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Treating Vascular Eye Diseases

Principal Investigator: LI, DEAN Y**Institution Receiving Award:** UTAH, UNIVERSITY OF**Program:** PRMRP**Proposal Number:** PR081410**Funding Mechanism:** Advanced Technology/Therapeutic Development Award**Partnering Awards:****Award Amount:** \$2,989,476.00[View Technical Abstract](#)

PUBLIC ABSTRACT

In the United States, the developed nation, and throughout the population of our active/retired military personnel, the predominant mechanism of catastrophic loss of vision is pathologic angiogenesis and endothelial hyperpermeability of the retinal or choroidal vascular beds. New and dysfunctional blood vessels leak, bleed, or stimulate fibrosis that in turn precipitates edema, hemorrhage, or retinal detachment compromising vision. The major diseases sharing this pathogenic mechanism include proliferative diabetic retinopathy (DR), nonproliferative diabetic macular edema (DME), and age-related macular degeneration (AMD). Fifteen million Americans over the age of 65 suffer from AMD and 10% of them will experience visual loss as a result of choroidal neovascularization. Over 16 million Americans are diabetic and over 400,000 new patients suffer from retinal edema or neovascularization. Given that the current number of 200 million diabetics worldwide is likely to double in 20 years and that over 8% of such patients suffer from microvascular complications, the number of patients with visual loss from diabetic eye disease is set to explode. Other causes of blindness from vascular eye diseases include retinopathy of prematurity and ischemic retinal vein occlusion and are less prevalent, but also lack effective treatment. Thus, the medical need is great and in recent years the scientific and clinical path for drug development has become clear.

Much attention has been focused on vascular endothelial growth factor/vascular permeability factor (VEGF/VPF), which stimulates endothelial migration, proliferation, sprouting, and permeability. Strategies that reduce VEGF-mediated angiogenesis and vascular edema are now the treatment of choice for AMD. The primary approach has been the use of antibodies that recognize VEGF and thus block its biologic activity. At present, these strategies have only been shown to be effective in treating AMD, and there is no clear evidence that a similar approach will be effective in treating diabetic retinopathy and macular edema.

The need for monthly intravitreal injections of VEGF antibodies for AMD and the lack of any pharmacologic intervention for diabetic eye disease have intensified the search for new and better drugs. Unfortunately, most other therapeutic approaches adopt the same biologic strategy of blocking VEGF. This is despite the growing evidence that factors and cytokines other than VEGF contribute to disease pathogenesis by destabilizing the mature vessels to overgrow and leak fluid.

We offer a radically different approach and support this approach with proof-of-concept experiments in validated and predictive animal models. Our approach is to stabilize blood vessels by activating a receptor expressed on the surface of blood vessels in the eye, the Robo4 receptor. This prevents the blood vessels from leaking and growing. This approach has the added benefit that it can be commercially viable because it is either superior to or synergistic with anti-VEGF approaches.

In this grant application, we focus on developing a protein that will activate the Robo4 receptor and conform to specifications needed for production, delivery, dosing, and safety. At the completion of this grant application, we plan to be within 18-24 months of filing for permission from the Food and Drug Administration to initiate clinical trials for this biologic. We will also explore the feasibility of identifying a small molecule therapeutic and, if successful, adopt this therapeutic approach. At the completion of the

proposed experiments, we hope to begin a high throughput screen to find small molecule inhibitors that activate the Robo4 pathway, are effective for vascular eye diseases, and are deliverable topically by eye drop.

In summary, we will develop a novel class of protein therapies for vascular eye diseases and test the feasibility of developing a novel class of small molecule therapies.

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