The implantable biomaterials supporting tissue repair are gaining more interest from researchers focusing on regenerative medicine. The structure of biomaterials can be equipped with cues that favor regeneration by acting as potent cell regulators in the tissue microenvironment. Recent studies are focused on structural and mechanical cues of biomaterials evoking epigenetic changes. Epigenetic marks may lead to distinct changes in gene expression that are caused by remodeling of the chromatin and activation or inactivation of specific groups of genes. Such changes modulate a set of cell functions, including proliferation, differentiation, and reprogramming. To date, the possibility of providing exogenous molecules able to remodel the chromatin that will lead to the activation or inactivation of genes has been poorly studied.

The number of patients suffering from peripheral nerve injuries is steadily increasing each year. Injuries resulting from motor vehicle accidents are pointed out as the main cause of peripheral nerve damage. According to the World Health Organization between 20 and 50 million people suffer from collision or crash non-fatal injuries annually. Despite an intrinsic regenerative capacity of the peripheral nervous system, most cases of peripheral nerve damage require therapeutic interventions to support peripheral nerve regeneration and functional recovery. Complete recovery of lost sensory and motor functions can be rarely achieved due to the complex biochemical composition of the human body. Standard methods for the treatment of peripheral nerve injuries encompass end-to-end coaptations, autografts, and allografts. Despite being effective, they have numerous disadvantages: the creation of tension between sutured nerve stumps, the need for a second surgery along with the sacrifice of the donor's nerve, and the necessity of toxic immunosuppression, just to name a few. Over the past two decades, researchers have focused their attention on replacing these traditional approaches to peripheral nerve injury treatment using the achievements of biomedical engineering. The most promising direction for researchers in the fields of tissue engineering and regenerative medicine is the design of nerve guidance conduits that will support the recovery of normal functions of peripheral nerves (Figures 1A and B). The recent advances in molecular biology aid the discovery of efficient tools for the regeneration of nerve cells.

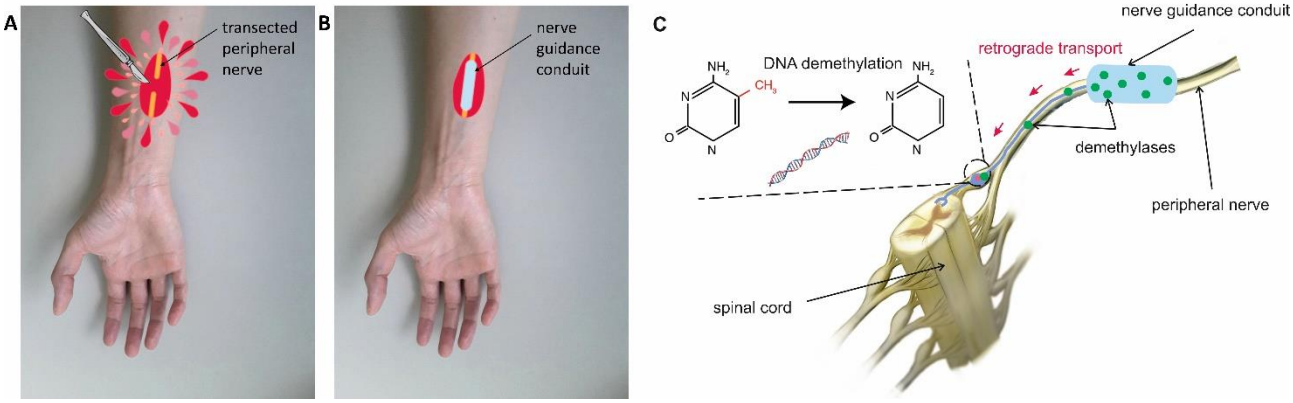

Figure 1. (A) Transection injury of peripheral nerve and (B) implantation of nerve guidance conduit to bridge nerve stumps. (C) The schematic conception of the therapy to be developed in the presented project. Implantation of nerve guidance conduit embedding demethylases to bridge nerve stumps. Demethylases are released from the nerve guidance conduit and retrogradely transported to the cell nucleus. Pro-regenerative gene expression is triggered via DNA demethylation.

In the presented project, we will develop a nerve guidance conduit able to release molecules that induce changes in gene expression including genes critical for-improved cell regeneration (Figure 1C). Recent studies indicate that DNA demethylation is a fundamental mechanism for reprogramming the cellular state of mature mammalian neurons to permit axonal outgrowth. Active DNA demethylation is necessary to de-repress pro-regenerative genes crucial for proper axon regeneration As DNA methylation is promoted by Ten-eleven translocation methylcytosine dioxygenases, we will test these enzymes for their capacity for the demethylation of the nuclear genome. Moreover, measurement of the outgrowth kinetics of axons will indicate demethylase concentration inducing optimal nerve regeneration.

In order to understand the molecular and cellular mechanisms involved in DNA methylation that favor successful peripheral axons regeneration, we will perform a comprehensive investigation of changes in the gene expression patterns after the introduction of nerve guidance conduits carrying demethylases into in *vitro* cultured nerve cells and *in vivo* animal model. In the longer run, the project results will help point the way towards novel therapeutic approaches providing better recovery of lost sensory and motor functions after transection injury of peripheral nerves.