There is a great interest in understanding basic processes that allow the regeneration of tissues in the human body. Most of the organs in mammalian organisms, including humans, must be supported to maintain their function by the existence of a vital pool of multipotent cells called adult stem cells (SCs), which are essential not only for physiological tissue renewal but also to regenerate tissues after injury. Thus, understanding adult SCs regulators that tightly govern the tricky balance of signaling pathways that either activate or inhibit SCs stability is an important question in basic biology and regenerative medicine. Recently, my laboratory discovered the intrinsic molecular mechanism of a competitive balance of BMP/WNT signaling as the fundamental axis to regulate hair follicle Stem Cells (HFSCs) rest and stimulation. However, there is a gap in our scientific knowledge regarding how BMP/WNT signaling integrates the regulation of different molecular networks between hair Stem Cells and different surrounding compartments called niche environments during hair rest and regeneration. Based on that discovery, we proposed a model in which hair Stem Cells coalesce their intrinsic and extrinsic mechanisms with neighboring niche cells, resulting in the preservation of their stemness and hair regenerative potential during an organism's lifespan. **Primarily, in this proposal, we focus on the question of how the intrinsic fluctuation of gene networks in hair Stem Cells affects the surrounding niche environment for proper hair regeneration.**

We would like to address this question *in vivo* using two different genetically modified mouse models targeting hair follicle Stem Cells precisely to either inhibit or activate the hair cycle. Since our laboratory recently developed these two mouse models, we are uniquely equipped to address this question with great accuracy. Furthermore, these *in vivo* approaches combined with the "top-notch" single-cell technology will allow us for the first time to observe the changes in the whole composition of niche cells neighboring hair Stem Cells along with molecular changes in each individual cell, which would happen during both states: rest and regeneration. Moreover, in this proposal, we would like to investigate the correlation between the changes in gene expression with the knowledge of the open chromatin state in each individually investigated single cell. The open chromatin state will help us understand how genes are regulated in each cell.

Indeed, our preliminary data are very encouraging since we were able for the first time to observe the changes in the whole skin, demonstrating the composition of the niche cells in the close vicinity of HFSCs during hair re-regeneration. Subsequently, we would like to expand these studies to include the spatial transcriptomics of individual cells to localize their position precisely in the niche near hair follicle Stem Cells during either prolonged hair cycle rest or precocious activation. Finally, in this proposal, we would like to validate identified niche cells and their molecular signaling during hair regeneration assay after *in vivo* transplantation.

The expectation is that this research will shed light on the interaction between hair Stem Cells and surrounding niche cells during both states. Furthermore, this will help us discover molecular mechanisms in the niche cells that preserve hair Stem Cells' stemness and their regenerative hair potential. Thus unveiling the composition and molecular interactions between hair Stem Cells and niche compartments might be an essential step forward in developing a treatment for human baldness and skin regeneration after injury in the future.