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Apelin-VEGFC mRNA combined therapy for the treatment of secondary lymphedema

Secondary lymphedema is an unmet medical need that corresponds to a severe lymphatic dysfunction leading to the accumulation of fluid and fibrotic adipose tissue in a limb. In western countries, it develops after cancer treatments, raising an important ethical issue in treating cancer survivor patients without reactivating the tumor with pro-lymphangiogenic therapy. Therefore, we used a biological RNA delivery approach called FlashRNA®, based on a novel class of chimeric lentiviral platform, that allows the delivery of transient multiple biological mRNA molecules.

Recently, VEGF-C, the major lymphangiogenic growth factor, was found to be not sufficient to restore the lymphatic function in lymphedema. As lymphedema is a multifactorial pathology with lymphatic dysfunction, adipose tissue accumulation, and fibrosis, a multiple therapy appears to be the solution to cure this harmful condition.

By performing gene expression analysis of dermolipectomies from women who developed secondary lymphedema after breast cancer, we identified a significant decrease in apelin expression. The effect of the lack of apelin in aggravating lymphedema was confirmed in apelin-KO mice. In a mouse model of lymphedema, apelin improves lymphatic pumping function and reduces tissue fibrosis. In lymphatic endothelial cells, apelin controls the expression of genes involved in extracellular matrix remodeling and valve maintenance.

When combined apelin to VEGF-C, double mRNA delivery abolished lymphedema and restored the lymphatic flow compared to single mRNA delivery. Therefore, we proposed to use the APLN-VEGF-C mRNA delivery vector for a phase I/II gene therapy clinical trial that will be launched in Toulouse University Hospital.

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