Numerous advances were spotlighted at this year’s ARVO meeting in Seattle.

BY ARON SHAPIRO

Formula for breakthroughs in research: Take young researchers, put them together in virtual seclusion, give them an unprecedented degree of freedom, and turn up the pressure by fostering competitiveness.

– James D. Watson

In ophthalmology and vision science, once a year many of Watson’s secluded researchers come up for air at the Association for Research in Vision and Ophthalmology (ARVO) Annual Meeting, to showcase emerging trends and hot topics. This column highlights some of the research presented at ARVO 2016 in Seattle that may be of interest to posterior segment specialists.

Several novel therapeutic agents and devices that utilize new modes of administration to reduce patient burden are being developed for a number of ocular indications, including age-related macular degeneration (AMD), diabetic macular edema (DME), and retinitis pigmentosa (RP).

DRUGS AND BIOLOGICS

Treatment of chronic retinal diseases such as neovascular AMD often requires intravitreal injections. AMD affects the choroid and retina, and therefore the ability to specifically target these tissues might be beneficial in modulating disease progression. The efficacy of aflibercept (Eylea, Regeneron) administered by suprachoroidal rather than intravitreal injection was evaluated in a rat model of laser-induced choroidal neovascularization. Administration of aflibercept via this route led to a reduction in neovascular area after 21 days of treatment, indicating that suprachoroidal injection of an anti-VEGF agent may be another treatment option for ocular diseases such as wet AMD.

Studies with brolucizumab (formerly known as RTH258 and ESBA1008, Alcon), a single chain anti-VEGF antibody fragment, are ongoing for the treatment of neovascular AMD. A 2-year, phase 3 safety and efficacy study is assessing the use of this agent. The study will include approximately 1600 patients, about two-thirds of whom about will be treated with brolucizumab, and a third of whom will be treated with aflibercept in a control group. With a smaller molecular size than that of other anti-VEGF molecules, brolucizumab may allow delivery of higher doses to achieve a longer duration of effect, thereby requiring fewer injections and decreasing patient burden.

In a phase 1 study, an anti-VEGF and anti-angiopoietin (Ang2) monoclonal antibody (RG7716, Hoffmann-La Roche) was well tolerated and improved BCVA and optical coherence tomography (OCT) parameters in patients with wet AMD with previous exposure to anti-VEGF therapy. This is a dual-action molecule targeting both VEGF and Ang2, and it is therefore hoped it has the potential for higher therapeutic effectiveness.

A small molecule antiangiogenic VEGF-independent compound (SH-11037, Indiana University and Gachon University in Korea) was evaluated experimentally, in combination with aflibercept, to characterize the therapeutic potential of this combination to suppress angiogenic pathways in the development of wet AMD. Researchers found that these agents appeared to synergistically inhibit human retinal endothelial cell proliferation in vitro and to suppress laser-induced choroidal neovascularization lesions in mice in vivo, suggesting that SH-11037 could be used in combination with standard anti-VEGF therapy for the treatment of wet AMD.

A selective ROCK/JAK/PDGFR-b kinase inhibitor (AR-13154, Aerie Pharmaceuticals), alone and in combination with aflibercept, was investigated in rat laser-induced choroidal neovascularization and mouse oxygen-induced ischemic retinopathy models. AR-13154 significantly inhibited retinal neovascularization in both models, therefore holding promise as a future treatment option for wet AMD and proliferative diabetic retinopathy, either as monotherapy or in combination with other anti-VEGF agents.

Efforts to decrease the frequency of intravitreal injections of anti-VEGF therapies are aimed at reducing the burden on patients and improving clinical outcomes. A study examining a biodegradable intravitreal implant that releases an
anti-VEGF biologic agent demonstrated complete release of solid-state protein over several months at therapeutically relevant levels in vitro. According to the authors, this proof-of-concept study supported advancing the implant formulations for in vivo pharmacokinetic and tolerability evaluation in nonhuman primates. A novel depot formulation of sunitinib malate (GB-102, Graybug Vision), a potent dual VEGFR/PDGRF inhibitor containing biodegradable microparticles, was developed to deliver pharmacologically active levels of sunitinib to the retina, retinal pigment epithelium (RPE), and choroid. Intravitreal injections of two dose levels of GB-102 (0.2 mg and 1.0 mg) were well tolerated and nontoxic in pigmented New Zealand rabbit eyes over the first 4 months of study. This finding suggests that this formulation could reduce administration to only two to three times per year for treatment of neovascular AMD, according to the authors. An antibody that inhibits the complement factor 5 (C5) portion of the complement pathway to form C5 convertase (tesidolumab [LFG316], Morphosys/Novartis) was administered by intravitreal injection in patients with advanced AMD. In this proof-of-concept study, the primary objective was to evaluate the rate at which patients required retreatment with anti-VEGF therapy by day 85 of treatment. Monthly doses of 5 mg tesidolumab were well-tolerated. The serum concentrations of the drug were lower than serum C5, indicating that the drug did not suppress complement activity. There was no statistically significant difference in the rate of anti-VEGF retreatment between the tesidolumab and sham treatment groups.

A first-in-human study found that a kallikrein inhibitor (KVD001, KalVista Pharmaceuticals) was safe and well tolerated in patients with DME. Improvement in retinal edema and visual acuity occurred in most study eyes, lending support for further evaluation in well controlled prospective studies to investigate its potential effectiveness as a new treatment for DME, the study authors said. The first-in-class small molecule AKB-9778 (Aerpio Therapeutics) is an inhibitor of human protein tyrosine phosphatase beta (HPTPβ) that activates the Tie2 pathway to block vascular leakage and angiogenesis. Results from a phase 2a study demonstrated that, after 3 months of treatment with AKB-9778 and ranibizumab (Lucentis, Genentech), the effect of anti-VEGF therapy on central subfield thickness and visual acuity was enhanced in patients with DME. Vitreomacular adhesion (VMA) can progress to vitreomacular traction (VMT), a condition in which the vitreous gel has abnormally strong adhesion to the retina, tending to pull forward over time and cause vascular and retinal distortion, and in turn potentially resulting in retinal edema, bleeding, optic nerve damage, visual impairment and blindness. The availability of a nonsurgical treatment option could reduce the risks associated with pars plana vitrectomy for VMT. In a phase 2 trial in 106 patients, a synthetic antiangiogenic and vireolytic oligopeptide (Luminate [ALG-1001], Allegro Ophthalmics) was effective at the highest dose in 65% of patients, achieving release of VMA/VMT by day 90, compared with 10% of patients who received placebo. [Editors’ Note: Baruch Kuppermann, MD, PhD, discusses ALG-1001 in “Breaking Bridges with Integrin Therapy” in this issue’s cover series, starting on page 35.]

GENE AND CELL THERAPY
Transformative genetic therapies enabling personalized medicine were among the trending topics discussed at ARVO this year. The clustered regularly interspaced short palindromic repeats (CRISPR)/Cas technique allows directed, specific splicing of a disease-associated gene, thereby removing the genetic identity of a particular condition. Although some challenges such as incorrect splicing still must be addressed, the potential of this approach resulted in a burst of presentations at this year’s ARVO.

In one study, CRISPR-based gene editing was used to delete the most common mutation in the CEP290 gene, restoring function without risking overexpression toxicity for the treatment of CEP-290–associated Leber congenital amaurosis. In another study, genetically modified human induced pluripotent stem cell (iPSC) retinal cell reporter were developed using CRISPR technology for the treatment of RP. This study identified new mechanisms of retinal development that could improve the efficacy and speed of photoreceptor generation.

Other more traditional gene therapy techniques employed nonpathogenic viruses as delivery vectors, adding to the decade-long stream of progress in this area of research. One of the many applications of viral-based gene therapy included a study of RetinoStat (Oxford BioMedica), an endostatin- and angiostatin-expressing lentiviral vector. In this study, RetinoStat was administered subretinally to 21 patients with advanced neovascular AMD who had shown poor response to anti-VEGF treatment. The treatment was safe and resulted in stabilization of visual acuity and decreased vascular leakage.

In retinal genetic therapy, the most widely used vectors for gene delivery are based on adeno-associated virus (AAV). The advantage in using AAV for the gene therapy is that it induces minimal immune response and mediates long-term transgene expression in a variety of retinal cell types. In one study, intravitreal delivery of AAV-mediated expression of stanniocalcin-1 (STC-1) resulted in significant photoreceptor preservation in two rodent models of RP.

This year’s poster display also included focus areas such as directed differentiation and transplantation of retinal cells, use of progenitor cells to understand congenital disorders, and therapeutic application of iPSC–derived RPE. According
to one poster, subretinal transplantation of autologous iPSCs was successful, and a graft was well-tolerated 1 year after transplant. Two studies used allogenic RPE derived from human embryonic stem cells (hESCs) to treat wet AMD or Stargardt disease. Both study treatments were well tolerated, paving the way for efficacy trials, according to the authors.

Research studies also investigated the effect of stem cell secretory products and vesicles on cell differentiation and tissue repair. In one study, microvesicles secreted by hESC-induced de-differentiation and transdifferentiation in Müller cells.

DEVICES

Retinal prostheses are in development for sight restoration in patients blinded by advanced AMD or RP. These devices typically work by transmitting visual information to the retina by electrically stimulating surviving retinal neurons. In four patients with subfoveal geographic atrophy (GA) that severely affected their central vision, with implantation of the Argus II (Second Sight Medical Products) electronic epiretinal prosthesis within the regions of GA, patients were able to successfully integrate central (artificial) and peripheral (natural) vision. In follow-up out to 24 weeks, central visual function was successfully provided by the implant.

In another study, a suprachoroidal-transretinal stimulating prosthesis elicited phosphens in three patients with advanced RP. Implantation of the electrode array close to the fovea centralis resulted in the greatest improvements in visual tasks with this device.

One study employed quantitative spectral-domain OCT to develop a predictive model of GA, designed to forecast regions of potential future GA appearance. A statistical model developed from the data has potential as a biomarker for use in drug efficacy and device studies, according to the authors.

CONCLUSION

ARVO is always a great melting pot of ideas and developments in vision and ophthalmology, and this year was no exception. We look forward to the next meeting, to be held in Baltimore in spring 2017.