Reformulating Anti-VEGF for Extended-release Delivery in the Treatment of Retinal Diseases

Preclinical studies support feasibility of novel microparticle approach.

BY GARY P. COOK, PHD

The introduction of anti-vascular endothelial growth factor (anti-VEGF) therapy in 2005 transformed the treatment paradigm of age-related macular degeneration (AMD) and other retinal diseases. Retina specialists now have several pharmacotherapeutic options to delay vision loss and even improve vision in patients. Despite these advances, optimal treatment of AMD and other retinal diseases is hindered by the frequent dosing requirements of current therapies.

AMD is a chronic disease that requires continuous, long-term treatment in order to suppress VEGF, a protein that plays a critical role in angiogenesis and permeability of the blood vessels. Recent studies evaluating injection frequency and visual outcomes of anti-VEGF therapies have shown that treating on an as-needed basis leads to undertreatment and significantly less vision gain than monthly treatment.[1] Chronic treatment, however, poses a challenge to patients, practitioners, and caregivers because patients must receive intravitreal injections every 4 to 6 weeks. This frequent dosing schedule may result in poor compliance and inconsistent treatment efficacy, and it puts patients at ongoing risk for injection-related complications such as endophthalmitis.

According to a recent survey of 90 retina specialists (60 in the United States and 30 in Europe, all with large clinical practices), reducing dosing frequency is the greatest realistic unmet need in wet AMD therapy.[2] The need for reduced dosing frequency is just as great, if not greater, in retinal diseases that affect working-age adults and may require long-term management such as diabetic macular edema and retinal vein occlusion.

To address this critical unmet need in anti-VEGF therapy, Eyetech Inc. (Palm Beach Gardens, FL), is working with SurModics Pharmaceuticals, Inc. (Birmingham, AL), to develop an extended-release formulation of pegaptanib sodium injection (Macugen), currently known as pegaptanib-ER.

APPLYING MICROPARTICLE TECHNOLOGY TO A SELECTIVE INHIBITOR OF VEGF

Pegaptanib sodium, an antagonist of the VEGF isoform 165, was the first anti-VEGF therapy approved by regulators for ocular use and remains the only approved selective VEGF inhibitor. The reformulation of pegaptanib sodium as an extended-release therapy is based on SurModics' proprietary microparticle technology. This process uses bioresorbable, polymeric particles to encapsulate a therapeutic agent, in this case pegaptanib sodium, and enable its gradual release over an extended period of time.

The goal of the development process for pegaptanib-ER is to maintain a therapeutically relevant concentration of pegaptanib for an extended period of time so that the dosing interval can be extended from once every 6 weeks to once every 4 to 6 months. The potential benefits of this extended-release formulation include increased convenience for patients and practitioners; reduced risk of infection due to less frequent exposure to injections; and improved treatment efficacy, as compliance will improve and the drug will be delivered more consistently.

Under a licensing and development agreement, Eyetech has the worldwide rights to the pegaptanib

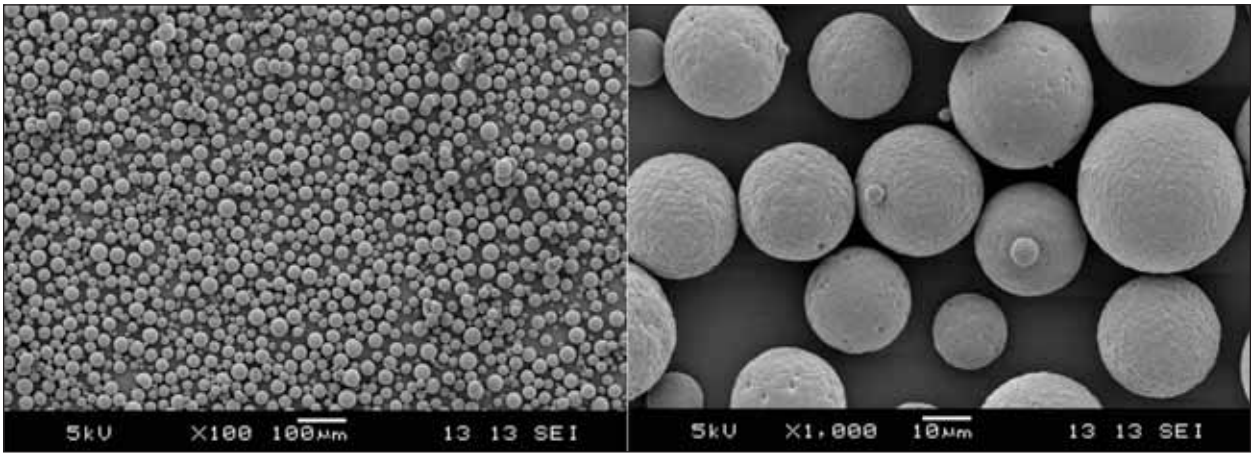

Figure 1. Microparticle technology uses a novel oil/water emulsion technique to provide PLGA-based pegaptanib-ER microparticle formulation.

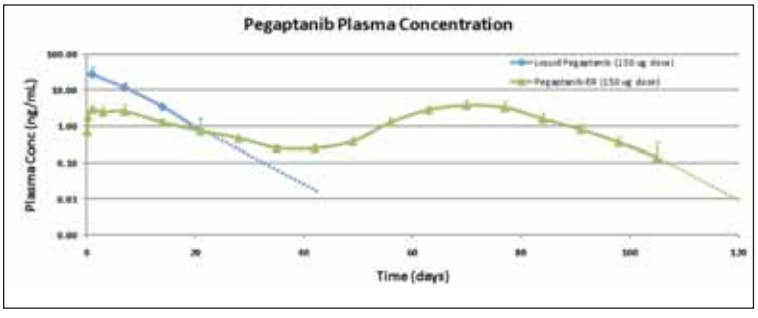

Figure 2. In a preclinical pharmacokinetic study in six rabbits, researchers achieved sustained release of pegaptanib over 100 days following injection as measured by plasma concentration.

microparticles program. Eyetech has filed for three patents in the United States and internationally, which, if issued will expire in 2026.

PRECLINICAL STUDIES SUPPORT FEASIBILITY OF ER DESIGN

As a first step in the development process, researchers prepared a microparticle formulation of pegaptanib sodium using a novel oil/water emulsion technique (Figure 1). The process has the potential to denature complex therapeutic agents. An important attribute of pegaptanib sodium, an RNA-based aptamer, is that the aptamer can be denatured or unfolded and refolded without loss of activity. This is in contrast to the typical behavior of proteins, which are often difficult to refold into their active conformation after being denatured. The resulting formulation for pegaptanib sodium is a polylactic co-glycolic acid (PLGA) polymer-based particulate in which pegaptanib sodium is evenly distributed throughout the polymer for slow release of the drug over time.

Using this prototype formulation, the development team set out to demonstrate that pegaptanib could be released as an intact, active molecule. Through in vitro studies, investigators successfully showed that they could entrap the pegaptanib molecule in the PLGA polymer and it could be released intact without degradation. They then demonstrated that the released, intact molecule remained functionally active and did not lose specificity to its target. A cell-based gene expression assay in which cells exposed to VEGF upregulate the expression of tissue factor was employed to demonstrate that pegaptanib released in vitro from pegaptanib-ER retained the ability to bind and sequester VEGF165-mediated functional activity.

Overcoming these critical hurdles laid the groundwork for further development of pegaptanib-ER and allowed researchers to move into animal studies to further demonstrate the feasibility of the extended release formulation. In a pharmacokinetic study in six rabbits, the team evaluated plasma concentrations following intravitreal injection of the liquid and extended-release formulations of pegaptanib sodium. They analyzed plasma concentrations because pharmacokinetic research conducted for the registration of pegaptanib sodium showed a direct correlation between vitreous humor and plasma concentrations.

When a specified dose of the liquid formulation of pegaptanib sodium was administered, investigators observed that the presence of pegaptanib could be detected for about 1 month following injection. When the same dose of pegaptanib sodium, reformulated within PLGA particles, was administered via a single intravitreal injection in the same study design, investigators observed that they could detect the pegaptanib for more than 100 days following injection. These findings showed that without

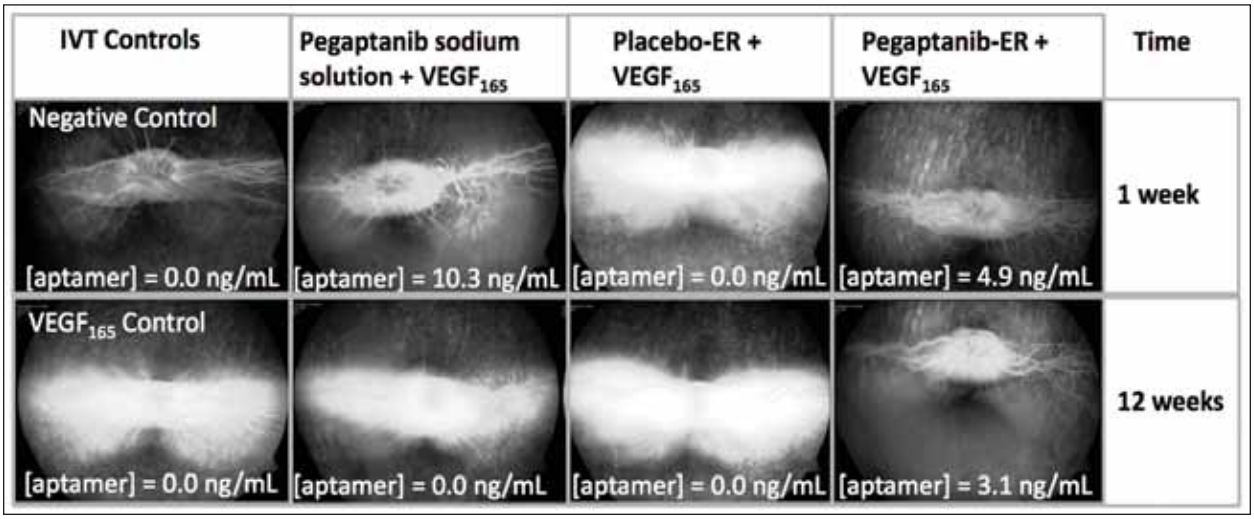

Figure 3. Pegaptanib-ER demonstrated functional and measurable activity over 12 weeks in VEGF165 intravitreous challenge model. Top row shows after intravitreous (IVT) data at 1 week after dosing; bottom row is 12 weeks after IVT dosing. Negative control is bovine serum albumin, positive control is VEGF165. Pegaptanib solution is pegaptanib sodium dissolved in isotonic phosphate buffer, placebo-ER is formulation prepared without pegaptanib sodium, and pegaptanib-ER is the prototype pegaptanib sodium extended-release formulation. Listed aptamer concentrations are plasma pegaptanib levels for each experimental condition.

increasing the dosage of pegaptanib sodium, it is possible to increase the amount of time during which the animal subject was exposed to pegaptanib from a single intravitreal injection. Researchers anticipate that the extended exposure effect would be similar in humans (Figure 2).

In a second animal study, researchers assessed VEGF165-induced vascular permeability in rabbits to show functionality of pegaptanib released from pegaptanib-ER over an extended period of time. Rabbit eyes were challenged with an intravitreous dose of VEGF165. At 48 hours, researchers conducted fluorescein angiography to assess increased vascular permeability. They found that intravitreal administration of VEGF165 in control animals led to increased vascular permeability, as previously reported.[3] Animals dosed with pegaptanib sodium solution or pegaptanib-ER immediately prior to VEGF165 challenge showed a reduction in VEGF165-induced permeability, as assessed by fluorescein angiography. The effects of the pegaptanib sodium formulations were assessed again at 1 and 12 weeks (Figure 3). Investigators also measured the pegaptanib plasma levels of animals and determined that detectable levels of pegaptanib correlated with reduced vascular permeability after VEGF165 challenge. This study showed that a single intravitreal administration of pegaptanib-ER formulation can deliver bioactive pegaptanib over an extended period of time.

BUILDING ON PEGAPTANIB-ER PROOF OF PRINCIPLE

The totality of preclinical data for pegaptanib-ER serves as proof of principle that pegaptanib sodium can be successfully reformulated to be released over the course of several months without losing functional biologic activity. It remains to be shown whether the concept that has been proven technically achievable can be translated into a clinically relevant treatment paradigm for patients.

Pegaptanib-ER is continuing to be evaluated as a next-generation treatment for AMD that overcomes one of the most pressing treatment challenges associated with the disease. The studies conducted to date have powerful implications not only for AMD but also for other retinal diseases that require long-term management with anti-VEGF pharmacotherapy. In 2011, the companies will initiate toxicology studies as a next step in the pegaptanib-ER development process. ■

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