In Advances in Retinal Drug Delivery, Yi Jiang, MD, covers Dr. Avery’s lecture on the wide variety of drug delivery methods that are currently available to retina specialists, as well as some in development. In The Science Behind Advanced Surgical 3D Imaging, Neepa Shah, MD, summarizes Dr. Chow’s presentation, which provided insights and tips for how best to use the Ngenuity 3D Visualization System in the OR.

—Timothy G. Murray, MD, MBA

ADVANCES IN RETINAL DRUG DELIVERY
An overview of available methods and some of those in development.

Presentation by Robert L. Avery MD; summary by Yi Jiang, MD

Intravitreal injections have become a major part of retina practices around the world. However, there are other methods of delivering drugs to the retina. These include topical drug delivery, suprachoroidal injection, dissolvable implants, iontophoresis, and gene therapy. Robert L. Avery, MD, provided a comprehensive review of retinal drug delivery methods currently available, others that are still in development, and some that never quite worked out.

TOPICAL THERAPIES

Dr. Avery began with a review of topical drugs being developed or investigated for the treatment of retinal diseases. Pazopanib (Votrient, GlaxoSmithKline/Novartis), a tyrosine kinase inhibitor with approved applications in oncology, was recently found not to reduce the number of as-needed ranibizumab (Lucentis, Genentech) injections nor to provide anatomic benefit compared to treatment with ranibizumab alone.

PAN-90806 (PanOptica), a selective inhibitor of VEGFR2, showed good binding affinity and efficacy in animal models of ocular angiogenesis and choroidal neovascularization. Dr. Avery showed OCTs of a patient with wet age-related macular degeneration (AMD) who was treated with PAN-90806 in a phase 1/2 study. The study found maximal reduction of intraretinal fluid at 8 weeks, with return of intraretinal fluid after treatment ceased. VA and OCT improvement were also demonstrated at 8 weeks; however, corneal toxicity occurred when higher doses were administered.

Similarly, in a phase 2 study of the compound in patients with proliferative diabetic retinopathy (PDR), six of 10 patients with both PDR and diabetic macular edema (DME) experienced a moderate reduction in DME. One patient needed rescue panretinal photocoagulation. Dr. Avery noted that enrollment is ongoing for a study involving a suspension formulation of PAN-90806 using a transscleral route to the choroid, which may minimize corneal toxicity.

The integrin inhibitor SF0166 (SciFluor Life Sciences) is a small molecule selective inhibitor of alpha-v beta-3 that has efficacy on multiple pathways and may have improved penetration to the posterior pole because of its fluorination. In a phase 1/2 study in patients with wet AMD, 33% of anti-VEGF-naïve patients responded positively, as evidenced by positive OCT changes. A phase 1/2 study in patients with DME found that 19 of 38 patients experienced decreases in central subfield thickness (CST) by day 56 of treatment with SF0166.

SUPRACHOROIDAL INJECTION

According to Dr. Avery, suprachoroidal injections of triamcinolone particles have been shown to achieve good posterior segment penetration in animal models. He spoke about clinical trials of suprachoroidal triamcinolone acetonide (CLS-TA, Clearside Biomedical) in noninfectious uveitis, retinal vein occlusion (RVO), and DME, but focused mainly on the phase 2 TANZANITE trial in patients with RVO. This trial compared treatment with a combination of CLS-TA and aflibercept (Eylea, Regeneron) to treatment with aflibercept alone as needed. The primary endpoint was the number of additional aflibercept injections required. This study found a statistically significant (61%) reduction in need for additional treatment with aflibercept alone as needed. The primary endpoint was the number of additional aflibercept injections required. This study found a statistically significant (61%) reduction in need for additional treatment with aflibercept in the combination arm. Dr. Avery noted that the drug is now progressing to phase 3.

INTRAVITREAL RESORBABLES

Dr. Avery said the leader in the field of intravitreal resorbable implants is the dexamethasone intravitreal implant 0.7 mg (Ozurdex, Allergan). The phase 3...
MEAD study found a greater reduction in CST at all time points in eyes receiving the dexamethasone implant compared with sham-treated eyes, with a peak at 1 to 3 months. In a phase 2 trial by the Diabetic Retinopathy Clinical Research Network, patients with persistent DME with vision loss received ranibizumab injections plus the dexamethasone implant or sham injection every 12 weeks. In the primary endpoint of mean change in VA, there was greater increase in letter score change in pseudophakic patients receiving the combination (5.1 with combination vs 2.0 with ranibizumab alone) at 24 weeks, and the inverse (4.1 with ranibizumab alone vs 1.1 with combination) in phakic patients. There was also greater reduction in CST with the combination over 24 weeks, although the combination group did not show significantly improved VA over ranibizumab alone. The trial has been discontinued. Sunitinib maleate is a kinase inhibitor that targets receptors for VEGF, platelet derived growth factor, and other growth factors. It is approved by the US FDA as Sutent (Pfizer) for use in oncology. Graybug Vision is developing a biodegradable microparticle formulation of sunitinib (GB-102) for ophthalmic use. Injected intravitreally to form a depot in the vitreal cavity, GB-102 has been found to reduce vascular permeability and choroidal neovascular lesion size in animal models and is now undergoing dose escalation phase 1 trials and noninferiority studies against aflibercept in phase 2 trials.

Another kinase inhibitor, AR-13503, is being developed by Aerie Pharmaceuticals in collaboration with DSM Polymer Technology, in the form of a bioerodible rod implant. Ocular Therapeutix is working with Regeneron on the development of the anti-VEGF antibody implant OTX-IVT, a shape-changing depot in the form of a fiber made through an organo-gel process for long-acting drug delivery. Sirolimus is an mTOR inhibitor, an immunosuppressant that targets T-cell mediated inflammation. It is FDA-approved as Rapamune (Pfizer) for prophylaxis of organ rejection. Santen was developing an intravitreal formulation for treatment of noninfectious uveitis. Delivered intravitreally, the drug formed a depot with slow diffusion and minimal systemic exposure. In the phase 3 SAKURA study, the primary endpoint, absence of vitreous haze at 5 months, was not met, and development of sirolimus is on hold, Dr. Avery said.

Envisia Therapeutics has presented primate data on its extended-release hydrogel implant containing aflibercept, showing sustained vitreous concentrations at 3 months. Dr. Avery said. He also briefly mentioned a dual antibody fragment that targets VEGF that was being developed by GlaxoSmithKline. It was shown to deliver protection for 6 months in a primate model of wet AMD. However, there were problems with the particles entering the anterior segment due to lens accommodation, and development is on hold.

**Drug Pumps**

Dr. Avery discussed the Posterior MicroPump (Replenish), with a mechanism of action (electrolysis) he compared to that of a mini insulin pump. The pump is programmable and refillable.

The Ranibizumab Port Delivery System (RPDS, Genentech) is designed to provide sustained delivery when placed under the conjunctiva in the pars plana. The phase 2 Long-Acting Delivery of Ranibizumab trial is examining the frequency of refills. The trial includes three treatment arms with different formulations and one control arm. Dr. Avery said results of this trial will be reported soon.

**Encapsulated Cell Technology**

Encapsulated cell technology is an implantable protein-making chamber containing genetically modified cells that produce a desired therapeutic molecule. Dr. Avery said encapsulated cell technology was originally investigated as a treatment for AMD, but this line of investigation was abandoned because of its inability to generate enough of the anti-VEGF molecule. The current iteration, NT-501 (Neurotech), is being evaluated for treatment of patients with macular telangiectasia. The implant produces cilary neurotrophic factor, or CNTF, a growth factor that stimulates and protects neural cells. Recent phase 1 and 2 trials have reported positive data.

**Gene Therapy**

The final topic that Dr. Avery discussed was gene therapy, which involves two kinds of delivery: First, the therapy is delivered to the posterior segment, generally by subretinal injection after vitrectomy; second, the therapy is simply injected into the vitreous cavity. In both, the therapeutic payload is delivered to target cells through use of a vector, in most cases to date in the form of a disabled virus. He first highlighted the landmark publication by Maguire et al showing the safety and efficacy of gene transfer for Leber congenital amaurosis and demonstrating the broader possibilities of gene therapy.

Many other gene therapy trials are now in progress. Dr. Avery discussed HMR59 (Hemera Biosciences), a complement-blocking gene therapy using an adeno-associated virus 2 (AAV2) vector. Its protein product, CD59, blocks membrane attack complex formation and prevents complement damage. This therapy is being evaluated for slowing the progression of dry AMD.

Dr. Avery also reviewed a phase 1/2 study in patients with wet AMD.
THE SCIENCE BEHIND ADVANCED SURGICAL 3D IMAGING

Key concepts for using the Ngenuity 3D surgical viewing system.

Presentation by David R. Chow MD, FRCS(C); summary by Neepa Shah, MD

Three-dimensional heads-up viewing systems have revolutionized the way vitreoretinal surgeons can operate. Large-screen 3D viewing provides surgeons with improved resolution, image depth, and clarity, as well as increased comfort while operating. David R. Chow, MD, FRCS(C), a consultant for Alcon, provided an overview of the scientific principles behind the Ngenuity 3D Visualization System (Alcon). Dr. Chow explained the basic scientific principles of the Ngenuity system compared with standard operating microscopes to help vitreoretinal specialists navigate 3D viewing to maximize the advantages that these systems offer.

DEPTH OF FIELD

Dr. Chow defined depth of field as “the axial extent in a patient’s eye that a physician considers to be of acceptable sharpness.” The Ngenuity system calculates depth of field using an equation that takes the properties of light and accommodation into account. Using this method of calculation, the Ngenuity system provides 2.9 times greater depth of field than, for example, the OPMI Luma 700 operating microscope (Carl Zeiss Meditec), Dr. Chow said.

Increasing zoom decreases depth of field in both types of systems, but this decrease is disproportionately greater in conventional microscopes than in the 3D viewing system, he said. Additionally, the effect of accommodation is negated in 3D viewing, so that an older surgeon with less accommodation can still be afforded the same view as a younger surgeon, which is not the case with conventional microscopes. Decreasing the viewing distance to the 3D monitor increases magnification but reduces depth of field.

DEPTH RESOLUTION

Dr. Chow said that depth resolution is important for performing fine motor tasks such as peeling internal limiting membrane, and that the Ngenuity system provides greater depth resolution than a standard microscope. Depth resolution can be increased by increasing zoom/magnification or decreasing viewing distance.

ADVANTAGES OF OPERATING AT LOWER LIGHT LEVELS

The ability to operate at low light levels is one advantage that the Ngenuity system provides. Dr. Chow said. The retina is exposed to about 6.8 lumens of light using the default settings of the light pipe on the Constellation Vision System (Alcon), creating a phototoxicity threshold of about 14 minutes, Dr. Chow said. By contrast, he said, the Ngenuity system allows surgeons to operate at much lower levels of light (0.74 to 1.5 lumens). These lower light levels increase the phototoxicity threshold to more than 2.5 hours, improving safety.

FOCUSBING THE NGEUUNITY SYSTEM

Dr. Chow explained that the
Ngenuity system is “parfocal,” meaning that the system will remain in focus at all magnifications but not at all depths. It is best to focus on the posterior pole with the Ngenuity system, he said, because the anterior retina and mid vitreous may often still be in focus due to the system’s depth of field.

**HOW TO WHITE-BALANCE**

Finally, Dr. Chow said, it is important to white-balance the specific illumination that you are using with your system to maximize image quality. He stressed the importance of understanding how to properly achieve white balance so that viewing and video quality are maximized.

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