

Researchers describe protease inhibitor that may aid in diabetic retinopathy treatment

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Researchers from Joslin Diabetes Center, Boston, and ActiveSite Pharmaceuticals, Inc., San Francisco, announced today that they have demonstrated that a specific inhibitor of the protease plasma kallikrein, ASP-440, developed by ActiveSite Pharmaceuticals, may provide a new therapeutic approach for treatment of diabetic retinopathy, the most common eye-related complication of diabetes. The study, which was partly funded by the Juvenile Diabetes Research Foundation (JDRF), is published in the February 2009 issue of the journal *Hypertension*.

In the published study, led by Edward P. Feener, Ph.D., an Investigator in the Section on Vascular Cell Biology at the Joslin Diabetes Center and Associate Professor of Medicine at Harvard Medical School, continuous systemic administration of ASP-440 proved effective in decreasing hypertension-induced increased retinal vascular permeability in rodents, by as much as 70%. Increased retinal vascular permeability is a characteristic finding in diabetic retinopathy and a primary cause of diabetic macular edema, a leading cause of visual impairment associated with diabetes. Hypertension is a known risk factor for the development of retinopathy. ASP-440 was also found to be effective in lowering the elevated blood pressure in these animals.

"These findings represent a pivotal step towards understanding the importance of plasma kallikrein as a target in diabetic eye disease and how its inhibition may support the development of a safe and effective therapy for diabetic retinopathy," said Barbara Araneo, Director of Complications Research for the Juvenile Diabetes Research Foundation. "While further studies are needed to determine the therapeutic potential of ASP-440, the research underscores the relevance of the kallikrein system in diabetic microvascular disease."

In previous JDRF-funded research, Joslin

researchers identified plasma kallikrein as a potential therapeutic target in people with diabetic retinopathy. "This recent study suggests new opportunities to inhibit plasma kallikrein and reduce retinal blood vessel leakage," said Dr. Feener. "While these results are encouraging, more work is needed to understand plasma kallikrein's role in other retinal functions, as well as other diabetic complications, which can occur concurrently with diabetic retinopathy."

"We are very encouraged by the pharmacological activity demonstrated by ASP-440 in this model of hypertensive retinal vascular permeability," said Tamie Chilcote, Ph.D., Vice-President, Lead Discovery, for ActiveSite Pharmaceuticals. "We look forward to further studies in collaboration with Dr. Feener to better establish the therapeutic potential of this and other plasma kallikrein inhibitors for treatment of retinopathy."

Diabetic Retinopathy

Diabetic retinopathy is the most common and most serious eye-related complication of diabetes. It is a progressive disease that causes retinal swelling and destroys small blood vessels in the retina, eventually leading to vision problems. In its most advanced forms, known as "diabetic macular edema" and "proliferative retinopathy," it can cause moderate to severe vision loss and blindness. Nearly all people with type 1 diabetes show some symptoms of diabetic retinopathy usually after about 20 years of living with diabetes. Approximately 20 to 30 percent of patients develop the advanced form. Those with type 2 diabetes are also at risk.

Over time, the disease progresses to its advanced or proliferative stage, and fragile new blood vessels grow along the retina. However, these fragile vessels can hemorrhage easily, and blood may leak into the retina and the clear, gel-like vitreous that fills inside of the eye. Unless quickly treated,

this can result in spots, floaters, flashes, blurred vision, vision loss, and even temporary blindness. In later phases of the disease, continued abnormal vessel growth and the formation of scar tissue may cause serious problems such as retinal detachment and glaucoma, both of which can cause permanent blindness. Diabetic macular edema, which involves swelling in the retina that transiently or permanently impairs vision, can occur at any stage of diabetic retinopathy. Treatment to prevent or reverse this condition remains a major unmet clinical need.

Source: Juvenile Diabetes Research Foundation International

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