Adult stem cells are fundamental for proper organ maintenance and tissue regeneration. The tips of mammalian digits including human can regenerate after amputation, like those of amphibians but it was unknown why this capacity is limited to the area associated with the nail. Recently, cells in the nail matrix, which contribute towards nail differentiation and visible nail formation, received notable attention for their ability to coordinate mammalian digit regeneration. Indeed, highly proliferating nail stem cells have been proposed to be localized within the nail matrix and are necessary for mammalian digit regeneration mechanisms. In addition, at the same time, my laboratory has identified a novel dormant stem cells population which exists in continuously growing nails. Interestingly, these previously unreported slow dividing stem cells population of the nail is organized in a ring-like configuration within the proximal fold, area where skin epidermis bends inward ventrally and become nail epidermis which localizes on the border between epidermis and nail at the fingertips. We observed that nail slow dividing cells express the skin stem cell marker, keratin 15 (K15). Therefore we were able to mark and then follow these cells in mouse model showing that K15 labeled cells, originating in the proximal fold, contribute long term to the nail structure and epidermis surrounding nail, thus their possess stem cells characteristic with dual function. Upon nail regeneration, these K15-derived nail proximal fold stem cells actively deliver progeny to the nail matrix which then differentiate into nail plate (visible part of nail at fingertip). Similarly, we also demonstrated that the nail slow dividing stem cells can actively participate in functional nail regeneration after transplantation. Gene expression analysis of isolated nail slow dividing stem cells from proximal fold revealed a requirement for Bone Morphogenetic Protein (BMP) signaling in proper nail formation and differentiation. Thus, we have identified a novel population of stem cells with dual function within the nail proximal fold region which displays plastic homeostatic dynamics capable of responding to injury and suggest a common, coordinated mechanism of protective barrier formation which could occur between the nail and adjacent epidermis. Since, our discoveries provided a direct link between nail proximal fold stem cells, nail matrix and nail differentiation, therefore, we hypothesize that these stem cells are a crucial source of cells during nail homeostasis and are necessary to respond after an injury to regenerate the nail and subsequently digit in mammals. In this proposal, we will employ several different approaches to test and validate our hypothesis. Previously, we have demonstrated that nail proximal fold stem cells actively participate and deliver progenitor cells to the nail matrix and differentiate to the nail plate which results in nail organ regeneration, thus, here we would like to challenge the system to test it under digit regeneration conditions after digit-tip amputation. Further, we would like to isolate and establish culture condition for nail proximal fold stem cells in test-tube and then transplant them into mouse model during digit-tip regeneration assay. Finally, since our research have demonstrated that BMP signaling guide stem cells towards nail differentiation, we would like to address the role of molecular BMP-WNT signalings hierarchy during nail differentiation and its correlation with the potential of nail proximal fold stem cells in digit regeneration. We assume, that further characterization of nail proximal fold stem cells may help fill the gaps in our current understanding of nail biology and could not only offer novel forms of treatment for patients with nail and digit defects but could revolutionize in a broader sense, and also provide new regenerative therapies for amputees in the future.