Although there has been much focus and subsequent success generating treatments targeted at wet age-related macular degeneration (AMD), minimizing the treatment burden and enhancing treatment efficacy remain unmet needs in therapy for this chronic disease. Additionally, there are no treatments available for dry AMD.

Fortunately, there is no shortage of ongoing research for the progressive disease; an initial clinicaltrials.gov search yielded 360 hits of open AMD studies. In this column, we will review the status of a few of these potential therapeutic strategies.

**DRY AMD**

Reduction of toxic byproducts and extracellular deposits in the retina has been a targeted treatment strategy for patients with dry AMD. Amyloid deposits have been found to accumulate in the drusen of AMD patients, which establishes amyloid beta (Aβ) as a viable AMD target. RN6G (PF4382923, Pfizer) is an intravenously administered, humanized monoclonal antibody that binds with high affinity to the Aβ peptides Aβ_{40} and Aβ_{42}. Such peptides have been implicated in neurodegenerative disorders, such as Alzheimer, in which massive neuronal death due to apoptosis is a common characteristic. It is hoped that treatment with anti-Aβ antibodies may produce improvements in retinal function deficits evident in AMD by preventing the accumulation of Aβ_{40} and Aβ_{42}. RN6G is currently under development as a treatment for patients with geographic atrophy (GA) secondary to dry AMD. Two phase 1 studies, including a single ascending-dose study and a multiple ascending-dose study, have been completed. A phase 2 multicenter, randomized, multidose study is currently under way.

Visual cycle modulation programs are also emerging as a treatment approach for dry AMD. Toxic waste products such as lipofuscin and A2E have been shown to accumulate in the retinal pigment epithelium as a byproduct of visual cycling, so modulation of the cycle seems a logical approach. A phase 2a program for ACU-4429 (emixustat hydrochloride, Acucela) has been completed, and a phase 2b/3 study began in February of this year for the treatment of GA associated with dry AMD. This small, nonretinoid visual cycle modulator specifically targets RPE65, the trans-to-cis-retinal isomerase. A phase 1 dose escalation trial of ACU-4429 demonstrated linear pharmacokinetics across doses, and the drug was well-tolerated in healthy subjects.

Another company also targeting toxic byproducts is Aldexa, previously known as Neuron Systems Inc. Aldehydes are toxic mediators known to be elevated in patients with dry AMD. Aldexa’s lead compound, NS2, binds to malondialdehyde (MDA), 4-hydroxynonenal (HNE), and retinaldehyde, three common toxic aldehydes. Therapies targeted at lowering the excessive levels of these aldehydes in AMD patients represent an innovative strategy for potential treatment.

Evidence indicating that tetracyclines are active against many molecular pathways suspected to be involved in the pathogenesis of dry AMD, and they may also slow the progression of GA, has prompted the investigation of doxycycline (Oracea, Galderma Laboratories LP) for GA treatment. Doxycycline, a matrix metalloproteinase (MMP) inhibitor, is a broad-spectrum antibiotic that is clinically useful due to its broad antimicrobial properties. Doxycycline is currently approved for treating the inflammatory lesions of rosacea and appears to be well tolerated. The TOGA trial, a multicenter phase 2/3 study to assess the efficacy and safety of daily oral administration of doxycycline compared with placebo on the rate of change in area of GA, is set to enroll patients in 2013.
New efforts in stem cell replacement therapy are also creating noise for degenerative diseases of the retina. Embryonic stem cells may provide a potential therapy to replace damaged RPE cells and to sustain visual function for suffering patients. Advanced Cell Technology (ACT) has initiated 2 separate phase 1/2 trials to test the safety of the human embryonic stem cell (hESC)-derived RPE cellular therapy for dry AMD and for Stargardt macular dystrophy. Each patient will receive a single uninocular subretinal infusion of MA09-hRPE cells in 1 of 4 dose levels. A phase 1/2a study to evaluate the safety and tolerability of MA09-hRPE cellular therapy in patients with advanced dry AMD is also being conducted with CHA Biotech, a Korean-based biotechnology company that entered into a licensing agreement with ACT in 2009. ACT confirmed in a press release that the vision of a patient enrolled in 1 of the clinical trials involving the company’s RPE cells derived from hESCs has improved from 20/400 to 20/40 following treatment.

iScience Interventional and Johnson & Johnson have partnered for site-specific subretinal drug delivery. A phase 1/2a multicenter, randomized study is evaluating the safety and clinical response of a single, subretinal administration of human umbilical tissue derived cells (CNT2476) using the iTrack Model 275 microcatheter in patients with visual impairment associated with GA.

MC-1101 (MacuCLEAR) is a topically administered eye drop that works by increasing ocular blood flow in the choroidal vessels, preventing the rupture of Bruch membrane. A successful phase 1b/proof of concept human clinical trial demonstrated that MC-1101 was safe and well tolerated. A phase 2/3 vehicle-controlled, double-masked, single-center study is currently being conducted over the course of 2 years.

The fluocinolone acetonide implant (Iluvien, Alimera Sciences) is being investigated as a possible treatment for patients with bilateral GA, and a second trial, the MAP study, is evaluating the implant for wet AMD. Alimera is also considering nicotinamide adenine dinucleotide phosphate (NADPH) oxidase inhibitors to treat dry AMD, particularly GA.

**WET AMD**

The current standard of care for wet AMD works to bind and inhibit preexisting VEGF that causes bleeding and fluid leakage into the eye. Allegro’s integrin peptide therapy, ALG-1001, collectively turns off the production of aberrant blood vessels, reduces the leakage of aberrant blood vessels, and inhibits the growth of aberrant blood vessels. ALG-1001, a small molecule oligopeptide that targets multiple integrin receptor sites that play a key role in cell signaling and regulating cellular shape, motility, and the cell cycle, is being investigated for treatment of several vascular eye diseases including wet AMD, diabetic macular edema (DME), and symptomatic vitreomacular adhesion. In a phase 1 study in 2011 including 15 end-stage DME patients, 8 of the 15 patients had 3 to 5 lines of best corrected visual acuity (BCVA) improvement as well as a 30% to 80% reduction in central retinal thickness. Interim data on a phase 1b/2a dose-ranging, monotherapy study in wet AMD was presented this year. In this first-in-human 6-month wet AMD study, the drug appeared safe and well tolerated, and a treatment effect was seen to last more than 4 months off-treatment. There was also a robust response in the 3.2 mg dose group of at least 3 months off-treatment in all subjects. A demonstrated mean BCVA improvement of +8 ETDRS letters as measured by in this group corresponded to a 30% decrease in central macular thickness and improvement in retinal architecture. ALG-1001 has the potential to serve as a standalone therapy or as combination therapy. In May, Allegro and Senju Pharmaceutica announced a collaboration and license agreement to develop and market integrin peptide therapy in Japan.

Allergan, together with Molecular Partners, is seeking alternative options for wet AMD with AGN-150998, an anti-VEGF DARPin. The phase 2 REACH study is currently examining this small target-binding protein in two stages: first, in a dose-escalation assessment of the safety of AGN-150998 administered as an intravitreal agent, and second in a comparison of the safety and treatment effects between the drug and ranibizumab.

Midstage trial results showed some product differentiation over ranibizumab but not enough to support moving the product directly into a phase 3 program. The current study results are slotted to be presented at the American Academy of Ophthalmology meeting in November; meanwhile, Allergan plans to further evaluate its DARPin treatment by adding another arm to the existing trial.

Last year, Ophthotech Corp. announced positive results with its Fovista anti-PDGF therapy (1.5 mg) administered in combination with ranibizumab compared with ranibizumab monotherapy. Formerly known as E10030, Fovista is an aptamer targeted against PDGF-B, which regulates neovascular pericytes. The prospective, randomized, controlled phase 2b trial evaluated 449 patients who were randomized to receive 1 of the following treatment regimens administered every 4 weeks for 24 weeks: Fovista 0.3 mg/ranibizumab; Fovista 1.5 mg/ranibizumab; or sham/ranibizumab.
Patients receiving the combination of Fovista 1.5 with anti-VEGF therapy gained a mean of 10.6 letters of vision on the ETDRS chart compared with 6.5 letters for those receiving anti-VEGF monotherapy.22 Additional studies examining this anti-PDGF therapy are anticipated to begin in the near future.

Oraya Therapeutics is bringing about novel techniques for wet AMD therapy by using radiation, which has been used medically, most notably for cancer, for its antiangiogenic, antiinflammatory, and antifibrotic effects. In March, results of the INTREPID study, which evaluated stereotactic radiotherapy in conjunction with as-needed anti-VEGF therapy, met its primary endpoints demonstrating that a single dose of Oraya therapy significantly reduced the need for injections in wet AMD patients, with a favorable safety profile 1 year post administration.23 A second phase 2 study (ENDEAVOUR) has been initiated to confirm these results with respect to the number of anti-VEGF injections and frequency of visits during the first year after treatment.24

All eyes are also on Ohr Pharma’s wet AMD study featuring a topical formulation of squalamine targeted for wet AMD. Squalamine, a small molecule inhibitor of multiple growth factors (VEGF, PDGF), was acquired in 2009 from Genaera, which had previously conducted studies using an intravenous formulation of the drug and has reformulated it into a twice-daily, self-administered eye drop. The eye drop solves several of the issues associated with intravenous delivery such as suboptimal dosing, patient compliance, and the commercial challenges of a weekly intravitreal infusion for the intended patient population. Preclinical data presented recently highlighted the potential therapeutic value of the program by demonstrating that the eye drop formulation was safe and well tolerated. Additionally, squalamine concentrations in the posterior sclera/choroid were well above the target therapeutic levels. In May 2012, the squalamine eye drop program was granted fast track designation by the US Food and Drug Administration (FDA), and a phase 2, double-masked, placebo-controlled clinical trial is currently enrolling patients.25

The number of active clinical trials for both wet and dry AMD is evidence of the need for additional therapies for wet AMD and for a first-ever FDA-approved treatment for the dry form of the disease.  

Aron Shapiro is Vice President of Retina at Ora Inc., in Andover, MA. Ashley Lafond is a medical writer at Ora Inc.