

Topical Multitarget Agent Readying for Phase 2 Trial

Efficacy studies will determine how on target TG100801 is in humans.

BY CONNI BERGMANN KOURY, EDITOR-IN-CHIEF

TargeGen, Inc. (San Diego, CA) has recently completed a single-center phase 1 clinical trial of TG100801 in healthy volunteers. The agent—a small molecule, topically applied, multitarget kinase inhibitor—is being developed for the treatment of age-related macular degeneration (AMD), diabetic macular edema (DME), and diabetic retinopathy (DR).

According to a news release, phase 1 results suggest that TG100801 is well-tolerated in humans at the low and high doses tested when applied topically for 14 days. The company plans to initiate phase 2 clinical trials in patients with neovascular AMD later this year.

Richard Soll, PhD, CSO and Vice-President, Research and Development for TargeGen, spoke about TG100801 during Angiogenesis 2007,¹ held recently in Key Biscayne, Fla. He also spoke with *Retina Today* in a phone interview.

TG100801 is the first topically applied, multitargeted vascular endothelial growth factor receptor (VEGFR)/Src kinase inhibitor to advance into the clinic, Dr. Soll said. “Agents such as TG100801 exhibit efficacy in vivo after topical application in models of angiogenesis and permeability, and have the potential to address underlying inflammation associated with AMD, proliferative DR, and DME.”

RATIONALE

Investigators at TargeGen began thinking about how to go beyond simply VEGF in AMD, as well as DME and DR. These diseases are characterized by more than that, Dr. Soll said. A second issue is how to get around the invasive, injectable, drug-delivery issues. “These two questions led us to kinase inhibitors,” Dr. Soll said.

The company had been working in the area of vascular biology, with specific interest in Src kinases and their role in reducing vascular permeability. TargeGen’s scientific founder Dave Cheresch found that Src inhibitors could reduce edema

associated with myocardial infarction and stroke.²

“In further work with Dr. Martin Friedlander’s lab at Scripps Research Institute, the investigators injected VEGF directly into the eye of Src and Yes knockout rodents, and found out that those animals were refractory toward leak induced by VEGF. They further showed that a Src inhibitor reduced VEGF-induced leak in the eye of a normal animal.” This provided validation that VEGF-mediated leakage was mediated by Src-family kinases, Src and Yes, specifically.

In these early experiments, however, the Src inhibitor was delivered via a systemic injection.

Many of the growth factors that are involved in angiogenesis signal through Src. Additionally, Dr. Soll said, members of the Src family play an important role in inflammation and the signaling of inflammatory cells. “So now there is a potential opportunity to think beyond VEGF and angiogenesis, even beyond leak and getting into some antiinflammatory aspects,” he said.

MULTITARGET INHIBITION

TargeGen investigators then decided to test a multitarget inhibitor that had anti-Src/Yes, anti-VEGF, and antiplatelet-derived growth factor activity. Dr. Friedlander tested the agent—TG100572—topically in his leak model. “He administered the drug once, topically, in rodents and then injected VEGF. He saw about 60% reduction in permeability or leak,” Dr. Soll said. When the drug was given three times, investigators saw an 80% to 85% reduction in leak.

When TG100572 was converted to the prodrug TG100801 (which lacks any kinase activity), a single drop of the prodrug as an eyedrop produced complete inhibition to VEGF-induced angiogenesis in the Friedlander model. This suggested to us higher penetration of the drug to the back of the eye was achieved via the prodrug approach in the course of a single administration.

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The company proceeded to benchmark its agent against pegaptanib (Macugen; OSI/Eyetechnology and Pfizer, both in New York, NY) and bevacizumab (Avastin; Genentech, San Francisco) in the rodent leak model using human VEGF. The topical agent was as effective as the other two, which were administered intravitreally (pegaptanib) and systemically (bevacizumab). Thus, this suggested that a topically applied agent could achieve the same level of efficacy compared to accepted therapies given by the intravitreal or systemic route.

In a leak model of retinal ischemia, TargeGen researchers were able to see nearly a 30% to 50% reduction with the agent. "We are now using optical coherence tomography (OCT) to measure the reduction in retinal thickness in animals, and we are seeing profound changes with the drug."

Investigators worked with angiogenesis models in the lab of Peter Campochiaro, MD, at Johns Hopkins. When the agent was topically administered three times over the course of this experiment, there was a 35% to 50% reduction in neovascularization. "The level of reduction in neovascularization is striking, in that the effect is comparable to agents like VEGF-trap, integrin antagonists, and combretastatin—and all of those drugs are given either intravitreally or systemically. So now we are coming in with a topical agent and getting exciting results," Dr. Soll said. TargeGen researchers ultimately reproduced those findings in the clinical formulation, using twice a day dosing over 14 days as opposed to the original three times daily.

"In addition we were able to demonstrate inhibition of VEGF signaling in a developing mouse model. On day 8, we administered the active drug TG100572. The next day, we looked at inhibition of phosphorylation of downstream kinase signaling molecules—in particular FAK, which is downstream of VEGF and Src—and found the agent inhibits FAK signaling."

Dr. Soll said that there is encouraging *in vitro* evidence for addressing some inflammatory aspects of AMD as well. "TG100572 has desirable attributes and now we are pushing into the human setting. We are finalizing phase 2 trial designs and will conduct a small OCT trial to see if the drug affects retinal thickness."

Although it is very early right now, this area holds a lot of interest, Dr. Soll said.

"Our efficacy studies in humans will determine how on target we are." ■

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1. Soll R. Topically efficacious multitarget kinase inhibitors for AMD, DME, and PDR. Presented at the Angiogenesis 2007 meeting, Feb. 23-24, 2007. Key Biscayne, Fla.

2. Weis S, Shintani S, Weber A, et al. Src blockade stabilizes a FliK/cadherin complex, reducing edema and tissue injury following myocardial infarction. *J Clin Invest.* 2004;113:885-894.