Inflammatory skin diseases such as atopic dermatitis, psoriasis, alopecia areata and especially diabetic wound are considered as major public issues with increasing prevalence due to the rapid industrialization of modern society. Despite their significance, to date no fundamental therapy exists. One of the most promising approaches in the treatment of inflammatory skin disorders is mesenchymal stem cell (MSC)-based therapy that involves the use of the cells themselves or their secretomes. Due to their beneficial regenerative and immunomodulatory abilities MSCs have been considered for treatment of inflammatory skin diseases and abundant studies including clinical trials have been conducted within last decade. However, the obtained results are still not satisfactory and MSC-based therapy is still not considered to be the standard of care at the clinic. The reason for that is that cell-based therapy has also many limitation such as poor survival of transplanted cells and differences in secretory potential of MSCs depending on their source and the individual features of the donor. Moreover, proper analysis of the available data is complicated due to a lack of standardization for the isolation, phenotype characterization, *ex vivo* expansion and normalization of administration mode.

To address all mentioned difficulties associated with the use of whole MSCs, we propose to consider as a potential skin treatment option a recently established by our laboratory Human Adipose Tissue Mesenchymal Stem Cell (HATMSC) line and its secretome. In contrast to primary cells, employment of already established MSC cell line will allow for non-invasive (without the need to collect cells from the patient) but high-yield production of unique bioactive mixture.

We have already proved that the developed cell line is capable of secreting a potent angiogenic cocktail that promotes human skin origin cell proliferation in an *in vitro* chronic wound model. The developed by us HATMSC cell line undoubtedly has the potential to be used in clinic, especially in the field of chronic wounds and other inflammatory skin diseases for which gold-standard treatments fail. However, before this appealing idea can be introduced into clinical trials, a profound analysis at the basic cellular level research needs to be done. Because the effective healing of chronic skin diseases requires a comprehensive treatment, in the scope of this project we intent to further investigate therapeutic properties of the HATMSC secretome focusing on immunomodulatory, regenerative and antimicrobial capability. To achieve this we planned a series of *in vitro* and *in vivo* experiments. Specifically, attempts will be made to pre-condition HATMSCs with Interferon gamma (INFγ) and Interleukin-1 beta (IL-1β) in order to tailored their secretion profile to ameliorate anti-inflammatory activity. Immunomodulatory activity of the developed HATMSC secretome is planned to be tested on the cells of the immune system such as macrophages and natural killer cells. Regenerative activity of the secretome will be investigated *in vitro* using a complex 3D model of skin which will allow testing HATMSC secretome properties while maintaining the 3R principle. To counteract skin infections, which often accompany skin diseases antimicrobial properties of the obtained HATMSC secretome will be also investigated on the most common pathogens found in the wounds, including *Staphylococcus aureus*. Finally, following confirmation of the HATMSC secretome activity *in vitro,* its biological function will be also investigated *in vivo* in the ischemic rabbit ear model using Hyaluronic Acid–Collagen Hydrogel drug delivery system.

It is expected that within this project we will optimise HATMSC cells culture conditions to increase the production of the immunomodulatory, regenerative and antimicrobial factors and confirm their effectiveness. All of this will allow for a broadening of current knowledge on the MSC-secreted factors as potential therapeutic agents for chronic skin diseases and while translated into clinic, will provide a more effective and widely available but less-expensive treatment for patients with diabetic wound, atopic dermatitis, psoriasis or alopecia areata.