New Innovations in AMD Therapy May Be Promising

BY SAMIR PATEL, MD

Ventures in Translation features innovators in the field of vitreoretinal disease. Successful translation of scientific ideas to useful medical treatments and technologies requires many elements. Each of the innovators featured here has a story to tell that often combines an exceptional understanding of disease, foresight, perseverance, and an ability to obtain funding for an unrecognized technology. The stories featured here will provide a snapshot of what it has taken to bring these breakthroughs to our patients. The authors will range from scientists to clinicians to bankers to venture capitalists, and some will do a little of all.

The inaugural article in the January/February 2008 issue of Retina Today featured Samir Patel, MD. This installment is a continuation of the first article by Dr. Patel, who continues his discussion on how treatment for age-related macular degeneration (AMD) has evolved beyond anti-vascular endothelial growth factor (VEGF) therapy to agents targeting other points in the AMD disease cascade. Along with David Guyer, MD, and Tony Adamis, MD, Dr. Patel cofounded Eyetech, which began as a virtual company that resulted in pegaptanib sodium (Macugen), the first Food and Drug Administration-approved anti-VEGF agent for choroidal neovascularization (CNV). Dr. Patel served as a founder, Chief Medical Officer, and Board Member of Eyetech. Currently he is Cofounder, President and CEO of Ophthotech, an early stage company that is identifying and studying new drugs for treating neovascular diseases of the eye.

This month’s issue will describe Dr. Patel’s new venture, Ophthotech, and the molecular entities that the company is investigating to improve outcomes in treatment of AMD with CNV.

-Elias Riechel, MD

Currently, the approval of nonselective vascular endothelial growth factor (VEGF) antagonists such as ranibizumab (Lucentis, Genentech) and bevacizumab (Avastin, Genentech) is clearly a major step forward in age-related macular degeneration (AMD) therapy. The tremendous breakthrough in biotechnology, as mentioned in the first installment of this column (Retina Today, January/February 2008), has continued. Our understanding of the molecular events driving angiogenesis and drusen biogenesis has progressed at an unprecedented rate. Therefore, a large number of attractive targets have emerged in the signaling cascade for AMD, setting the stage for combination therapy for wet AMD and perhaps the first breakthrough for dry AMD.

This compelling opportunity has given rise to the birth of Ophthotech Corp. (Princeton, NJ), cofounded by me, serving as the president and CEO, and David Guyer, MD, the executive chairman. In addition, the management team consists of many experienced executives responsible for the accelerated approval of pegaptanib sodium (Macugen) at Eyetech (New York). We have completed a first round of financing with strong support from our investors—lead investor, SV Life Sciences (London, UK), HBM BioVentures (Baar, Switzerland) and Novo A/S (Bagsvaerd, Denmark). After examining a myriad of attractive assets with strong scientific underpinnings at an ideal stage of development, we have acquired three compelling molecular entities: E10030, an antiplatelet-derived growth factor (PDGF) aptamer; volociximab, a
monoclonal antibody targeting \(\alpha_5\beta_1\) integrin; and an anticomplement aptamer targeting the C5 component of the complement cascade.

**COMBINATION THERAPY**

Although anti-VEGF agents have been shown to inhibit further growth of neovascular tissue in AMD, they are unsuccessful in inducing regression of choroidal neovascularization (CNV). This is also the case with VEGF antagonism in ocular and tumor angiogenesis models. Targeting endothelial cells and pericytes of the neovascular tissue via PDGF-B signaling in combination with anti-VEGF agents has been shown to induce regression in developmental, corneal, choroidal and tumor angiogenesis models. We believe combination therapy with E10030 (Ophthotech), an anti-PDGFB aptamer, plus an anti-VEGF agent holds great promise for enhanced efficacy. A phase 1 trial with a combination of E10030 and ranibizumab is being initiated.

**TARGETING SURVIVAL FACTORS**

Multiple studies have shown that extracellular matrix proteins exert direct effects on endothelial cells via integrins. Specifically, integrin \(\alpha_5\beta_1\) is a critical survival factor for proliferating endothelial cells, and its antagonism has been shown to result in an antiangiogenic response as well as neovascular regression. Target validation has been demonstrated in vitro studies as well as in vivo developmental, tumor and ocular angiogenesis models. Volociximab, an \(\alpha_5\beta_1\) integrin antagonist, is a monoclonal antibody which has exhibited potent anti-angiogenesis in the rabbit and primate CNV models. We intend to commence clinical studies in AMD patients with volociximab shortly.

**BLOCKING COMPLEMENT ACTIVATION**

Recently, multiple labs with publications in *Science* and *The New England Journal of Medicine* have shown that polymorphisms in genes coding for the complement regulatory proteins may account for approximately 50% to 75% of AMD cases and may increase the likelihood of AMD by 7.4 to 10 times. Independent university labs have also shown that AMD is an inflammatory disease. There is strong evidence that this inflammation in AMD is complement-mediated. Complement activation has been implicated in drusen biogenesis, and complement inhibition has been shown to be effective in laser CNV models. Ophthotech’s anti-C5 aptamer blocks a key step in the activation of the complement cascade. This anti-C5 aptamer will enter phase 1 trials for wet and dry forms of AMD shortly.

Concurrently, Ophthotech has started a compelling drug delivery program for its new molecular entities. Hopefully, these efforts will translate into enhanced visual acuity, alleviation of the treatment burden and open a new chapter for dry AMD therapy.

**MOVING AHEAD**

In summary, we are currently at the dawn of pharmacotherapy for AMD. Advances in targeted therapeutics coupled with strategies employing combination therapy hold great promise for our patients as we look above and beyond anti-VEGF treatment.

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