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Nanotechnology Enabled Regenerative Medicine for Neurological Disorders

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Regenerative therapy has evolved significantly in recent years with promising approaches to restore function of diseased, damaged and aged tissues and organs. It is a highly interdisciplinary field that has been made possible by the intersection of recent advances in bioengineering, stem cell biology and nanotechnology. Incorporation of nanotechnology may allow better control over physicochemical and biological properties of a biomaterial compared to conventional technologies. Nanotechnology applications to regenerative therapy have all the potential to revolutionize tissue regeneration and repair, and ultimately personalized medicine. This theme issue of *Advanced Drug Delivery Review* provides comprehensive and critical reviews of recent developments, future directions, and possible challenges in advancing regenerative therapy for treating neurological disorders using nanotechnology. This issue has covered the fabrication, characterization, imaging, and theranostic applications of nanotechnology-based systems in central nervous system (CNS) including brain and spinal cord, eye and peripheral nerve regeneration. It also reviews in detail the progress of nanotechnology in speeding up stem cell research and development for regenerative neurological medicine. Furthermore, this theme issue discusses nanoneurotoxicity and hurdles in nanomedicine clinical translation and strategies for pre-clinical evaluation of nanocarriers for regeneration and repair in the nervous system. Nanomaterials as tools for understanding CNS disease pathology, neuroplasticity as a target for biomaterial-based therapies for stroke, nanotheranostics as a combined diagnostic and therapeutic entity for personalized medicine in neurological disorders, nanomaterials as gene delivery devices to reprogram cells for ocular regeneration, nanomaterials as immunomodulators to restore healthy immune system for neuronal regeneration, and the use of zebrafish as a model for evaluating neuroregenerative therapeutics are some of the unique and promising topics featured in this theme issue.

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In general, regenerative therapies following injury can be considered as either exogenous cell-based therapies to replace injured cells or endogenous strategies that enhance intrinsic regenerative capacities in the organ. The first article of this theme issue by S. Kannan and coworkers [1] explores nanotechnology-based strategies to enhance endogenous regenerative pathways in the brain. The authors discuss nanotechnology-based approaches that target cellular and extracellular components to enhance neural regeneration while suppressing cellular and extracellular inhibitory mechanisms triggered by injury that could impair repair and plasticity in the brain. In the perspective review by the Ferriero group [2], the unique challenges in considering advanced regenerative therapies in the newborn brain are discussed. Newborn brains are immature and actively changing due to normal brain development. Ferriero et al. discuss that regenerative strategies need to be tailored to the gestational age at injury for enabling appropriate development and growth. Although injury to the spinal cord remains devastating, significant advances have been made in developing novel therapies for regeneration of the spinal cord in the last decade. Schmidt et al. [3] provide a thorough insight on the fabrication of nanomaterials ranging from nanoparticles, nanofibers, nanotubes to quantum dots and their therapeutic effects, especially targeting inhibitory environment, in spinal cord injury. They also highlight emerging technologies including optogenetics, immunotherapy and genome editing through CRISPR/Cas9 for spinal cord repair, where nanomaterials have synergistic roles to play.

Several preclinical studies focused on advanced regenerative therapies have shown promise, however, clinical translation of these still remains challenging. Development of these therapies is expensive and complex requiring close collaboration between researchers, physicians, regulatory bodies and industry. Fatemi and group [4] provide a detailed overview of the challenges involved in translating regenerative therapies from the lab to the clinic. Pandit et al. [5] present a comprehensive insight and design of histological, bio-imaging, molecular and behavioral modalities to screen brain-targeted nanosystems in pre-clinical models. Agrahari et al. [6] thoroughly review the effects of the composition of cell culture and biological matrices and nanoformulations' physicochemical properties on the *in vivo* performance of nanoformulations for brain-targeted drug delivery. The authors also discuss the related analytical techniques under industrial settings to provide an enhanced understanding of the optimal design of brain-targeted nanoformulations for a successful clinical translation.

Besides the comprehensive coverage of nanomaterials for developing CNS therapies, this theme issue combines four papers by R. Kannan et al. [7], Shoichet et al. [8], Yang et al. [9] and Song et al. [10] addressing the opportunities and challenges in leveraging the tremendous variety of nanomaterials for understanding CNS disorders. It is important to recognize that despite the common features between many CNS disorders, each presents a unique facet, and the nanoparticles must be tailored to address the specific pathophysiology of a particular disorder. R. Kannan and group [7] highlight how intrinsic association between dendrimers and disease pathology can be used for microglia-targeted therapies for neuroinflammation, producing promising neurobehavioral improvements in multiple CNS models, an approach that is entering clinical trials for an unmet pediatric CNS disorder and beyond. Biomaterials can be vital tools enabling us to interact with brain cells and tissue, sensing their health and communicating it to a device, or using external stimuli to

manipulate brain cells to improve therapeutic outcomes. Shoichet et al. [8] identify factors and targets that influence post-stroke plasticity processes and discusses the role of biomaterials in enhancing the efficacy of treatment strategies for stroke. The manuscript by Yang et al. [9] provide a critical review of biodegradable materials that function as electroactive, photoactive and magnetic materials facilitating management of neurological disorders. If biomaterials enable nerve regeneration in a safe manner, it would be a major advance in CNS disorders. In a similar vein, Song and group [10] discuss how nanomaterials can enable improved functionality of stem cell therapies for CNS disorders. For example, appropriately tailored nanoparticles can be tools for superior directed differentiation, reprogramming, post-implant imaging, and drug delivery, addressing many challenges in stem cell therapies. They outline the need for more *in vivo* studies for further translation. Furthermore, this theme issue includes extensive review by Gendelman et al. [11] on theranostic strategies targeting neurological disorders, that is, bringing together diagnostic and therapeutic agents to be delivered from the same platform. This work provides a comprehensive overview of disease history, epidemiology, pathogenesis and therapeutics for a spectrum of neurodegenerative disorders in the CNS, and obstacles in diagnosis and as well as various treatment modalities for the disorders. They then discuss how neurotheranostics especially macrophage-based theranostic and nanotechnology play important roles in developing personalized medicine for neurodegenerative disorders.

Nanotechnology enables regenerative medicine for neurological disorders not only in the brain but also in the eye and peripheral nervous system. Lowe et al. [12] comprehensively review various nanoscaffolds including electro-spun nanofibers, self-assembled peptides and nanotopographies used for cornea, lens, and retina regenerations. They summarize nanomaterials as carriers for gene and immunomodulators to reprogram cells and restore healthy immune system, respectively, for ocular tissue regeneration. They provide current perspectives in nanotechnology for tracking cells in the eye and personalized regenerative ophthalmology. Reis and group [13] provide a comprehensive review of all the various nanomaterials that have been evaluated for peripheral nerve regeneration. They discuss how carbon nanomaterials, carbon nanotubes, carbon nanofibers, graphene nanomaterials, nanodiamonds, and inorganic, metallic and polymeric nanoparticles have been explored both *in vivo* and *in vitro* in various nerve injury models and have shown promise in regeneration of peripheral nerves, especially across large gaps (>30mm).

The zebrafish is a well-established and cost-effective vertebrate model for whole-organism phenotypic and compound screening. Due to its rapid regenerative capacities, this model system also allows direct correlations between observed phenomena and functional recovery. Finally, Mumm et al. [14] give a comprehensive review on the advantages of zebrafish model in neuroregenerative imaging and therapeutics. They describe how zebrafish allow direct visualization of dynamic cellular and molecular processes governing endogenous stem cell niche activities during regeneration. They also discuss how zebrafish model can help to study the pharmacokinetics of nanocarriers and screen nanoparticle-based drugs to find lead drugs that can promote enhanced neuroregeneration.

Together, this theme issue assembles cutting-edge articles from leading experts in the field. We express our sincere gratitude to all authors who contributed to this timely and broadly

informative theme issue of *Advanced Drug Delivery Reviews*. This special issue would not have been possible without the critical evaluations by the reviewers and the assistance provided by the journal editorial staff members to ensure that the submissions are evaluated and published at high standards. Also, our sincere acknowledgement to Dr. Hamid Ghandehari, Editor-in-Chief and Dr. María J. Vicent, Executive Editor of *Advanced Drug Delivery Reviews*, for giving us the opportunity to develop this theme issue. We sincerely hope this theme issue will accelerate integrative engagements in nanotechnology and regenerative medicine to move this exciting new field forward for revolutionary solutions to regenerate compromised, lost or damaged cells and tissues to treat neurological disorders and improve the quality of life of patients in the future.

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