Adult stem cells appear to be remarkably flexible in their ability to reconstitute different tissue lineages and organs, raising great interest in assessing the therapeutic potential of those stem cells. Therefore understanding basic processes that are important for adult stem cell (SC) regulation is very important, since these cells are not only crucial for normal tissue renewal, but they can also regenerate tissues after injury. In addition, deregulation of normal stem cell may result in cancer formation.

In adult skin, individual hair contains a reservoir of stem cells localized in a specialized region, called the bulge. Because skin and hair are easily accessible and amenable to constant visual monitoring, it is an ideal tissue to address questions about stem cells regulation as well as use then this knowledge towards stem cells - based therapy. Thus, understanding adult stem cells regulators which precisely govern the intricate balance of signaling pathways which either activate or inhibit stem cells is a very important question in basic biology and regenerative medicine.

In the proposed research, we would like to understand the molecular mechanism of two different signaling pathways called: BMP and WNT in stem cells regulation using skin and hair as a model system.

Currently, my laboratory shed light on how a competitive balance of BMP/WNT signaling regulate hair stem cells, but there is a gap in our scientific knowledge regarding how BMP/WNT signaling integrate the regulation of different molecular networks in hair stem cells during hair cycle. In our study, we would like to unveil how exactly BMP and WNT signaling pathways operate inside of hair stem cells and what changes these pathways cause at the molecular level affecting cyclic regeneration of hair. Our previous results emphasize the critical role of BMP pathway in activation of its downstream components: pSmad factors during postnatal maintenance of hair stem cells quiescence. However, it still remains to be elucidated how a different pSmad factors (pSmad1, pSmad5 and pSmad8) regulates maintenance of hair quiescence and activation during hair cycle.

To address these in hfSCs, we develop unique system which will allow us for prolong time to activate pSmad factors (which normally are very unstable and briefly inactivated) resulting in inhibition of hair regeneration. This approach has been highly advantageous, enabling us to monitor, isolate and characterize live hair stem cells following inducible activation of pSmads in live mouse model. Thus, it allows us to study how different pSmad factors regulate network of downstream target genes in hair stem cells.

In addition we will study molecular mechanisms of intrinsic Wnt signaling in hair stem cells during cyclic hair regeneration, since our data proposed that Bmp inhibition directly regulates Wnt activation of hair stem cells. In particular, we will focus on Wnt7b at the beginning of hair cycle, which recently we showed that it is important in activation of hair regeneration. Here, we will be testing molecular mechanisms how WNT7b works in hair stem cells using our recently generated mouse model. Ultimate goal will be to understand how changes in the hair stem cells gene network regulate hair regeneration.

This is an important basic science question in SC biology, since we and other groups have shown that BMP/WNT signaling are key regulators of SC homeostasis in different adult systems.

Thus, further understanding the molecular mechanisms through which BMP/WNT signals in hfSCs might be highly instructive to find out the common mechanisms that underlie stem cell regulation and how the different stem cells in other organs determine tissue-specific regeneration as well as cancer formation. This insight might be very useful in translating these basic discoveries to novel forms of stem cells therapy with applications for human diseases as cutaneous wound healing, androgenetic alopecia or burn alopecia. As BMP/WNT signaling has a key regulatory role in maintaining different types of adult stem cell homeostasis, the implication for future therapy might be potentially much broader and not limited to skin regeneration, alopecia and skin cancer.