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Effect of sphingosin-1-phosphate lyase inhibitor on skin allograft and transplant rejection avatar model

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Objectives: Sphingosin-1-phosphate (S1P) signaling controls the egress of activated lymphocytes from secondary lymphoid organs. But it is unclear if inhibition of S1P signaling targeting S1P lyase would attenuate incidence of allograft rejection. We developed new active compound, SD911 which suppress S1P lyase (SPL). In this study, we evaluated whether treatment of SD911 reduce the risk of the transplant rejection using in-vitro and in-vivo model.

Methods: Using CD4+T cells from mouse spleens stimulated with the T cell receptor (TCR), we examined the differentiation of native T cells into Th1, Th2, Th17 and regulatory T cells (Treg), and their cytokine production during treatment by SD911. The therapeutic effect of SD911 was evaluated in a skin allograft mouse model by single intravenous infusion. In addition, we established transplant rejection patient avatar model by injection of PBMC of patients diagnosed with kidney transplant rejection into NGS (NOD scid gamma mouse) and we examined the suppression of immune cell infiltration during treatment of SD911 in this model.

Results: Under TCR stimulation, SD911 treatment significantly reduced the population of pro-inflammatory T cells and their cytokine production but increased the number of Treg cells compared with control group. Mice treated with the SD911 exhibited prolonged skin allograft survival times accompanied by improved immunologic regulation. In avatar mouse model mimicking kidney transplant rejection, SD911 treated groups showed reduced pathogenic or inflammatory T cell infiltration in kidney tissue.

Conclusions: These results suggest that inhibition of S1P lyase may be a therapeutic target to attenuate the effect of kidney transplant immune disorder.