In the Rearview: Highlights of Happenings From 2015

A brief look at significant events, innovative products, and other notable headlines from the past year.

FROM THE STAFF OF *RETINA TODAY*

The end of the year is approaching, and it is a fitting time to review all that has happened in the world of retina over the past 12 months. Like pages in a scrapbook, this article collects many of these happenings; it is unfortunately not possible to include each and every milestone in retina from 2015. If we missed anything of great importance, rest assured we did so unintentionally. Aside from being categorized in groups and by quarter, the following entries appear in no particular order of significance.

DRUG, THERAPY, AND PRODUCT NEWS

Quarter 1

The US Food and Drug Administration (FDA) approved the anti-VEGF drug **ranibizumab** (**Lucentis, Genentech**) for the treatment of diabetic retinopathy (DR) in people with diabetic macular edema (DME).

In March, the FDA accepted **Neurotech's** Investigational New Drug (IND) application and gave the company the nod to proceed with conducting a phase 2 clinical study of **NT-503 encapsulated cell therapy (ECT)** for the treatment of recurrent subfoveal choroidal neovascularization (CNV) secondary to age-related macular degeneration (AMD). NT-503 is a VEGF receptor protein continuously produced by Neurotech's ECT implant.

Regeneron started the year with an announcement that **aflibercept** (**Eylea**) had been recommended for approval by the European Committee for Medicinal Products for Human Use for the treatment of visual impairment due to macular edema secondary to central or branch retinal vein occlusion (CRVO/BRVO). European Commission regulators subsequently approved aflibercept for this indication. In March, the FDA approved aflibercept injection for the treatment of DR in patients with DME.

CONGRESS REPEALS SGR

After years of patchwork fixes, Congress passed a bill to repeal the sustainable growth rate (SGR) formula. In April, President Obama signed the bill, and the Medicare Access and CHIP Reauthorization Act of 2015 (MACRA) became law.

In addition to repealing the SGR formula, the MACRA replaced the multiple quality reporting systems used by Medicare—the Physician Quality Reporting System, electronic health records Meaningful Use, and the value-based payment modifier—with a single program called the Merit-based Incentive Payment System (MIPS), a point system designed to reward physicians who provide high-quality health care with bonuses.

Although it remains to be seen whether the MACRA places physicians in a better situation—the high costs of Medicare Part B drugs, for example, may ultimately count against a retina specialist's MIPS score—retina specialists are pleased that the unsustainable SGR formula was finally repealed.

George A. Williams, MD, section editor of Pennsylvania Avenue Updates for *Retina Today* and federal affairs secretary for the American Academy of Ophthalmology, thoroughly summarized and evaluated the MACRA in the September issue: *bit.ly/1HZyX0Z*.

The US Patent and Trademark Office (USPTO) issued two patents (Nos. 8962321 and 8961956) for **Ocata's hemangio-derived mesenchymal cells** (HMCs). According to the company, its HMC technology introduces a new era of cell therapy for ophthalmic diseases such as noninfectious uveitis and inflammatory diseases of the retina, as well as other nonophthalmic diseases. The patents also broadly protect the manufacture of HMCs and the therapeutic use of these cells in the

treatment of ophthalmic and other diseases.

In a draft guidance, the UK's National Institute for Health and Care Excellence (NICE) recommended the **dexamethasone intravitreal implant** (**Ozurdex, Allergan**) for the treatment of DME in pseudophakic patients. The document specifically recommends dexamethasone as a treatment option in patients whose DME is not responsive to noncorticosteroid treatment or in cases in which such treatment is not suitable.

Quarter 2

The USPTO issued **Ocata** four new patents (Nos. 9040770, 9040039, 9040038, and 9045732) that expand the scope of protection of four previously issued patents covering the company's **retinal pigment epithelium (RPE) transplant technology**. These patents extend protection to include all formats and formulations of RPE cells including suspensions and sheets of cells for use as therapeutic agents and the use of these formulations for treating ophthalmic diseases such as dry AMD and Stargardt macular dystrophy.

NightstaRx received both FDA and European Medicines Agency orphan drug designation for its lead program, a **gene therapy** to treat choroideremia.

In June, **Bayer's** Japanese subsidiary received approval for **aflibercept** injection by the Ministry of Health, Labour, and Welfare in Japan for the treatment of patients with macular edema secondary to BRVO or CRVO.

Quarter 3

Eyegate signed a licensing agreement with **Valeant** in July that granted Valeant exclusive worldwide commercial and manufacturing rights to the **EyeGate II Delivery System** and **EGP-437** combination product in the field of uveitis. EGP-437 incorporates a reformulated topically active corticosteroid, dexamethasone, and delivers it to ocular tissues using the EyeGate II Delivery System. The agreement also gives Valeant a right of last negotiation to license the product for other indications.

In September, the FDA's Office of Orphan Products Development granted orphan drug designation to **TxCell**'s personalized T-cell immunotherapy **Col-Treg** for the treatment of chronic noninfectious uveitis. Based on the properties of autologous collagen 2–specific regulatory T lymphocytes, Col-Treg also has orphan drug designation in the European Union and is classified as an advanced therapy medicinal product by the European Medicines Agency.

Ocata received a new patent (No. 9080150) for its **RPE therapy** for macular degenerative diseases. Additionally, the company was awarded a small business innovation research grant from the National Eye Institute to fund IND-enabling preclinical development of its proprietary photoreceptor progenitor product for the treatment of retinal degenerative diseases such as retinitis pigmentosa (RP) and photoreceptor dystrophies.

Neurotech enrolled the first patient in a proof-of-concept study in September. The randomized, active-controlled, masked study will evaluate the safety and efficacy of **NT-503 ECT** compared with **aflibercept** intravitreal injections for the long-term treatment of CNV secondary to AMD. Neurotech expects enrollment to be completed by the end of the year and plans to report top-line data from the program in the first half of 2017. For perspective on the ECT technology,

PROTOCOL T RESULTS RELEASED

In March, the results of the Diabetic Retinopathy Clinical Research Network (DRCR.net) Protocol T study were published in *The New England Journal of Medicine*.[1] The study compared the safety and efficacy of ranibizumab, bevacizumab (Avastin, Genentech), and aflibercept for treating center-involved DME. The data showed that all three anti-VEGF agents worked well in treating the disease in the full study population and that, for patients with baseline vision of 20/50 or worse, aflibercept use resulted in significantly improved vision outcomes compared with the other two drugs.

Controversy ensued. Critics of the study noted that researchers used a 0.3-mg dose of ranibizumab—the dosage approved by the FDA for treatment of DME—instead of the 0.5-mg dose approved in Europe. Others suggested that analysis of results at the 1-year endpoint was premature, as the DRCR.net planned Protocol T to be a 2-year study.

Still, some retina specialists viewed the results of the study as a reliable signpost in a confusing storm of drugs, disease, and patient needs. Speaking with Jonathan Prenner, MD, and Richard Kaiser, MD, on the *Retina Today* Journal Club, Carl Regillo, MD, said that Protocol T tried to "mimic what we do in practice," and that although the study "represents a somewhat narrower version of what we might have in practice," it may be useful for retina specialists trying to decide on a first-choice anti-VEGF agent for patients with particular baseline characteristics (watch it here: bit.ly/1XbaBTm).

1. Wells JA, Glassman AR, Ayala AR, et al. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema. *N Engl J Med.* 2015;372(13):1193-1203.

reread "The Future of Long-Term AMD Treatment" from our October issue (bit.ly/1l7zvYa), in which *Retina Today's* Chief Medical Editor, Allen C. Ho, MD, ponders whether this novel drug-delivery platform could become a new standard of care.

Quarter 4

MacuHealth officially launched its supplement **MacuHealth Plus** at this year's American Academy of Ophthalmology meeting in Las Vegas. The product was developed and formulated for patients with AMD and, according to the company, is fortified with meso-zeaxanthin and contains a lower level of zinc (25 mg vs 80 mg) than the AREDS2 recommended supplement.

Bayer received European approval for **aflibercept** injection for the treatment of visual impairment due to myopic choroidal neovascularization (CNV).

STUDY UPDATES

Quarter 1

During the first quarter of 2015, patient dosing was completed in **Ocata** phase 1/2 studies of its **RPE therapy** for dry AMD and Stargard macular degeneration. Next up, the company said, was the initiation and execution of a phase 2 study for AMD and a pivotal study for Stargard macular degeneration.

Clearside enrolled the first patient in its phase 2 randomized, controlled, masked, multicenter clinical trial for the treatment of macular edema associated with noninfectious uveitis using Clearside's proprietary formulation of **triamcinolone acetonide (CLS-TA)**, which is administered via suprachoroidal injection using the company's proprietary microinjector. Roughly 30 patients will be randomly assigned to receive either a single 4.0-mg dose or a single lower dose of 0.8 mg of CLS-TA. The primary efficacy endpoint will be the mean change from baseline in retinal thickness at 2 months after treatment.

Quarter 2

At the Association for Research in Vision and Ophthalmology annual meeting, **Ohr** presented results from the 9-month phase 2 IMPACT study evaluating **0.2% squalamine lactate ophthalmic solution** (**OHR-102**) combination therapy for the treatment of wet AMD. In the modified intent-to-treat population with lesions containing classic CNV (OHR-102 n = 37, ranibizumab monotherapy n = 28), mean gains in visual acuity at month 9 were + 11 letters for the OHR-102 combination arm and + 5 letters in the ranibizumab monotherapy arm. Furthermore, 44% of patients receiving OHR-102 combination therapy achieved a 3-line or greater vision gain at 9 months compared with 29% in the ranibizumab monotherapy group.

THE BEGINNING OF THE ICD-10 ERA

Last year, the Centers for Medicare and Medicaid Services postponed the deadline for implementation of ICD-10-CM to October 1, 2015. Hopefully the extension gave practices and physicians extra time to prepare for the change. Although ICD-10-CM has many similarities to ICD-9-CM, the new document tends to require more clinical knowledge than the old one to appropriately choose diagnoses and prepare billing claims. Although clinicians may balk at the sheer number of codes (approximately 69 000) associated with the new system, within ophthalmology, retina practices will use fewer codes than many other ophthalmic subspecialties, notes Riva Lee Asbell, author of *Retina Today's* Coding for Retina column. If you find yourself behind the curve on implementing ICD-10-CM in your practice, or if perhaps you just want a quick refresher, Ms. Asbell put together a comprehensive primer on preparing for this new era of coding and billing in the October 2014 issue (bit.ly/1O5Nklt).

Second Sight Medical Products announced positive 3-year results from a multicenter clinical trial of the **Argus II Retinal Prosthesis System**. Of 30 patients enrolled, 29 remained implanted with functioning Argus II systems 3 years after implantation. With the Argus II System, improvements in visual function and orientation and mobility were maintained out to 3 years. Additionally, up to 89% of patients performed statistically better with the Argus II compared with native residual vision in visual function tasks at year 3.

Five-year data demonstrated long-term effectiveness and safety of **VisionCare's Implantable Miniature Telescope** in patients 65 years and older with dry AMD. Investigators reported that both younger (aged 65 to < 75) and older (aged ≥ 75) patients had clinically significant visual acuity gains at 2 years and 5 years after implantation of the telescope and that younger patients, not surprisingly, retained more of the vision gains at 5 years and experienced somewhat fewer adverse events compared with older patients.

In June, **NightstaRx** announced that the University of Alberta had begun enrolling and dosing patients in a phase 2 open-label clinical trial of the company's **gene therapy** for the treatment of choroideremia. The gene therapy approach uses an adeno-associated virus (AAV) vector to deliver a wild-type copy of the

Rab-escort protein 1 (REP-1) gene (AAV2-REP1) into cells of the eye.

Allegro began enrolling patients in a phase 2 clinical trial evaluating the safety and efficacy of the integrin peptide therapy **ALG-1001** (**Luminate**) for inducing posterior vitreous detachment in patients with nonproliferative DR. In the article "A Dual-Mechanism Drug for Vitreoretinal Disease," Baruch D. Kuppermann, MD, PhD, provided a closer look at the potential for anti-integrin drugs in ophthalmic use (bit.ly/1l7zBis).

At the International Society for Stem Cell Research meeting, **Ocata** announced positive results in 31 patients who received its **RPE cell therapy** for macular degeneration. All patients experienced improved or stable BCVA, suggesting that human embryonic stem cell-derived cells may provide a potentially safe new source of cells for regenerative medicine.

Ophthotech completed patient recruitment for its first phase 3 pivotal trial of **pegpleranib** (**Fovista**) anti–platelet-derived growth factor therapy in combination with ranibizumab for the treatment of patients with wet AMD.

Quarter 3

The first patient with dry AMD to receive **Second Sight's Argus II Retinal Prosthesis System** was reported, and the device was successfully activated about 2 weeks after implantation. This implant is part of a feasibility study that aims to evaluate the safety and utility of the Argus II System on visual function in individuals with dry AMD. Study participants will be followed for 3 years.

Allegro announced that a phase 2 clinical trial evaluating its integrin peptide therapy **ALG-1001** in patients with vitreomacular traction (VMT) or vitreomacular adhesion (VMA) met its primary endpoint. Sixty-five percent of 106 patients in the study treated with the 3.2-mg dose of ALG-1001 achieved release of VMT or VMA by day 90 (end of study) compared with 9.7% of patients in a placebo control group.

Ohr reported positive final results of its phase 2 clinical study for **OHR-102** in patients with macular edema secondary to BRVO or CRVO. According to the company, the results demonstrated that, following an initial 10-week combination therapy treatment period, patients who continued to receive a combination of topical squalamine twice a day plus ranibizumab achieved greater visual acuity gains than patients in the control group who received ranibizumab alone.

Top-line results from an investigator-sponsored phase 2 study of the sustained-release, injectable **fluocinolone acetonide microinsert** (**Medidur**) for posterior, intermediate, or panuveitis were shared by **pSivida**. Through the last follow-up visit reported, no eyes treated with the fluocinolone acetonide microinsert had any recurrence of uveitis. Fellow eyes treated with standard of care, including steroid eye drops, averaged 2.33 recurrences.

The FDA accepted **Retrosense Therapeutics'** IND application for **RST-001**, which the company is developing as a first-in-class gene therapy application of optogenetics for the treatment of RP. RetroSense is expected to initiate a phase 1/2 clinical trial by the end of 2015 to evaluate the safety and potential efficacy of RST-001.

Aerpio presented data from the TIME-2 phase 2a study of **AKB-9778** for the treatment of patients with DME. AKB-9778 is a first-in-class stabilizer of the Tie2 pathway in clinical development for diabetic eye disease and RVO. According to the company, the combination of AKB-9778 (dosed at 15 mg twice a day) and ranibizumab injection provided a clinically significant benefit in reduction of central subfield thickness compared with ranibizumab alone.

Data from a 4-year clinical trial suggested that rigorous **evaluation of the peripheral retina** may help more accurately assess **risk of DR severity progression**. The study found that eyes with diabetic lesions that were predominantly located in the peripheral retina had a 4.7-fold increased risk of progression to proliferative diabetic retinopathy and a 3.2-fold increased risk of progression in DR severity by two or more steps. Following these findings, Sunil Gupta, MD, reviews the top "10 Reasons to Image the Peripheral Retina" on page 79 of this issue.

Ocata reported that it had enrolled the first patient in a phase 2 clinical trial assessing its proprietary **RPE cells** in patients with atrophic AMD. The trial will evaluate safety and efficacy of the RPE cells compared with a parallel control group. Interim top-line results from the first cohort are expected in Q2 of 2016, and further interim results are expected by the end of 2016.

Quarter 4

Ophthotech completed patient recruitment for its second phase 3 pivotal trial of **pegpleranib** in combination with ranibizumab for the treatment of patients with wet AMD. The company said it expects to announce initial top-line data from both phase 3 trials in Q4 2016. A third phase 3 trial investigating pegpleranib in combination with aflibercept or bevacizumab was still recruiting patients at the time of press.

Clearside Biomedical completed enrollment in a phase 2 clinical trial (Dogwood) of its proprietary

formulation of CLS-TA for the treatment of macular edema associated with noninfectious uveitis. Top-line data are expected by the end of 2015.

Eyegate announced interim data from a phase 1b/2a clinical trial of its **iontophoretic dexamethasone phosphate ophthalmic solution** (**EGP-437**) in patients with macular edema. The ongoing multicenter, open-label trial has thus far enrolled 19 patients with postoperative macular edema or macular edema associated with RVO or DR. The primary objective of the trial is to evaluate the safety and efficacy of iontophoretic EGP-437 in patients with macular edema. A positive response was observed in some patients, with pseudophakic eyes responding better than phakic eyes. The extension stage of the trial will recruit an additional 15 patients.

NEW INSTRUMENTS AND TECHNOLOGIES

Quarter 1

CenterVue introduced the **Eidon** automated retinal imaging system, which employs confocal scanning, provides true-color imaging, and is capable of imaging both the central and peripheral retina, offering a viewing angle of 110˚. Could high-resolution images such as those obtained with the Eidon open up new opportunities for early diagnosis? Farrell C. Tyson, MD, addresses this question on page 83 of this issue in "The New Age of Retinal Imaging."

Nidek introduced its **Retina Scan Duo OCT**, which combines high-definition optical coherence tomography (OCT) and a fundus camera into a single system.

DORC obtained FDA 510(k) clearance for sales of its **Eva** retina and cataract surgical system in the United States. Nicholas D. Chinskey, MD, and Gaurav K. Shah, MD, offered their experience with the Eva in the September issue of *Retina Today* (bit.ly/1YivAWM).

Quarter 2

OD-OS's Navilas 577+ laser system received marketing clearance from the FDA. The device is indicated for use in retinal photocoagulation in the treatment of clinically significant DME, proliferative DR, subretinal neovascularization, CRVO, BRVO, lattice degeneration, retinal tears, and retinal detachments.

Quarter 3

The FDA granted 510(k) clearance to **Zeiss Medical Technology** for its **AngioPlex OCT Angiography**. According to the company, Cirrus HD-OCT with AngioPlex requires only a single additional OCT scan to generate an OCT angiography image. Parent company **Carl Zeiss Meditec** announced a new imaging solution for small practices: **Primus 200** offers clinicians a compact, easy-to-use OCT system that provides essential applications for retina.

Bausch + Lomb received 510(k) clearance from the FDA for an **adjustable chandelier fiberoptic illuminator** in 23- and 25-gauge version, which has been designed specifically for the **Stellaris PC Vision Enhancement System**. In the September issue of *Retina Today* (bit.ly/1MX9IrU) Carl C. Awh, MD, described how this instrument could be helpful to surgeons.

MERGERS AND ACQUISITIONS IN 2015

- In February, **Nikon** acquired retinal imaging company **Optos** for $400 million.
- **Actavis** completed its acquisition of **Allergan** in March in a cash and equity transaction valued at approximately $70.5 billion, making the combined company one of the world's top 10 pharmaceutical businesses by sales revenue.
- **Valeant** completed its acquisition of surgical device company **Synergetics** in October at a price per share of $6.50. Synergetics will become a wholly owned subsidiary of Valeant.
- At the end of October, **Allergan** confirmed discussions regarding a potential business combination transaction with **Pfizer**. If the deal goes through, Pfizer would benefit from a lower corporate tax rate because it would be considered an Ireland-based company. No new announcements had been made at press time.

STAY IN THE KNOW

A glance through this 2015 refresher shows how hot the field of retina is right now. There will be plenty more to keep an eye on in 2016, including clinical trial updates and new drug and product indications since 2015. There is no doubt that next year will be filled with just as many new developments, if not more. It is an exciting time to be a retina specialist. Embrace the current climate of innovation and growth! ■