4 ml) significantly decreased mean inflammatory cell count on the anterior and posterior eye segment compared to contralateral vehicle-treated eyes, and no local inflammation at the site of injection was detected (21).

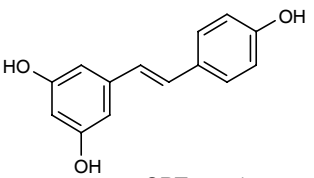
3. Midostaurin



Novartis's protein kinase C (PKC) inhibitor midostaurin (PKC-412) demonstrated potential efficacy in preventing retinal inflammation in a murine model of EIU. PKC-412 dose-dependently reduced plasma and retinal levels of proinflammatory IL-6, monocyte chemoattractant protein-1 (MCP-1) and macrophage inflammatory protein-1$\alpha$ (MIP-1$\alpha$) that were elevated after lipopolysaccharide (LPS)-induced EIU, hence preventing leukocyte recruitment into the retina (by more than 90%) (22).

*Optic neuritis*

1. SRT-501, SRT-647



SRT-501 (resveratrol)

Optic neuritis is a common inflammatory and demyelinating condition of the optic nerve that is often associated with multiple sclerosis (MS). Researchers at Sirtris Pharmaceuticals have investigated the effects of SRT-501 (resveratrol) and SRT-647, two histone deacetylase SIRT1 activators, in a model of experimental autoimmune encephalitis (EAE) in mice. Modulating SIRT1 activity with SIRT1 activators like resveratrol has demonstrated neuroprotective activity in models of axonal degeneration. Induction of EAE by active immunization with proteolipid protein peptide resulted in optic neuritis with evident inflammatory cell infiltrates and RGC loss in two-thirds of mouse eyes. Animals treated with intravitreal resveratrol at 100 $\mu$M or SRT-647 at 66.67 mM on days 0, 3, 7 and 11 after immunization experienced a dose-dependent decrease in RGC death that reached control levels by day 14. A single dose of resveratrol of 100 $\mu$M on day 11 was sufficient to attenuate RGC loss and preserve axon function at day 14. These findings suggest that activating SIRT1 might protect from neuronal damage in patients with optic neuritis associated with MS. However, as

SIRT1 activator treatment did not reduce optic nerve inflammation, concomitant use of immunomodulatory therapies may be advised (23). Resveratrol is also in phase I clinical studies at Sirtris for the treatment of type 2 diabetes and obesity.

## Results of clinical studies

*SNJ-1656 (Y-39983)*

The safety of Senju's SNJ-1656 (Y-39983) has been demonstrated in a randomized, double-blind, placebo-controlled phase I clinical study conducted by Japanese researchers. SNJ-1656 is a new Rho-associated coiled coil-forming protein kinase (ROCK) inhibitor that has shown potential for the topical treatment of glaucoma. This trial evaluated different doses of SNJ-1656 ophthalmic solution (0.003%, 0.03%, 0.05% or 0.1%) in 45 enrolled healthy volunteers. Following a single instillation, all doses of SNJ-1656 significantly reduced IOP compared to placebo at 2 and 4 h. Similar results were obtained in repeated instillation tests where 0.05% and 0.1% SNJ-1656 was given once or twice daily for 1 week. Only topical adverse events were reported, with conjunctival injection (bulbar and palpebral conjunctiva) being the most significant (24).

*Bevacizumab*

Clinical trial data on intravitreal bevacizumab (Avastin®; Genentech, Roche) in vision disorders continue to accumulate, with results from several trials conducted by the PanAmerican Collaborative Retina Study Group (PACORES). The pharmacokinetics of bevacizumab after intravitreal injection were assessed in serum and vitreous samples from patients treated with an injection of 1.25 mg. Peak intravitreal bevacizumab levels were detected 2-5 days after injection and vitreal drug had an elimination half-life of 10 days. Serum levels paralleled those of vitreous levels, but the drug was detected in the serum of only 15% of patients (25).

PACORES evaluated intravitreal bevacizumab in patients with CNV not associated with AMD in a study including 69 patients (69 eyes) treated at 8 centers in 7 countries. With one or more injection of 1.25 or 2.5 mg administered, a visual acuity improvement of 2 or more lines was seen in 69% of eyes and stability in visual acuity was noted in 29% (26). A similar PACORES investigation in CNV related to AMD in 87 patients (92 eyes) showed that after a mean follow-up of 6.8 months, best-corrected visual acuity remained stable in 35.9% of eyes, improved in 50% of eyes by 2 or more lines and declined by 2 or more lines in 14.1% of eyes. Mean central macular thickness also decreased significantly (27).

PACORES also investigated the treatment in 64 patients (78 eyes) with diabetic macular edema. Best-corrected visual acuity remained stable in 41.1% of eyes, improved in 55.1% of eyes by 2 or more lines and declined by 2 or more lines in 3.8% of eyes after a mean follow-up of 6.3 months. Mean central macular thickness decreased significantly (28). Further investigation into the same doses of intravitreal bevacizumab included 36 eyes with macular edema secondary to branch retinal vein occlusion. After a mean follow-up of 29.4 weeks, central macular thickness was significantly decreased and visual acuity improved by 3 or more lines in 27 eyes while remaining stable in 9 eyes; none lost more than 3 lines of visual acuity (29).

*Ranibizumab*

Ranibizumab (Lucentis®; Novartis, Genentech) has been investigated in several large studies in patients with AMD. PROTECT, an open, multicenter phase II study, included 32 patients with AMD who were treated with verteporfin photodynamic therapy (PDT) plus ranibizumab 0.5 mg given at baseline and then monthly for 3 months. Severe vision loss did not occur, and most patients (69%) required only the initial PDT. Reduced visual acuity was seen in 6 patients (30).

In the PRospective OCT (ocular coherence tomography) imaging of patients with neovascular AMD Treated with intra-Ocular Lucentis (PrONTO) study, 40 patients received 3 consecutive monthly injections of ranibizumab 500 μg. Mean visual acuity scores improved by 9.3 letters at 1 year, with 82.5% of patients having no loss in letters from baseline. There were no drug-related adverse events (31).

The NEI VFQ-25 was used to evaluate patient-reported vision-related function in the phase III MARINA trial in which patients with neovascular AMD were randomized to sham treatment or ranibizumab 0.3 or 0.5 mg. After 2 years, vision-related function improved with ranibizumab 0.5 mg relative to sham treatment, regardless of whether the study eye was the better- or worse-seeing eye at baseline (32).

In the randomized, double-blind phase III ANCHOR study in patients with neovascular AMD, 423 patients received ranibizumab 0.3 mg plus sham PDT, ranibizumab 0.5 mg plus sham PDT or PDT plus sham ranibizumab injection. The superiority of ranibizumab was seen by 1 month after the initial treatment and increased over 12 months, and some patients without initial benefit had an increase in visual acuity by month 12 (33). In ANCHOR, NEI VFQ-25 results showed that greater improvements in visual function were seen with ranibizumab than with PDT alone for near activities, distance activities and vision-related dependency through 12 months (34). Also in ANCHOR, changes in anatomic characteristics of CNV lesions were assessed with fluorescein angiography and OCT. All key anatomic outcomes significantly favored ranibizumab over PDT at 12 months (35).

In the ANCHOR and MARINA studies, fellow eyes with neovascular AMD which did not receive ranibizumab treatment had relatively stable visual acuity over 1 year, and a potential benefit of ranibizumab 0.5 mg over sham injection was seen in these eyes in the MARINA trial (36).

Patients with neovascular AMD who received monthly ranibizumab 0.3 mg in one of three phase I/II trials (n=67) were included in an open-label extension study where the dose was increased to 0.5 mg. Continuous treatment for up to 3.8 years was well tolerated, and improvements in visual acuity seen in the initial studies were generally maintained (37).

The addition of ranibizumab 0.5 mg appeared to improve the efficacy of therapy with verteporfin PDT and intravitreal triamcinolone 4 mg in a randomized, double-blind study in 15 patients with CNV secondary to AMD. On visual acuity assessments, more patients given triple therapy lost < 15 letters after 6 months (100% *vs.* 71.4%) and 3 of 8 patients given triple therapy had an improvement of 3 lines or more (38).

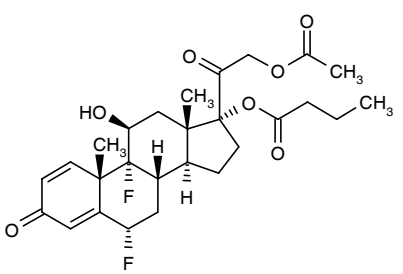
Ranibizumab is also being investigated in the phase II Lucentis in the Treatment of Macular Edema (LIME) study including, to date, 20 patients with diabetic macular edema. The randomized, open-label trial is comparing standard focal laser therapy to 3 monthly intravitreal injections of ranibizumab 0.5 mg. Mean change in best-corrected visual acuity at 3 months was +4.2 letters with ranibizumab and –2.0 letters in the laser arm, and a greater decrease in central retinal thickness was seen in the ranibizumab arms (39).

*VEGF Trap*

The VEGF blocker VEGF Trap (aflibercept; Regeneron Pharmaceuticals) demonstrated activity in a small study in patients with diabetic macular edema. A single intravitreal injection of VEGF Trap 4 mg was administered to 5 patients, none of whom developed severe ocular or serious systemic adverse events related to the treatment. Best-corrected visual acuity improved 6-10 letters in 4 patients 4 weeks after the injection, and a mean decrease in centerpoint retinal thickness of 115 μm was measured at 4 weeks. Further studies in this indication are planned (40).

Preliminary results of the CLEAR-IT-2 trial in patients with neovascular AMD have also been reported. Patients enrolled in the randomized, phase II investigation received intravitreal injections of VEGF Trap of 0.5, 2 or 4 mg given at 4- or 12-week intervals over a 12-week period. To date, no serious ocular adverse events, intraocular inflammation or serious drug-related systemic adverse events have been seen (41).

*Difluprednate*



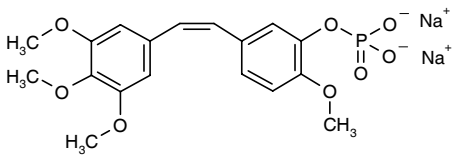
Difluprednate (Epitopic®) is undergoing phase III clinical development at Sirion Therapeutics for the treatment of anterior uveitis and postoperative ocular inflammation.

A multicenter, double-blind, comparative phase III study included 200 patients with ocular inflammation following ocular surgery who were randomized to receive difluprednate ophthalmic emulsion (DFBA) 0.05% or betamethasone 0.1% in the affected eye 4 times a day (q.i.d.) for 14 days. Efficacy was evaluated at days 3, 7 and 14. DFBA was noninferior to betamethasone in reducing anterior chamber cell scores at day 14 compared to baseline, but superior at day 7. Moreover, DFBA showed significantly improved changes in total symptom score over betamethasone. Increased IOP was observed in both groups and resolved with or without IOP-lowering drugs (42).

The safety and efficacy of DFBA in treating anterior uveitis were further evaluated in a phase III clinical study involving 136 patients randomized to receive DFBA 0.05% or betamethasone 0.1% q.i.d. for 14 days. Again, DFBA was equally effective as betamethasone in improving anterior chamber cell score from baseline on day 14, but was superior on day 7. In contrast to DFBA, betamethasone had to be withdrawn in 3 of 67 patients due to uveitis aggravation. IOP elevation was similar in both groups (43).

DFBA also showed positive results in an open phase III clinical study that recruited 19 patients with severe uveitis refractory to betamethasone 0.1% treatment. DFBA 0.05% q.i.d. for 14 days significantly improved anterior chamber cell score from baseline at all observation days. Also, DFBA caused a significant reduction in total sign and symptom scores and anterior chamber flare from baseline at all time points. In all, 26.3% of patients reported adverse drug reactions, including punctate keratitis and IOP elevation, which were mild to moderate and transient (44).

*Combretastatin A4 phosphate*



None of the pathological myopia patients with subfoveal CNV treated with OxiGene's combretastatin A-4 phosphate (CA4P) in a randomized, double-blind, multicenter phase II study lost 3 lines of best-corrected visual acuity at 3 months. The primary efficacy variable of the Early Treatment Diabetic Retinopathy Study (EDTRS), visual function, was completed at month 3 by 13 of 21 enrolled patients. The study evaluated i.v. doses of 27, 36 and 45 mg/m$^2$ given twice 1 week apart, with up to 3 additional doses possible. The effect on visual acuity may have been dose-related, with increasing doses associated with fewer lines of visual acuity lost or increases of

1-2.9 lines. Most adverse events were mild in severity, and no drug-related serious adverse events occurred (45).

*I-vation™ Intravitreal Implant*

Researchers at SurModics presented preliminary results from the ongoing STRIDE (Sustained Triamcinolone Release for Inhibition of Diabetic Macular Edema) phase I study evaluating the safety and tolerability of the I-vation™ Intravitreal Implant with triamcinolone acetonide in patients with diabetic macular edema. In this double-blind, multicenter study, patients were randomized to receive either a slow-release or a fast-release formulation, both containing 925 μg triamcinolone. Six-month interim analysis revealed that both formulations were well tolerated, with only mild increases in IOP. At 6 months, best-corrected visual acuity at any degree had improved in 85% and 76% of patients in the slow- and fast-release groups, respectively. A mean macular thickness decrease of 50 μm occurred in 62% (slow) and 65% (fast) of treated patients (46).

**Common pathogenic mechanisms in Alzheimer's disease, glaucoma and AMD**

A common link between ocular neurodegenerative diseases such as glaucoma or AMD and Alzheimer's disease (AD) has been suggested. The presence of β-amyloid (Aβ) peptide and amyloid oligomers in drusen deposits of AMD patients (47, 48) and the finding that Aβ can trigger RGC apoptosis (49) suggested common pathogenic mechanisms for these diseases. Recent findings have provided additional support for this hypothesis.

A recent study has shown reduced RGC apoptosis in a rat model of chronic ocular hypertension via Aβ peptide blockade using different interventions, including: an Aβ antibody, the amyloid protein-binding agent Congo red and a β-secretase II inhibitor. Best results were obtained with intravitreal injections of the Aβ antibody, which led to a significant and prolonged reduction in RGC apoptosis at 3 and 8 weeks after surgical IOP elevation (50).

Further studies investigated whether Aβ targeting in experimental glaucoma had an effect on neurotransmission from RGCs to the central superior colliculus, which receives RGC axon projections. Control eyes experienced a reduction in central synaptic transmission (decreased field excitatory postsynaptic potentials in response to optic tract stimulation) in response to activation of presynaptic group III metabotropic glutamate receptors with the $mGluR_4$ agonist L-AP4. However, eyes treated with the Aβ antibody experienced a further decrease upon L-AP4 treatment, likely indicating changes in synaptic plasticity of the optic nerve terminal in response to reduced Aβ levels (51). In addition, elevated levels of phosphorylated tau protein, a known marker of AD, were encountered in the retrolaminar region of the optic nerve head from patients with glaucoma, hence suggesting a potential role for phosphorylated tau in the pathogenesis of optic neuropathy (52).

Researchers at the LSU Eye Center in New Orleans have demonstrated that stress factors such as hypoxia, interleukin-1β or cholesterol are able to induce $Aβ_{42}$ peptide release from soluble amyloid precursor protein-α (sAPP-α) in human retinal epithelial, retinal endothelial and neural cells. These results suggest that common pathogenic mechanisms (increased γ-secretase-mediated $Aβ_{42}$, decreased sAPP-α) may be involved not only in AD pathogenesis, but also in retinal diseases such as AMD (53). Further attempts to discover conserved mechanisms in AD and AMD led to the identification of high levels of APP expression in the retina and retinal pigment epithelial cell layers. Also, light-induced stress caused elevation of *C*-terminal APP fragments that correlated with 50% photoreceptor loss and reduced nicastrin (part of the γ-secretase complex) levels, which was suggestive of impaired γ-secretase function. Thus, defective APP processing, in addition to Aβ toxicity, may contribute to the pathogenesis of retinal degeneration (54). Finally, an epidemiological study found a higher prevalence of early AMD in patients with AD compared to prevalence estimates found in the U.S. population (55).

**Natural remedies**

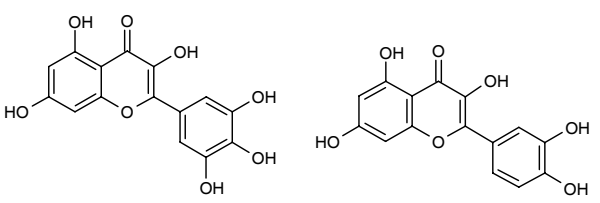
*Plant extracts*

Brazilian researchers have reported the healing effects of an Amazon green propolis extract on corneal wounds. Mice that received eye drops containing a 1% microemulsion of green propolis extract after corneal cauterization showed significantly smaller lesions at 12, 24 and 48 h than those treated with vehicle (56).

*Resveratrol*

Oral treatment with resveratrol was shown to inhibit tumor growth in mice bearing human uveal melanoma xenografts by 50% compared to vehicle-treated animals. Peritumoral injection of resveratrol, which provides locally increased drug concentrations, led to tumor regression. In addition, resveratrol antitumor effects were mediated via activation of the intrinsic apoptotic pathway, as evidenced by loss of mitochondrial membrane potential, cytochrome *c* and Smac/Diablo protein release and BAX translocation (57).

*Myricetin and quercetin*




Myricetin Quercetin

Acucela scientists have reported on the protective effects of myricetin in cultured retinal cells. Blue light exposure for 20 h induced the death of 70% of the photoreceptors in primary bovine retinal cell cultures, whereas addition of myricetin protected 100% of the photoreceptors, with an $EC_{50}$ of 9 μM (58). *In vivo*, i.p. injection of myricetin (50 mg/kg) protected mouse retina against light-induced damage in a dose-dependent manner. Myricetin showed an $ED_{50}$ of 27 mg/kg and full protection was observed at 50 mg/kg (59).

Quercetin, a heat shock protein HSP70 inhibitor, reduced CNV after PDT in rats, according to researchers at Harvard Medical School. HSP70 was shown to increase after PDT. Intraperitoneal injection of quercetin 1 h before PDT resulted in a higher rate of CNV lesion closure and a significantly smaller lesion size 1 week after this procedure compared to the control group. These results indicate that HSP70 inhibition may be useful as an adjuvant to PDT for the treatment of CNV (60).

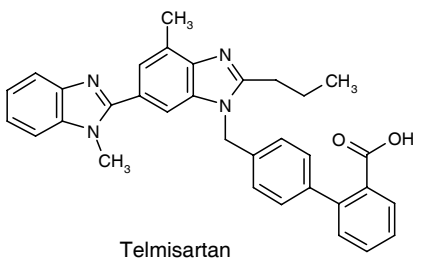
### *Omega-3 polyunsaturated fatty acids*

Results from the EUREYE study, an epidemiological study of prevalence and risk factors for AMD in elderly European populations, were reported at the ARVO meeting. In particular, this study found that daily dietary intake of omega-3 polyunsaturated fatty acids (PUFAs), via fish oil, was associated with a lower risk of developing neovascular AMD (OR = 0.47). The relative contribution of fish oil components, namely docosahexanoic acid and eicosapentanoic acid, to this reduced risk was 0.34 and 0.29, respectively. Fish oil consumption may protect against wet AMD in the elderly (61).

The effects of dietary intake of omega-3 PUFAs on retinal neovascularization were further investigated in a mouse model of oxygen-induced retinopathy. An omega-3 PUFA diet for 1 week was associated with 40% inhibition of retinal neovascularization compared to omega-6 daily intake. In addition, a 10-fold reduction in cyclooxygenase-2 (COX-2) mRNA 24 h after oxygen exposure was found in animals receiving omega-3 PUFAs (62).

## Drug repositioning

Finding new therapeutic uses for drugs that are already marketed, or for safe drug candidates that failed in clinical trials, is an emerging strategy known as drug repositioning. We highlight newly proposed uses for gentamicin and the angiotensin II type 1 receptor ($AT_1R$) blocker telmisartan.




Telmisartan

Retinitis pigmentosa is a hereditary degeneration of the retina involving genetic defects in rod photoreceptors that are associated with initial peripheral vision loss, which gradually progresses to tunnel vision and blindness. Researchers at the University of California and the Imperial College in London have demonstrated that gentamicin is able to delay photoreceptor degeneration in the SS334er rat model of retinitis pigmentosa caused by a premature stop codon. Gentamicin, as well as other aminoglycosides, is known to induce translational readthrough of premature stop codons, hence allowing translation of full-length proteins. In this study, s.c. gentamicin (50 μg/g) slowed the degeneration rate of photoreceptors, achieving control levels after approximately 2 months of treatment. These results provide proof of principle for the potential use of gentamicin in retinitis pigmentosa and other retinal diseases associated with nonsense mutations (63).

Japanese researchers investigated the potential role of the $AT_1R$ in corneal neovascularization. The expression of angiotensin II and the $AT_1R$ (mRNA and protein) was significantly higher in neovascularized corneas compared to normal corneas. Intraperitoneal administration of telmisartan markedly reduced the neovascularization area 7 days after corneal suture, suggesting that $AT_1R$ inhibition may provide benefit in the treatment of corneal neovascularization (64). In addition, telmisartan was also effective in protecting retinal neurons from early diabetic damage. Streptozotocin-induced diabetes caused downregulation of the synaptic vesicle-specific protein synaptophysin, upregulation of glial fibrillary acidic protein (GFAP; a marker for reactive glia) and signal transducer and activator of transcription 3 (STAT3) activation (upstream activator of GFAP expression), all of which could be rescued with telmisartan treatment for 5 days (65).

## New advances in corneal transplantation therapy

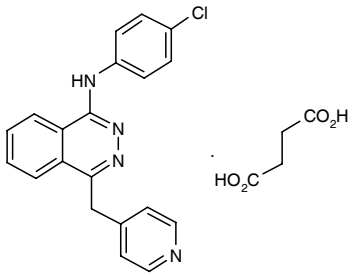
VEGF neutralization has been shown to improve graft survival in mouse models of high-risk keratoplasty. Therefore, researchers at the Harvard Medical School and the University of Erlangen in Germany, in collaboration with Regeneron, have investigated the effects of VEGF Trap (aflibercept) after keratoplasty in mouse corneas with regressed blood and lymphatic vessels. Mice receiving VEGF Trap (25 mg/kg i.p.) on the day of keratoplasty and 4, 7 and 14 days later showed inhibition of the regrowth of blood and lymphatic vessels and prolonged graft survival in 83% of treated corneas at day 21, while all control corneas were rejected at that time point (66).

A recent study carried out by scientists at Jerini Pharmaceuticals and the University of Erlangen demonstrated that integrin $\alpha_5$ inhibition may be useful in preventing corneal neovascularization after keratoplasty, thus reducing the risk of corneal rejection. Systemic administration of JSM-6427, an integrin $\alpha_5$ antagonist, reduced lymphangiogenesis before and after grafting by 54% and 49.8%, respectively, compared to controls (67).

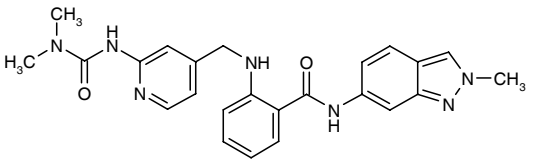
Another approach to prevent corneal allograft rejection is the application of gene-engineered dendritic cells secreting the fusion protein CTLA4-Ig, known to prevent T-cell activation, and the immunomodulatory viral IL-10 (vIL-10). Dendritic cells transduced with an adenovirus encoding CTLA4-Ig or vIL-10 were injected into mice 1 week before keratoplasty. Adoptive transfer of dendritic cells expressing CTLA4 resulted in a moderate trend towards rejection rate reduction, whereas significantly prolonged corneal allograft survival was seen in animals treated with vIL-10-expressing dendritic cells compared to controls (68).

Researchers at the Cole Eye Institute in Cleveland have shown that blocking the keratinocyte-derived chemokine CXCL1 may be a treatment option for preventing corneal graft rejection. Corneal allograft transplantation was associated with increased production of CXCL1 in vascularized, high-risk recipients, as well as upregulation of the T-cell chemoattractants CXCL9 and CXCL10. However, early *in vivo* neutralization of CXCL1 increased graft survival by 50%, which correlated with downregulation of CXCL9 and CXCL10 and reduced CD4-positive T-cell recruitment in the graft area (69).

Additional studies by the former Schering AG and the University of Erlangen showed that treatment with the tyrosine kinase inhibitors PTK-787/ZK-222584 (vatalanib succinate; Novartis, Bayer Schering Pharma) and ZK-261991 reduced corneal neovascularization in mice subjected to a corneal inflammatory stimulus. In particular, orally administered PTK-787/ZK-222584 (75 mg/kg) and ZK-261991 (50 mg/kg) reduced hemangiogenesis by 26% and 50%, respectively, and lymphangiogenesis by 61% and 76%, respectively. Moreover, ZK-261991 improved the graft survival rate (68%) compared to vehicle (33%) in mice that underwent allogeneic corneal transplantation (70).




Vatalanib succinate




ZK-261991

## References

1. Murata, Y., Masuko, S. *Peripheral and central distribution of TRPV1, substance P and CGRP of rat corneal neurons*. Brain Res 2006, 1085(1): 87-94.

2. Luna, C.L., Sesto, A., Acosta, M.C., Jimenez, M.C., Gallar, J., Belmonte, C., Jimenez, A.I. *TRPV1 siRNA topical treatment reduces the response to ocular surface irritation with capsaicin*. Annu Meet Assoc Res Vision Ophthalmol (ARVO) (May 6-10, Fort Lauderdale) 2007, Abst 373-B575.

3. Koh, J.Y., Sappington, R.M., Calkins, D.J. *Effects of TRPV1 overexpression and silencing on retinal ganglion cells survival in vitro*. Annu Meet Assoc Res Vision Ophthalmol (ARVO) (May 6-10, Fort Lauderdale) 2007, Abst 4358-B972.

4. Calkins, D.J., Sappington, R.M. *Elevated pressure induces TRPV1-mediated Ca2+-dependent apoptosis of retinal ganglion cells*. Annu Meet Assoc Res Vision Ophthalmol (ARVO) (May 6-10, Fort Lauderdale) 2007, Abst 4357-B971.

5. Li, G., Liedtke, W., Challa, P., Luna, C., Epstein, D.L., Gonzalez, P., Liton, P. *Expression of transient receptor potential (TRP) channels in the outflow pathway and ciliary body of porcine eyes*. Annu Meet Assoc Res Vision Ophthalmol (ARVO) (May 6-10, Fort Lauderdale) 2007, Abst 2066-B291.

6. Jimenez, A., Sesto, A., Pintor, J., Mediero, A., Peral, A. *Na+/K+ ATPase: A new target for treating ocular hypertension by RNAi*. Annu Meet Assoc Res Vision Ophthalmol (ARVO) (May 6-10, Fort Lauderdale) 2007, Abst 4809-B1002.

7. Liu, B., Chen, H., Neufeld, A.H. *Upregulation of Gadd45b in the aging retina*. Annu Meet Assoc Res Vision Ophthalmol (ARVO) (May 6-10, Fort Lauderdale) 2007, Abst 46-B155.

8. Bartoli, M., Cheng, G., Labazi, M., Liu, J., Steinle, J.J., Caldwell, R.B., Marcus, D. *Decreased antioxidant capacity in the aged and in the diabetic retina correlates with altered regulation of the thioredoxin system*. Annu Meet Assoc Res Vision Ophthalmol (ARVO) (May 6-10, Fort Lauderdale) 2007, Abst 3643.

9. Munemasa, Y., Piri, N., Kwong, J., Kim, S., Ahn, J., Song, M., Caprioli, J. *Expression of reduction-oxidation (redox) genes in glaucomatous rat retinas*. Annu Meet Assoc Res Vision Ophthalmol (ARVO) (May 6-10, Fort Lauderdale) 2007, Abst 56-B165.

10. Shimada, N., Ohno-Matsui, K., Kojima, A., Mochizuki, M., Morita, I. *Inhibition of cathepsin L causes a reduced neovascularization in the retina and choroid*. Annu Meet Assoc Res Vision Ophthalmol (ARVO) (May 6-10, Fort Lauderdale) 2007, Abst 1753-B613.

11. Bora, N.S., Kaliappan, S., Jha, P., Sivasankar, B., Harris, C.L., Morgan, B.P., Bora, N.S. *Role of complement regulatory protein, CD59, in the development of choroidal neovascularization in a mouse model of wet-type age-related macular degeneration*. Annu Meet Assoc Res Vision Ophthalmol (ARVO) (May 6-10, Fort Lauderdale) 2007, Abst 1769-B629.

12. Bora, N.S., Kaliappan, S., Jha, P. et al. *CD59, a complement regulatory protein, controls choroidal neovascularization in a mouse model of wet-type age-related macular degeneration*. J Immunol 2007, 178(3): 1783-90.

13. Komatsu, N., Miyazaki, D., Inoue, Y., Takeda, S., Higashi, H. *Therapeutic efficacy of CCR3 blockade for experimental allergic conjunctivitis*. Annu Meet Assoc Res Vision Ophthalmol (ARVO) (May 6-10, Fort Lauderdale) 2007, Abst 2319-B1017.

14. Prado, R., Son, J., Lu, Y., Chen, H., Song, P., Armstrong, C., Ansel, J. *Expression of trypsin and modulation of PAR-2, a trypsin receptor, in human conjunctival epithelial cells*. Annu

Meet Assoc Res Vision Ophthalmol (ARVO) (May 6-10, Fort Lauderdale) 2007, Abst 2306-B1004.

15. Stoller, G., Caballero, S., Hansen, G. et al. *A novel humanized monoclonal antibody against the bioactive lipid sphingosine-1-phosphate strongly inhibits choroidal neovascularization (CNV) in a murine model*. Annu Meet Assoc Res Vision Ophthalmol (ARVO) (May 6-10, Fort Lauderdale) 2007, Abst 1967.

16. Cheng, L., Tammewar, A., Falkenstein, I., Li, H.-X., Wong-Staal, F., Freeman, W.R. *Intraocular anti-angiogenic and antiproliferative properties of IMS 2186, a long lasting intravitreally injectable non-steroid small molecule*. Annu Meet Assoc Res Vision Ophthalmol (ARVO) (May 6-10, Fort Lauderdale) 2007, Abst 103.

17. Bingaman, D.P., Gu, X., Landers, R.A., Howe, W.E., Liu, C., Stacy, S., Romano, C. *AL-39324 is more potent and efficacious against ocular NV vs. other RTKi's*. Annu Meet Assoc Res Vision Ophthalmol (ARVO) (May 6-10, Fort Lauderdale) 2007, Abst 1747-B607.

18. Cumberlidge, G., Saragovi, H., Lane, K.J., Abelson, M.B. *An evaluation of D3, a novel TrkA receptor agonist, for ability to prevent retinal ganglion cell loss in a rat model of glaucoma*. Annu Meet Assoc Res Vision Ophthalmol (ARVO) (May 6-10, Fort Lauderdale) 2007, Abst 4367-B981.

19. Bosch, J.J., Iheagwara, U.K., Murray, T.G., Lotem, M., Ksander, B.R., Ostrand-Rosenberg, S. *Uveal melanoma cell-based vaccines activate CD4+ T lymphocytes that cross-react with primary and metastatic uveal melanoma cells*. Annu Meet Assoc Res Vision Ophthalmol (ARVO) (May 6-10, Fort Lauderdale) 2007, Abst 1945.

20. Cunningham, M.A., Li, Z., Chan, C.-C. et al. *Subcutaneous injections of LX211 prevent and reverse experimental autoimmune uveoretinitis in rats*. Annu Meet Assoc Res Vision Ophthalmol (ARVO) (May 6-10, Fort Lauderdale) 2007, Abst 2640-B730.

21. Trittibach, P., Tönz, M.S., Olac, A., Wolf, S., Sarra, G.-M. *Intravitreal administration of bevacizumab, a VEGF antibody, reduces the severity of endotoxin-induced uveitis in mice*. Annu Meet Assoc Res Vision Ophthalmol (ARVO) (May 6-10, Fort Lauderdale) 2007, Abst 2639-B729.

22. Liao, S.-M., Delgado, O., Yoo, D., Keating, M., Jaffee, B. *Suppression of retinal inflammation in endotoxin-induced uveitis by the kinase inhibitor, PKC412*. Annu Meet Assoc Res Vision Ophthalmol (ARVO) (May 6-10, Fort Lauderdale) 2007, Abst 2637-B727.

23. Shindler, K.S., Ventura, E., Elliott, P., Rostami, A.M. *SIRT1 activators attenuate retinal ganglion cell loss during acute optic neuritis*. Annu Meet Assoc Res Vision Ophthalmol (ARVO) (May 6-10, Fort Lauderdale) 2007, Abst 563-B20.

24. Tanihara, H., Inatani, M., Honjo, M., Toskushige, H., Azuma, J.-I., Araie, M. *Phase I clinical trial on intraocular pressure-lowering effects and safety of topical administration of a selective ROCK inhibitor, SNJ-1656, in normal volunteers*. Annu Meet Assoc Res Vision Ophthalmol (ARVO) (May 6-10, Fort Lauderdale) 2007, Abst 5573-B912.

25. Csaky, K.G., Gordiyenko, N., Rabena, M.G., Avery, R.L. *Pharmacokinetics of intravitreal bevacizumab in humans*. Annu Meet Assoc Res Vision Ophthalmol (ARVO) (May 6-10, Fort Lauderdale) 2007, Abst 4936.

26. Berrocal, M.H., Quiroz-Mercado, H., Wu, L. et al. *Intravitreal bevacizumab for the treatment of CNV not associated to age-related macular degeneration: Results of the Panamerican Collaborative Retina Study Group (PACORES)*. Annu Meet Assoc Res Vision Ophthalmol (ARVO) (May 6-10, Fort Lauderdale) 2007, Abst 4935.

27. Fromow-Guerra, J.J., Arevalo, F.J., Quiroz-Mercado, H. et al. *Primary intravitreal bevacizumab (Avastin) for the treatment of choroidal neovascularization (CNV) secondary to age-related macular degeneration (AMD): Results of the Pan-American Collaborative Retina Study Group (PACORES) at 6-months follow-up*. Annu Meet Assoc Res Vision Ophthalmol (ARVO) (May 6-10, Fort Lauderdale) 2007, Abst 4569-B250.

28. Arevalo, F.J., Fromow-Guerra, J.J., Quiroz-Mercado, H. et al. *Primary intravitreal bevacizumab (Avastin) for diabetic macular edema: Results of the Pan-American Collaborative Retina Study Group at 6-months follow-up*. Annu Meet Assoc Res Vision Ophthalmol (ARVO) (May 6-10, Fort Lauderdale) 2007, Abst 5027-B175.

29. Roca, J.A., Wu, L., Maia, M., Arevalo, F.J. et al. *Intravitreal bevacizumab (Avastin(R)) for the treatment of macular edema secondary to branch retinal vein occlusion: Results of the Pan-American Collaborative Retina Study Group (PACORES)*. Annu Meet Assoc Res Vision Ophthalmol (ARVO) (May 6-10, Fort Lauderdale) 2007, Abst 91-B200.

30. Holz, F.G. *Nine month safety and efficacy results from an open-label, multicenter, phase II study of same-day verteporfin and ranibizumab 0.5mg (PROTECT Study)*. Annu Meet Assoc Res Vision Ophthalmol (ARVO) (May 6-10, Fort Lauderdale) 2007, Abst 4566-B247.

31. Lalwani, G.A., Fung, A.E., Michels, S., Dubovy, S.R., Feurer, W.J., Puliafito, C.A., Rosenfeld, P.J. *An OCT-guided variable-dosing regimen with ranibizumab (Lucentis) in neovascular AMD: Two year results of the PrONTO Study*. Annu Meet Assoc Res Vision Ophthalmol (ARVO) (May 6-10, Fort Lauderdale) 2007, Abst 1834-B694.

32. Suner, I.J., Bressler, N.M., Chang, T.S., Fine, J.T., Dolan, C.M., Ward, J.F. *Vision-related function after ranibizumab treatment by better- or worse-seeing eye: 24 Month results from MARINA*. Annu Meet Assoc Res Vision Ophthalmol (ARVO) (May 6-10, Fort Lauderdale) 2007, Abst 1808-B668.

33. Heier, J.S., Chung, C., Schneider, S. *Time course of visual acuity changes with ranibizumab (Lucentis™) in the 2-year ANCHOR study of patients with neovascular age-related macular degeneration (AMD)*. Annu Meet Assoc Res Vision Ophthalmol (ARVO) (May 6-10, Fort Lauderdale) 2007, Abst 2872.

34. Schwartz, S.G., Bressler, N.M., Fine, J.T., Dolan, C.M., Yu, E.M., Ward, J.F., Chang, T.S. *Patient-reported visual function over 24 months in predominantly classic neovascular AMD: Results from ANCHOR, a phase III trial of ranibizumab and verteporfin PDT*. Annu Meet Assoc Res Vision Ophthalmol (ARVO) (May 6-10, Fort Lauderdale) 2007, Abst 1822-B682.

35. Sadda, S.R., Shapiro, H., Schneider, S. *Anatomic outcomes at 2 years in the ANCHOR study comparing ranibizumab (Lucentis™) and verteporfin photodynamic therapy (PDT) in predominantly classic neovascular age-related macular degeneration (AMD)*. Annu Meet Assoc Res Vision Ophthalmol (ARVO) (May 6-10, Fort Lauderdale) 2007, Abst 4561-B242.

36. Ciulla, T.A., Shapiro, H., Schneider, S. *Ranibizumab (LucentisTM) for neovascular age-related macular degeneration (AMD): 1-Year visual acuity (VA) results for fellow eyes with neovascular AMD in MARINA and ANCHOR*. Annu Meet Assoc Res Vision Ophthalmol (ARVO) (May 6-10, Fort Lauderdale) 2007, Abst 4573-B254.

37. Antoszyk, A.N., Shapiro, H., Shams, N. *Long-term (3-year) experience with Lucentis (ranibizumab) in patients with neovascular age-related macular degeneration: Extension study 2508*. Annu Meet Assoc Res Vision Ophthalmol (ARVO) (May 6-10, Fort Lauderdale) 2007, Abst 1810-B670.

38. Romero, R.M., Monares, G., De La Luz, J.C., Morales, A., Padilla, G., Niño-Pecina, A., Quiroz-Mercado, H. *Randomized, double blind, controlled study with verteporfin photodynamic therapy and intravitreal triamcinolone (IVTA) vs triple therapy with verteporfin photodynamic therapy, intravitreal triamcinolone and intravitreal ranibizumab in patients with subfoveal choroidal neovascularization (CNV) secondary to age-related macular degeneration (AMD)*. Annu Meet Assoc Res Vision Ophthalmol (ARVO) (May 6-10, Fort Lauderdale) 2007, Abst 72-B181.

39. Goodart, R.A., Faber, D.W., Mehr, D.S., Murphy, H., Gleed, J. *Lucentis in the treatment of macular edema (LIME): A phase II study evaluating the safety and efficacy of ranibizumab versus focal laser treatment in patients with diabetic macular edema*. Annu Meet Assoc Res Vision Ophthalmol (ARVO) (May 6-10, Fort Lauderdale) 2007, Abst 1431-B487.

40. Do, D.V., Nguyen, Q.D., Browning, D. et al. *Results of a phase I study of intravitreal VEGF trap in subjects with diabetic macular edema: The CLEAR-IT DME study*. Annu Meet Assoc Res Vision Ophthalmol (ARVO) (May 6-10, Fort Lauderdale) 2007, Abst 1430-B486.

41. Benz, M.S., Nguyen, Q.D., Chu, K., Cahn, A., Grimes, I., Ingerman, A., Cedarbaum, J. *CLEAR-IT-2: Interim results of the phase II, randomized, controlled dose- and interval-ranging study of repeated intravitreal VEGF trap administration in patients with neovascular age-related macular degeneration*. Annu Meet Assoc Res Vision Ophthalmol (ARVO) (May 6-10, Fort Lauderdale) 2007, Abst 4549-B230.

42. Ohji, M., Tano, Y., Hida, T., Sekiya, T., Ogawa, T. *Efficacy and safety results of a phase III study of difluprednate ophthalmic emulsion (DFBA), 0.05% in postoperative inflammation*. Annu Meet Assoc Res Vision Ophthalmol (ARVO) (May 6-10, Fort Lauderdale) 2007, Abst 3903-B807.

43. Ohno, S., Mochizuki, M., Usui, M., Masuda, K., Sekiya, T., Ogawa, T. *A phase III, non-inferiority study of difluprednate ophthalmic emulsion (DFBA), 0.05% in the treatment of anterior uveitis*. Annu Meet Assoc Res Vision Ophthalmol (ARVO) (May 6-10, Fort Lauderdale) 2007, Abst 3904-B808.

44. Mochizuki, M., Ohno, S., Usui, M., Masuda, K., Sekiya, T., Ogawa, T. *A phase III, open-label, clinical study of difluprednate ophthalmic emulsion (DFBA), 0.05% in the treatment of severe refractory anterior uveitis*. Annu Meet Assoc Res Vision Ophthalmol (ARVO) (May 6-10, Fort Lauderdale) 2007, Abst 3905-B809.

45. Wong, T.P., Brown, D.M., Benz, M.S. *Phase II clinical trial of intravenous combretastatin A4 phosphate in patients with subfoveal choroidal neovascular membranes (CNV) in pathologic myopia*. Annu Meet Assoc Res Vision Ophthalmol (ARVO) (May 6-10, Fort Lauderdale) 2007, Abst 1457-B534.

46. Dugel, P.U., Cantrill, H.L., Eliott, D., Mahmoud, T., Avery, R., Varner, S.E. *Clinical safety and preliminary efficacy of an intravitreal triamcinolone implant (I-vationTM TA) in DME*. Annu Meet Assoc Res Vision Ophthalmol (ARVO) (May 6-10, Fort Lauderdale) 2007, Abst 1413-B469.

47. Dentchev, T., Milam, A.H., Lee, V.M., Trojanowski, J.Q., Dunaief, J.L. *Amyloid-beta is found in drusen from some age-related macular degeneration retinas, but not in drusen from normal retinas*. Mol Vis 2003, 9: 184-90.

48. Luibl, V., Isas, J.M., Kayed, R., Glabe, C.G., Langen, R., Chen, J. *Drusen deposits associated with aging and age-related macular degeneration contain nonfibrillar amyloid oligomers*. J Clin Invest 2006, 116(2): 378-85.

49. Sillito, A.M., Guo, L., Maass, A. et al. *Alzheimer A-beta peptide induces macular retinal ganglion cell apoptosis*. Invest Ophthalmol Vis Sci 2006, Abst 4171-B700.

50. Guo, L., Salt, T.E., Luong, B.V. et al. *Targeting Alzheimer protein beta amyloid for treatment in glaucoma*. Annu Meet Assoc Res Vision Ophthalmol (ARVO) (May 6-10, Fort Lauderdale) 2007, Abst 4370-B984.

51. Georgiou, A.L., Guo, L., Cordeiro, M.F., Salt, T.E. *Assessment of central synaptic transmission in experimental glaucoma and its treatment in rats*. Annu Meet Assoc Res Vision Ophthalmol (ARVO) (May 6-10, Fort Lauderdale) 2007, Abst 207-B823.

52. Tseng, H., Kasmala, L., Proia, A., McKinnon, S. *Expression of protein markers of Alzheimer's disease in human glaucoma eyes*. Annu Meet Assoc Res Vision Ophthalmol (ARVO) (May 6-10, Fort Lauderdale) 2007, Abst 3269-B283.

53. Lukiw, W.J., Zhao, Y., Mukherjee, P.K., Bazan, N.G., Cui, J.G. *Common pathogenic mechanism involving altered beta-amyloid precursor protein (bAPP) processing in Alzheimer's disease (AD) and age-related macular degeneration (AMD)*. Annu Meet Assoc Res Vision Ophthalmol (ARVO) (May 6-10, Fort Lauderdale) 2007, Abst 17-B126.

54. Sambamurti, K., Venugopal, C., Suram, A., Pappolla, M., Rohrer, B., Annamalai, P. *Amyloid precursor protein metabolism in retinal degeneration*. Annu Meet Assoc Res Vision Ophthalmol (ARVO) (May 6-10, Fort Lauderdale) 2007, Abst 26-B135.

55. Baumritter, A., Clark, C.M., Martin, R. et al. *Prevalence of age-related macular degeneration among patients with Alzheimer's disease*. Annu Meet Assoc Res Vision Ophthalmol (ARVO) (May 6-10, Fort Lauderdale) 2007, Abst 2092-B701.

56. Martin, L.T., Paula, J.S., Rocha, E.M. et al. *Effect of an Amazon green propolis in cornea wound healing*. Annu Meet Assoc Res Vision Ophthalmol (ARVO) (May 6-10, Fort Lauderdale) 2007, Abst 807-B710.

57. van Ginkel, P., Darjatmoko, S., Subramanian, L., Bhattacharya, S., Polans, A.S. *Resveratrol inhibits tumor growth of human uveal melanoma and induces apoptosis via a mitochondrial pathway*. Annu Meet Assoc Res Vision Ophthalmol (ARVO) (May 6-10, Fort Lauderdale) 2007, Abst 1944.

58. Laabich, A., Manmoto, C.C., Kuksa, V. et al. *Protective effects of myricetin and related flavonols against A2E and light mediated cell death in bovine retinal primary cell culture*. Annu Meet Assoc Res Vision Ophthalmol (ARVO) (May 6-10, Fort Lauderdale) 2007, Abst 2545-B492.

59. Zhu, L., Laabich, A., Leung, D., Bavik, C., Kubota, R., Fawzi, A. *Protective effect of myricetin and related flavonols against light-induced retinal damage in mice*. Annu Meet Assoc Res Vision Ophthalmol (ARVO) (May 6-10, Fort Lauderdale) 2007, Abst 2493-B440.

60. She, H., Nakazawa, T., Matsubara, A., Connolly, E., Miller, J.W. *Quercetin, a heat shock protein 70 inhibitor, reduces choroidal neovascularization after photodynamic therapy in rats*. Annu Meet Assoc Res Vision Ophthalmol (ARVO) (May 6-10, Fort Lauderdale) 2007, Abst 1772-B632.

61. Augood, C., Chakravarthy, U., de Jong, P.T.V.M. et al. *Dietary omega-3 fatty acids and neovascular age related macular degeneration: The Eureye Study*. Annu Meet Assoc Res Vision Ophthalmol (ARVO) (May 6-10, Fort Lauderdale) 2007, Abst 1149.

62. Higuchi, A., Connor, K.M., Ademan, C.M. et al. *Omega-3 long-chain polyunsaturated fatty acids (LCPUFAs) suppress retinal COX-2 mRNA and retinal neovascularization*. Annu Meet Assoc Res Vision Ophthalmol (ARVO) (May 6-10, Fort Lauderdale) 2007, Abst 3416-B563.

63. Guerin, K., Gregory-Evans, C., Gregory-Evans, K., Flannery, J. *Gentamicin slows photoreceptor degeneration in the S334ter rat model of retinitis pigmentosa*. Annu Meet Assoc Res Vision Ophthalmol (ARVO) (May 6-10, Fort Lauderdale) 2007, Abst 1353-B40.

64. Usui, T., Sugisaki, K., Yokoo, S., Yamagami, S., Amano, S., Nagai, N., Ishida, S. *Inhibition of corneal neovascularization by blocking the angiotensin II type 1 receptor*. Annu Meet Assoc Res Vision Ophthalmol (ARVO) (May 6-10, Fort Lauderdale) 2007, Abst 1715-B575.

65. Kurihara, T., Ozawa, Y., Nagai, N., Inoue, M., Oike, Y., Okano, H., Tsubota, K., Ishida, S. *Neuroprotective effects of angiotensin II type 1 (AT1R) receptor blocker telmisartan on early diabetic retina*. Annu Meet Assoc Res Vision Ophthalmol (ARVO) (May 6-10, Fort Lauderdale) 2007, Abst 1389-B445.

66. Bachmann, B.O., Luetjen-Drecoll, E., Bock, F., Wiegand, S.J., Hos, D., Kruse, F.E., Cursiefen, C. *Administration of VEGF trap after keratoplasty in corneas with regressed blood- and lymphatic vessels ("low high-risk" corneas) leads to prolonged graft survival*. Annu Meet Assoc Res Vision Ophthalmol (ARVO) (May 6-10, Fort Lauderdale) 2007, Abst 194-B465.

67. Dietrich, T., Onderka, J., Bock, F., Hos, D., Zahn, G., Stragies, R., Kruse, F.E., Cursiefen, C. *Effect of integrin alpha 5 inhibition on lymphangiogenesis and recruitment of CD11b-positive macrophages in a murine model of high-risk keratoplasty*. Annu Meet Assoc Res Vision Ophthalmol (ARVO) (May 6-10, Fort Lauderdale) 2007, Abst 181-B452.