# Management of Mitochondrial Oxidative Stress and Neurogenesis Using Bioengineered Nanomedicine Platform

*A Thesis submitted by*

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# Chapter 5

# Conclusion and Future Perspective

## 5.1 SUMMARY

**1.** The thesis starts with an introductory chapter explaining how nanomedicine and nanotechnology create and apply nanomaterials for targeted therapies, diagnostics, and regenerative medicine, offering precise and effective healthcare solutions. A notable progress in this domain is the mitochondria-targeted administration of medicinal drugs to improve treatment effectiveness while reducing systemic adverse effects. Dysfunctional mitochondria are associated with diseases such as cancer and neurological disorders, including Alzheimer's and Parkinson's. Nanomaterials possess customisable characteristics and functionalisation potential, which facilitate the effective transport of antioxidants and pharmaceuticals across obstacles such as the BBB. Innovations that integrate nanotechnology with biological knowledge have shown significant potential in the treatment of mitochondrial-related disorders. The strategic design of mitochondria-targeted nanotherapeutics offers significant potential for tackling intricate diseases and enhancing precision medicine.

2. Chapter 2, entitled "**Mussel Inspired Polydopamine Nanocomposite as Bioactive Antioxidant for the Management of Oxidative Stress and Neurogenesis in Traumatic Brain Injury**", describes the design and development of nanomedicine for the mitigation of oxidative stress and enhances neurogenesis in TBI. The complex pathophysiological conditions, excessive release of reactive oxygen species (ROS) at the injury site, and limited regenerative capacities of the central nervous system (CNS) make TBI management a challenging task in the intricate landscape of brain injuries. Current pharmaceutical treatments have limited efficacy in penetrating the blood-brain barrier (BBB) and rapidly reaching inflamed brain regions. We developed new polydopamine (PDA)-coated mesoporous silica nanoparticles (PDA-AMSNs) that are inspired by mussels. These nanoparticles have great antioxidant properties and can transport a small molecule called Neuro Chemical Modulator (NCM), which is an inhibitor of GSK-3β, to the site of traumatic brain injury (TBI). We used a neuroprotective peptide hydrogel called PANAP to create these nanoparticles. An in vivo cryogenic brain injury model (CBI) was used to inject PDA-AMSNs loaded with NCM into the matrix of PANAP into the injured area. The logic AND gate circuit remains the principal focus as this technique is constructed explicitly. A single output signal, neurological functional recovery, is produced by two input signals, NCM and PDA-AMSNs. In a CBI, PDA-AMSN-D considerably reduced infarct volume, improved neurogenesis, revived BBB ageing, and sped up the recovery of neurological function.

3. Chapter 3, entitled "**Discovery of Mitochondriotropic Antioxidant based on Gallic Acid Attenuates LPS Induced Neuroinflammation via TLR-4, Nrf-2 / Keap-1 Signaling Pathway: Proof of Concept on Cellular and in Vivo Oxidative Stress Model**" describes the discovery of a gallic acid derived mitochondria targeting small molecule as a novel drug for the mitigation of oxidative stress and

Mitochondria are intricate organelles that are essential for biosynthetic reactions, energy metabolism, and stress response regulation. Aside from their well-documented role in cellular energy metabolism, they are also the principal sites of intracellular reactive oxygen species (ROS) synthesis, which can cause oxidative stress in excess but also acts as signalling molecules. One of the most common causes of neuroinflammation is mitochondrial malfunction. To that end, we have developed a triazine-derived mitochondriotropic antioxidant (Mito-TBA) that targets mitochondria in an effort to reduce neuroinflammation. This compound is based on gallic acid and the triphenylphosphonium (TPP) cation. By blocking LPS-induced TLR-4 activation and activating the Nrf-2/ARE pathway in PC-12-derived neurones, in vitro Mito-TBA-3 suppresses mitoautophagy and provides neuroprotection. The in vivo study found that Mito-TBA-3 improved memory function, reduced depressive symptoms, prevented neuroinflammation, and reduced levels of proinflammatory cytokines in rats modelled by LPS-induced neuroinflammation. Biophysical, in vitro, and in vivo studies all point to Mito-TBA-3 as a promising therapeutic candidate for neurodegenerative diseases associated with mitochondrial oxidative stress and as a powerful lead molecule in the fight against neurodegeneration, even surpassing the efficacy of the widely used non-steroidal anti-inflammatory drug aspirin.

Chapter 4, entitled as "**Brush-Induced Macroscopic Alignment of Self-Assembling Peptide Nanofibers: Potential Therapeutic Lead for Regeneration in Sciatic Nerve Injury**"describes the development of a novel ECM mimicking peptide nanofibrous hydrogel for the nerve regeneration in PNI. Damage to the peripheral nervous system can lead to debilitating neuropathies and other disabilities. To successfully reorganise the fascia surrounding a damaged peripheral nerve, it is necessary to reconnect the nerve sprouts at the lesion's anterior and Büngner bands at its distal ends. Autogenous nerve grafting is the procedure of choice for nerve transplantation at the moment. Unfortunately, the present neural scaffolds aren't very good at neuroregeneration since they don't have the necessary components, such as an extracellular matrix or properly aligned fibres that would improve electrical conductivity in a second phase. As an alternative to autografts, numerous nerve-guiding conduits have been developed by tissue engineering. However, autografts are the only kind of conduit that can restore damaged tissue to the same degree. With the goal of improving neurite outgrowth, we present here the design and construction of a nanofibrous ECM-imitating self-assembling peptide hydrogel that contains a neurodegenerative motif (NAP and NAV) and a self-assembling motif (K2(SL)6K2). For stem cell orientation, we found that the hydrogel's nanoscale topographic properties were critical. The sciatic nerve deficiency in rats was successfully repaired within 2 weeks after these peptide nanofibers were applied as a nerve growth control. After two weeks, we observed that the peptide hydrogel effectively promoted structural healing and functional reintegration. Examinations of the reinnervation of the gastrocnemius muscle, functional investigations, and morphological and histological analyses all corroborated this. It appears that the peptide hydrogel was instrumental in promoting nerve regeneration and function restoration. Finally, there is great hope for the treatment of sciatic nerve injuries with the peptide nanofibrous hydrogel.

## 5.2 Future Perspective

Neurological disorders, such as traumatic brain injuries (TBIs) and spinal cord injuries (SCIs), will be treated in the future with therapies based on nanotechnology and sophisticated biomaterials. Some of the problems with traditional medication treatments are their inability to cross the blood-brain barrier (BBB), their off-target effects, and their restricted capacity for regeneration. There are new and exciting options available, such as self-assembling peptide hydrogels and the antioxidative Gel/PDA-AMSN-D system. Reducing oxidative stress and increasing neurogenesis are two goals of the Gel/PDA-AMSN-D system, which integrates ROS-scavenging PDA-AMSN nanoparticles with a neuroprotective hydrogel. Reduced glial scarring, improved cognitive impairments, and reduced mitochondrial dysfunction are all areas where this method shows promise. To determine its effectiveness in traumatic brain injuries (TBI) and other central nervous system (CNS) injuries caused by oxidative stress, future studies should investigate the best way to dose it, determine its long-term safety, and launch clinical trials. Hydrogels of self-assembling peptides that contain neuroprotective sequences (such as NAP and NAV) promote brain regeneration and stem cell differentiation. The greater functional recovery in SCI mice revealed by these hydrogels suggests their potential use in advanced regenerative therapies. To assess their translational potential in various neurological disorders, improve their biocompatibility, and fine-tune their peptide designs, additional research is required. Collectively, this thesis methods highlight the need for multidisciplinary research to find solutions to the problems with current techniques for treating central and peripheral nervous system injuries and also point to a future when focused, multifunctional therapeutic systems will be the norm.