Project: **Targeting the inhibitory effect of high glucose concentrations on TGFβ signaling**

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Summary:
Diabetes mellitus is a disease characterized by an increased level of circulating blood glucose. A common complication, affecting about 15% of diabetic patients is the occurrence of delayed wound healing resulting in long-term injuries and amputation of the affected limbs. The unclear etiology, widespread occurrence, and high public cost stimulate interest in clarifying the mechanisms leading to this diabetic complication. With this project we propose to examine the hypothesis that high glucose concentrations inhibit the TGFβ signaling pathway by suppressing the expression of TGFβ receptor type II. Inhibited TGFβ signaling prevents activation of wound fibroblasts to myofibroblasts, which in turn prevents normal wound healing. In order to determine the validity of the hypothesis, we will examine four possible ways of glucose action on the type II TGFβ receptor gene: a) by specific transcription factors; b) by a change in the activity of the small GTPases; c) by inducing epigenetic changes and d) by promoting oxidative stress. These pathways will be studied through a multidisciplinary approach combining cell-biology, biochemical and biophysical methods. The confirmation of our hypothesis will result in a new understanding of the mechanisms governing the expression of TGFβ receptor type II, and the identification of inhibitors that are able to counteract the negative effects of glucose. This will help also to outline new possible ways of therapeutic treatments of diabetic wounds.

Key words: Diabetes, Glucose, TGFbeta receptor II, Wound healing