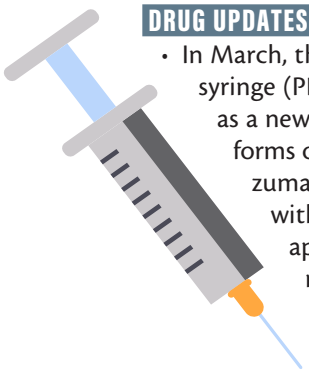
A REVIEW OF ALL THINGS RETINA

Looking back at some of the field's exciting developments over the past 12 months.

BY MICHELE CORRY, ASSISTANT EDITOR

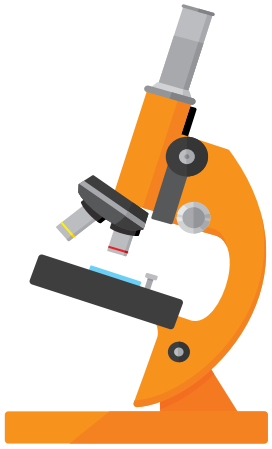
As we approach the end of another year filled with exciting research and fascinating technological advances, it can be difficult to keep from looking forward with anticipation to all that the coming year may hold in store. To fully appreciate what has taken place this year, let us take a moment to recap some of what has happened—much of which has been chronicled in the pages of *Retina Today*.

As you read through this retrospective, please bear in mind that it is by no means an exhaustive list of every happening in our corner of ophthalmology this year. It is presented in no order of preference.



DRUG UPDATES

- In March, the US FDA approved the 0.3 mg prefilled syringe (PFS) of *ranibizumab* (*Lucentis, Genentech*) as a new method of delivering the drug to treat all forms of diabetic retinopathy (DR). The ranibizumab 0.3 mg PFS is the first syringe prefilled with an anti-VEGF agent that has been FDA approved to treat both DR and diabetic macular edema (DME).
- In April, the FDA granted fast track designation for *AAV-RPGR* (*MeiraGTx*), for the treatment of X-linked retinitis pigmentosa (XLRP) due to defects in the retinitis pigmentosa (RP) GTPase regulator gene. MeriaGTx is conducting an open-label, phase 1/2 dose escalation clinical trial of AAV-RPGR in adult and pediatric patients diagnosed with XLRP. The FDA's fast track process is designed to expedite the development and review of drugs intended to treat serious conditions and fill unmet medical needs.
- In July, the FDA released plans to facilitate the development, approval, and market entry of *biosimilars* in the United States. FDA commissioner Scott Gotlieb explained that the Biosimilars Action Plan will use the agency's experience with generic drugs to promote competition among biosimilars. The agency will seek to improve the efficiency of the processes for development and approval of biosimilars and interchangeable products.
- In August, the FDA approved 12-week dosing for *aflibercept* (*Eylea, Regeneron*) based on 2-year data from the phase 3 VIEW 1 and 2 trials, in which patients with wet age-related macular degeneration (AMD) were treated with a modified 12-week dosing schedule with additional doses as needed.

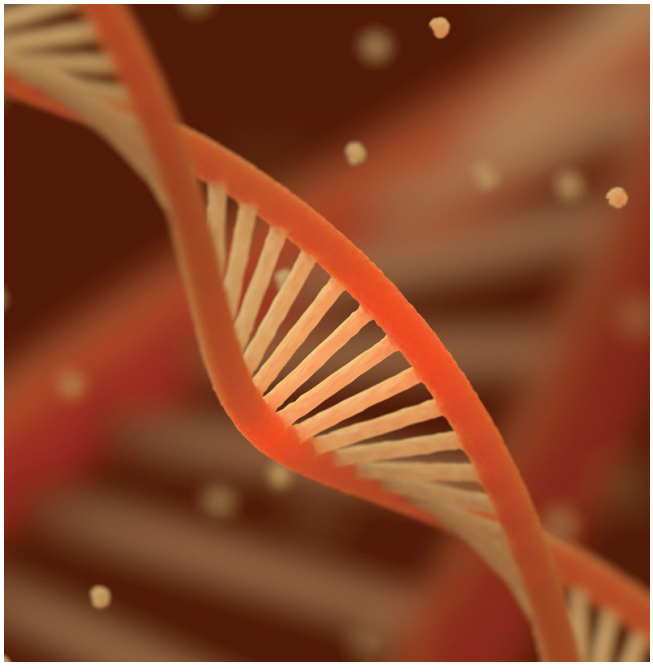


CLINICAL TRIAL UPDATES

Gene Therapy

• *GenSight Biologics* received approval from the UK Medicines and Healthcare Regulatory Agency to initiate the PIONEER phase 1/2 study of *GS030* in patients with RP. PIONEER is a first-in-man, multicenter, open-label, dose-escalation study to evaluate the safety and tolerability of GS030 in patients with RP. GS030 is the combination of a gene therapy (GS030-DP), administered via a single intravitreal injection, and a wearable optronic visual stimulation device (GS030 MD). Study participants will receive increasing doses of GS030-DP in a single intravitreal injection in their worse affected eye. A fourth extension cohort will then receive the highest tolerated dose.

• Proof-of-concept study results were published for an adeno-associated virus (AAV) gene therapy product candidate for the treatment of rhodopsin-mediated autosomal dominant RP (RHO-adRP), licensed by *Ophthotech*. The RHO-adRP product candidate combines, in a single AAV2/5 vector, a transgene expressing a highly efficient novel short-hairpin RNA designed to target and knock down endogenous rhodopsin (RHO) in a mutation-independent manner plus a human RHO replacement transgene made resistant to RNA interference. This construct, when tested in a naturally occurring canine disease model of RHO-adRP by investigators at the University of Pennsylvania, resulted in complete suppression of the endogenous RHO RNA while the human RHO replacement transgene produced up to 30% of normal RHO protein levels.



Pharmaceutical Therapy

• *Clearside Biomedical* announced positive top line results from its phase 2 clinical trial TYBEE, evaluating suprachoroidal *CLS-TA* in combination with intravitreal *aflibercept* in patients with DME over a 6-month period. This multicenter, randomized, masked, controlled phase 2 trial enrolled 71 patients who were naïve to treatment for DME. The patients were randomly assigned 1:1 to receive either quarterly treatment with suprachoroidal CLS-TA together with intravitreal aflibercept (the combination arm) or four monthly treatments of intravitreal aflibercept plus a sham suprachoroidal procedure (the control arm). Patients in either arm could receive intravitreal aflibercept treatment at months 4 and 5 as needed. The trial met its primary endpoint, mean improvement in BCVA from baseline at 6 months on the ETDRS scale. Patients in the combination arm gained an average of 12.3 letters, compared with 13.5 letters in the control arm. Additionally, administration of suprachoroidal CLS-TA together with intravitreal aflibercept met a key secondary endpoint, with a mean reduction from baseline of 208 µm in central subfield thickness at 6 months, compared with a 177 µm mean reduction in the control arm (P = .156). Further, 93% of patients in the combination arm had a greater than 50% reduction in excess central subfield thickness at 6 months, compared with 73% of patients in the control arm.

• A post hoc analysis of the Diabetic Retinopathy Clinical Research Network's Protocol T randomized trial by Bressler et al found that, in patients with DME, *aflibercept* and *ranibizumab* were more effective than *bevacizumab* (*Avastin, Genentech*) in preventing disease persistence, but all three drugs could lead to substantial gains in VA.[1] Among the 660 eyes randomly assigned to up to six monthly injections of aflibercept, bevacizumab, or ranibizumab, 114 eyes were excluded from analysis because of factors including missed visits and use of alternative treatment for DME. Persistent DME through 24 weeks was significantly more common with bevacizumab treatment (65.6%) than with aflibercept (31.6%) or ranibizumab (41.5%). At 2 years, the corresponding rates were 68.2%, 44.2%, and 54.5%, respectively. However, at 2 years, the percentage of eyes gaining 10 or more letters from baseline did not differ significantly among the three drugs, with or without chronic persistent DME. Overall, only three eyes with chronic persistent DME and two without persistent DME lost at least 10 letters.

• *Oxurion* (formerly ThromboGenics) reported top line results from a phase 1/2, single-masked, multicenter study to evaluate the safety and efficacy of two dose levels (4 mg and 8 mg) of *THR-317* (anti-PlGF) for the treatment of DME.[2] The study enrolled a total of 49 patients and included anti-VEGF–naïve patients as well as patients who had responded suboptimally to anti-VEGF treatment. THR-317 was found to be safe and well tolerated; no

OTHER RESEARCH FINDINGS

Thinning of the retinal nerve fiber layer (RNFL) may be a strong predictor of cognitive decline. Researchers found that healthy individuals with RNFL thinning were twice as likely to develop cognitive decline as their counterparts with normal RNFL.[3]

Microvascular changes in the retina may flag early Alzheimer disease. OCT angiography detected a significantly larger foveal avascular zone among 14 study participants with PET imaging that was biomarker-positive for preclinical Alzheimer disease than in 16 other participants without preclinical signs of Alzheimer disease.[4]

Microglia can completely repopulate themselves in the retina after being nearly eliminated, researchers found. The cells can also reestablish their normal organization and function. These findings point to potential therapies for controlling inflammation and slowing progression of rare retinal diseases such as retinitis pigmentosa and AMD, the investigators said.[5]

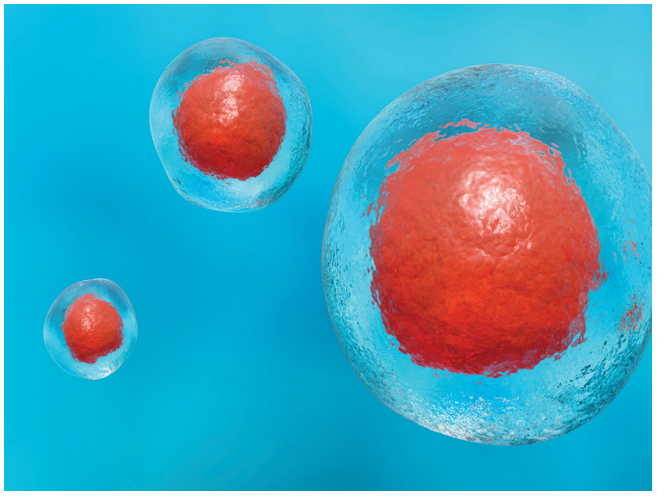
Researchers at Moorfields Hospital and the University College London Institute of Ophthalmology reported that machine learning technology has been trained, using thousands of historic depersonalized eye scans, to identify signs of eye disease and recommend how patients should be referred for care. The artificial intelligence system can recommend the correct referral decision for more than 50 eye diseases with 94% accuracy, matching world-leading eye experts.[6]

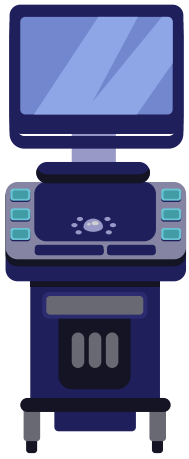
dose-limiting toxicities or relevant safety events were reported at either dose level. Of the anti-VEGF treatment-naïve study participants treated with THR-317 in the 8 mg group, 30% showed a ≥ 15-letter gain from baseline at day 90 versus 5.3% in the 4 mg group.

- *Regeneron* announced that the phase 3 PANORAMA trial evaluating *aflibercept* injection in moderately severe to severe nonproliferative DR (NPDR) met its 24-week primary endpoint. In the trial, 58% of aflibercept-treated patients experienced a 2-step or greater improvement from baseline on the Diabetic Retinopathy Severity Scale at week 24, compared with 6% of patients receiving sham injection.
- *Genentech* announced positive top line results from the phase 2 LADDER study evaluating the efficacy and safety of its investigational *Port Delivery System (PDS)* with *ranibizumab* in individuals with wet AMD. LADDER study participants implanted with the PDS received one of three concentrations of ranibizumab: 10 mg/mL, 40 mg/mL, or 100 mg/mL. Among PDS patients receiving the 100 mg/mL dose, approximately 80% were able to go 6 months or longer before needing their first refill. Of those receiving the 40 mg/mL or 10 mg/mL dose, 71.3% and 63.5%, respectively, were able to go 6 months or longer before the first refill. Patients in the PDS 100 mg/mL arm achieved gains in BCVA and reductions in central retinal thickness similar to those for patients receiving monthly ranibizumab 0.5 mg injections.
- In two clinical trials evaluating *abicipar pegol* (*Allergan*), SEQUOIA and CEDAR, both 8-week and 12-week treatment regimens met the prespecified primary endpoint of noninferiority to *ranibizumab*. The two trials are identical global phase 3 studies designed to assess the 1-year efficacy and safety of abicipar compared with ranibizumab in treatment-naïve patients with stable vision. In both studies, six or eight injections of abicipar demonstrated similar efficacy to 13 ranibizumab injections in the first year of the studies. The incidence of intraocular inflammation was higher in the abicipar arms compared with ranibizumab-treated patients in both trials. Regulatory filing for approval of abicipar is planned for the first half of 2019, according to the manufacturer.

Stem Cell Therapy

- Two patients with wet AMD who received a retinal pigment epithelium (RPE) stem cell patch experienced VA gains of 29 and 21 letters, according to a report in *Nature Biotechnology*.[7] Study participants were implanted with a monolayer of RPE cells derived from human embryonic stem cells (hESC) on a synthetic basement membrane.
- In a similar study by a different group, a stem cell–based retinal implant was found to be feasible for use in patients with advanced dry AMD.[8] The treatment consisted of a layer of hESC-derived RPE cells on an ultrathin supportive structure that was implanted in the retina. Patients who received the implant were followed for up to 1 year to assess safety. No severe adverse events related to the implant or the surgical procedure were seen. There was evidence that the implant integrated with the patients' retinal tissue. One patient had improvement in VA, and two patients had gains in visual function.





PRODUCT AND DEVICE UPDATES

- In January, the FDA granted *Pixium Vision* approval to begin a clinical feasibility study for its *Prima* miniaturized wireless photovoltaic subretinal implant in patients with atrophic dry AMD. The study will recruit up to five patients with vision loss resulting from atrophic dry AMD. The primary endpoint is restoration of visual perception and safety at 12-month follow-up.
- The FDA permitted marketing for the *IDx-DR* (*IDx Technologies*), the first medical device to use artificial intelligence to detect greater than a mild level of DR in adults with diabetes. The device uses an artificial intelligence algorithm to analyze images of the eye taken with the *NW400* retinal camera (*Topcon*). Users can upload digital images of patients' retinas to a cloud server on which IDx-DR software is installed. If the images are of sufficient quality, the software provides the user with one of two results. If a positive result is detected, the user is instructed that the patient should see an eye care provider for further diagnostic evaluation and possible treatment as soon as possible. This device is the first authorized for marketing that provides a screening decision without the need for a clinician to also interpret the image or results.
- *Alcon* introduced *Datafusion* software for its *Ngenuity 3D Visualization System* in July at the American Society of Retina Specialists annual meeting. The software integrates the viewing system with the *Constellation Vision System* (*Alcon*) for vitreoretinal surgery, allowing surgeons to track key data parameters in real time.
- *AngioAnalytics* (*Optovue*) software for OCT angiography blood vessel measurement and 3D projection artifact removal received FDA 510(k) clearance in June. AngioAnalytics provides objective data and analysis of the high-resolution imaging of retinal blood vessels performed by AngioVue (Optovue). Combined, the two technologies create color-encoded maps of vessel densities in the retina or optic nerve and provide analyses of areas where there is blood vessel loss or abnormal blood vessel growth, as well as several parameters to assess change to the foveal avascular zone. The new AngioAnalytics software also provides trend analysis, allowing physicians to objectively monitor retinal and vascular changes.
- *Ellex 2RT Retinal Rejuvenation Therapy* (*Ellex*) has shown promise as an effective intervention in selected cases of intermediate AMD in which patients exhibit large drusen but no signs of cell death. The LEAD multicenter trial did not meet its primary endpoint for the patient population as a whole; however, in a post hoc analysis, the treatment effect of Ellex 2RT was found to differ based on the clinical classification of AMD. Intervention with Ellex 2RT in patients who did not have coexistent reticular pseudodrusen at the start of the trial resulted in a 77% reduction in the rate of progression from early AMD to late AMD at 3-year follow-up, compared with sham treatment.

EYEWIRE TV

Opticon introduced R-Evo Smart for cataract and retinal surgeries. bit.ly/r-evosmart

LumiThera debuted the Valeda Light Delivery System for the treatment of dry AMD. bit.ly/LumiThera

An OCT angiography module for the Spectralis imaging platform (Heidelberg Engineering) is now available in the United States. bit.ly/spectralis

Quantel Medical introduced the Vitra 2 retinal photocoagulator. bit.ly/vitra2

WAITING IN ANTICIPATION

We can only hope that 2019 will bring continuing advances in these areas so that you can continue to provide your patients with the best care possible. The editors and publisher of *Retina Today* join you in looking forward to it. ■

1. Bressler NM, Beaulieu WT, Glassman AR, et al; Diabetic Retinopathy Clinical Research Network. Persistent macular thickening following intravitreous aflibercept, bevacizumab, or ranibizumab for central-involved diabetic macular edema with vision impairment. A secondary analysis of a randomized clinical trial. *JAMA Ophthalmol*. 2018;136(3):257-269.
2. ThromboGenics reports initial data from its clinical study evaluating THR-317 for the treatment of diabetic macular edema [press release]. ThromboGenics. April, 4, 2018. oxurion.com/content/thrombogenics-reports-initial-data-its-clinical-study-evaluating-thr-317-treatment-diabetic. Accessed October 18, 2018.
3. Ko F, Muthy ZA, Gallacher J, et al. Association of retinal nerve fiber layer with current and future cognitive decline: a study using optical coherence tomography. *JAMA Neurol*. 2018;75(10):1198-1205.
4. McNamara D. Retinal changes on OCT angiography may flag early Alzheimer's. *Medscape*. medscape.com/view-article/896364. Accessed October 18, 2018.
5. Zhang Y, Zhao L, Wang X, et al. Repopulating retinal microglia restore endogenous organization and function under CX3CL1-CX3CR1 regulation. *Sci Adv*. 2018; 4(3).
6. De Fauw J, Ledsam, JR, Romera-Paredes B, et al. Clinically applicable deep learning for diagnosis and referral in retinal disease. *Nat Med*. 2018;24(9):1342-1350.
7. da Cruz L, Fynes K, Georgiadis O, et al . Phase 1 clinical study of an embryonic stem cell-derived retinal pigment epithelium patch in age-related macular degeneration. *Nat Biotechnol*. 2018;36(4):328-337.
8. Kashani AH, Lebkowski JS, Rahhal FM, et al. A bioengineered retinal pigment epithelial monolayer for advanced, dry age-related macular degeneration. *Sci Transl Med*. 2018;10(435).