Description for the General Public

The wounded skin of adult mammals is incapable of regeneration. Instead, the tissue heals through reparative, fibrotic process completed with scar. On the contrary, mammalian fetal wounds which occurs in physiologically hypoxic environment heal faster and scar-free (regenerate). Among adult mammals the skin of nude mice, which is deficient in the transcriptional factor Foxn1, is capable of remarkable scar-free healing similar to mammalian fetuses during intrauterine life. Although the differences between reparative and regenerative ways of healing have been determined the mechanisms which guide the processes are still obscure. We showed that there are similarities in postwounded skin regeneration between fetuses and nude mice. Our study revealed that non-active in nude mice Foxn1 can act as a regulator of the skin wound healing process participating in re-epithelialization and being involved in scar formation. Recent data point out on hypoxia as a key environmental element controlling skin healing process. Hypoxia-inducible factor-1 alpha (Hif-1α) is a master regulator of oxygen homeostasis, which contributes to wound healing process. Hif-1 deficiency leads to formation of unhealing ulcers. On the contrary, Hif-1α overexpression has been associated in fibrotic disease. Recently, our data showed the significant differences in the expression of genes associated with hypoxia between skin of nude and wild type mice.

Collectively these data suggest that the interaction between Foxn1 and hypoxia associated elements during cutaneous wound healing process drives physiological decision considering the type of healing between regeneration or repair.

The project will be carried out in two different settings: (i) *in vivo* – with nude (Foxn1 deficient) mice and (ii) *in vitro* in which the mouse Foxn1 full-length cDNA will be transfected into nude keratinocytes for co-culture with dermal fibroblasts under hypoxic vs normoxic conditions to explore the mechanisms by which hypoxia and Foxn1 regulates functional phenotype of primary keratinocytes and dermal fibroblasts.

The proposed studies will be the first to examine the mechanistic link between hypoxia and Foxn1 in skin wound healing regulation. Understanding of the mechanisms can lead to the development of treatments that redirect scar-forming repair process towards regeneration and non-healing wounds to scar-forming. Moreover, since Foxn1 is expressed in human skin and pleiotropic effects of Foxn1 are similar in mouse and humans, data from the mouse model can provide insights into novel therapeutic targets in wound healing management, including non-healing (chronic) skin wounds in diabetic patients and overgrowing scars.