C.1. Description for the General Public

Skin, one of the largest organ in the body, fulfills multiple important functions. Therefore disruption of its integrity can lead to significant disabilities or even death. The process of skin wound healing in mammals occurs with fibrosis and, in contrast to the sporadically observed scar-free regeneration, results in scar formation. As a consequence the post-injured skin tissue never regains the architecture and functionality of uninjured tissue. Among the crucial regulators of the healing process are two specific biochemical pathways (TGFβ1, Wnt/β – catenin pathways) and according to the latest study, one specific transcription factor (Foxn1). Among the critical factors that affects the reparative process of wound healing is oxygen stress or "hypoxia" (1–2% of O_2 concentration as compared to 21% in room air). While hypoxia is recognized as a pro-fibrotic agent for the skin wound healing process, it provides a regenerative advantage to stem cells and helps to maintain their fate as an undifferentiated cell. Recent studies have shown that adipose tissue is a rich source of somatic stem cells, distinguished as *Adipose-Derived Stromal/Stem Cells* (ASCs). The existing reports, using mouse models of wound healing, have revealed that application of ASC cultured under room air or "normoxic" conditions (21% O_2) improves the process of healing, however, these conditions do not prevent tissue fibrosis.

This project integrates the combined effects of multiple variables including hypoxia, stem cells, and wound healing, and validates their potential clinical utility using two animals models, the mouse and the pig. The tests the following specific hypothesis: **Hypoxia triggers porcine Adipose-Derived Stromal/ Stem Cells (ASCs) functional features activating regenerative (scar-free) skin wound healing pathways.**

The present proposal will verify the effect of hypoxia on pASC regenerative capacities as a function of skin wound healing resolution with particular regard to the relevant, specific signaling pathways: TGFβ, Wnt/β–catenin and Foxn1. The outcomes of this study will have considerable input advancing the progress of the regenerative biology field. Anticipated outcomes will have the potential to increase the knowledge of (1) adipose tissue stem cells characteristics; (2) the role of hypoxia on pASC function; (3) the involvement of TGFβ, Wnt/β–catenin and Foxn1 pathways in the mechanism underlying wound healing. Furthermore, the many similarities between the anatomy of human and pig skin identify the pig as an excellent animal model for developing treatments to accelerate human skin wound healing. Consequently, this background and relevance has prompted us to choose the pig as both a donor of ASCs and as a recipient *in vivo* model of skin wounding thereby creating a pre-clinical model that will completely replicate human clinical wound healing . In this context, the use of pASCs as a regenerative cell therapy will provide fundamental information for regulatory authorities concerned about the safety and efficacy of human ASCs as applied to future tissue engineering and regenerative medical applications.