Scleroderma (SSc) is a multisystem idiopathic connective tissue disease with high morbidity and mortality. Exact cause for SSc is still remain unknown and there are no effective medical treatments available. Emerging data support a role for both a mechanical signal, e.g., matrix stiffness, and a chemical signal, e.g., transforming growth factor (TGF) beta1, in fibroblast activation, migration, and differentiation. Published work showed that TRPV4, an ion channel in the transient receptor potential vanilloid family, is activated by a range of mechanical and chemical stimuli.

We obtained evidence that: 1) increased numbers of TRPV4 positive myofibroblasts are present in skin tissues of patients with SSc compared to controls, 2) Trpv4−/− mice prevented skin fibrosis development as assessed by dermal thickness, subcutaneous fat deposition, macrophage accumulation, myofibroblast abundance, and collagen deposition in skin in a bleomycin model of SSc, 3) genetic ablation or pharmacologic antagonism of TRPV4 abrogates both matrix stiffness and TGFbeta1-induced normal dermal fibroblast differentiation, and 4) TRPV4 modulates profibrotic TGFbeta1 actions in a Smad-independent but PI3K-AKT-dependent manner. Altogether, these results, for the first time, showed that TRPV4 channel mediates fibrogenesis in SSc. Successful manipulation of the TRPV4 activity may be a targeted therapeutic approach to the treatment of SSc.