LS-BK SEMINAR

"FZD4-specific WNT Surrogate as Potential Novel Therapeutics for the Treatment of Diabetic Retinopathy"

Sungjin Lee

Principal Scientist, Surrozen Inc.

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- **Inquiry: Prof. Kyong-Tai Kim(279-2297)**
- **Abstract:**

It has long been known that Wnt proteins have a profound impact on maintenance and self-renewal of stem cells in a variety of tissues. While this pathway plays a crucial role in injury- or disease-related tissue repair, scientists have been unable to overcome the technical challenges inherent in developing a therapeutic based on modulating the Wnt pathway. Surrozen's technology overcomes hurdles that have constrained drug development efforts to date, and may pave the way for a broad pipeline of novel therapies.

Today, I would like to introduce the FZD4-specific agonist as one of the novel therapeutic molecules and present our recent studies on the drug development for the treatment of diabetic retinopathy.

Norrin/FZD4 signaling is indispensable for retinal vascular development and vessel function in humans and rodent models. This study examined whether a novel Norrin mimetic could promote the regeneration of damaged blood vessels and their functions in diabetic retinopathy animal models.

We generated an antibody-based bi-specific Norrin mimetic that targets specifically to FZD4 and low-density lipoprotein receptor-related proteins SZN-413, and evaluated its effects on damaged retinal vessels in mice and rabbit models. In oxygen-induced retinopathy (OIR) mice model, SZN-413 was intravitreally delivered and the avascular (AV) area and neovascularization (NV) area were measured on day 5. SZN-413 significantly reduced NV area size to a comparable level in the group treated with 60 ug Aflibercept (anti-VEGF). SZN-413 also showed dramatic reduction in AV area size, the reduction in AV area is significant stronger than the group treated with Aflibercept.

Furthermore, the impact on vascular leakage by SZN-413 was examined in VEGF-induced retinal vascular leakage rabbit model, in which the level of fluorescein leakage was measured at day 3 after the intravitreal delivery. The SZN-413 significantly reduced retinal vascular leakage by 78%. No observable abnormalities were detected in ocular exam in the studies.

The results strongly suggests that the pathological cellular responses can be modulated by the novel FZD4-specific Wnt (Norrin) mimetic, SZN-413, with possible therapeutic implication for diabetic retinopathy.