A “Snapshot” of the Advances in SCI Therapeutics

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It has been nearly 20 years since the “Decade of the Brain” when some in the field of spinal cord injury (SCI) predicted that a “cure” would be found within 10 years. Of course, the biological complexity of SCI is now much better appreciated, and the early headiness hoping for a simple therapy has sobered. The reversal of paralysis following SCI is among the most daunting challenges in all of neuroscience research. Despite significant improvements in the early medical and surgical management of SCI, coupled with a vastly improved understanding of SCI pathophysiology [1–4], there remain no effective treatments to improve neurological outcomes following SCI. In addition, there has not been any successful FDA-approved and widely accepted interventional therapy to limit or repair the injury and, thereby, adequately restore lost function.

In recent years, numbers of clinical trials, from neuroprotective agents to stem cells, have been launched [5] based on somewhat promising preclinical studies but, so far, these have all fallen short. Nevertheless, our complex patient population continues to suffer the neurological insults of SCI, and we

need to move forward in our search for better understanding and more effective interventions.

In this issue of *Neurotherapeutics*, we have assembled some of the cutting-edge work currently proceeding in the field of SCI. These review papers are organized to match the temporo-spatial progression of SCI, from acute considerations at the site of injury, to subacute processes at and beyond the injury, to chronic changes away from the site of injury. Consideration is then given to research in neurorehabilitation, with the latest in technological advances, the treatment of neurological sequelae in SCI, and the state of clinical trials. DiGiovanni et al. [6] begin with reviewing the acute cellular processes at the site of injury, starting with consideration of the epigenetic control of initiating and sustaining the transcriptional response for axonal regeneration. Next, Gensel et al. [7] and Gaudet et al. [8] consider the role of inflammation, glial cell biology and scar formation after SCI, with both their reparative and pathological features, as well as the interactions between glial cell populations after injury. They also review therapeutic strategies to alter those responses for better injury outcomes. Oudega et al. [9] then consider the interactions between inflammatory cellular responses and transplanted progenitor cells that have shown potential value as a therapeutic intervention in SCI to see if better repair strategies could be devised. Moving away from the site of injury, we cover the diaschisis effect of SCI, namely changes in remote uninjured neural circuitry that is nevertheless changed after SCI. Hollis et al. [10] begin with reviewing the importance of neural plasticity and reorganization at the level of the sensorimotor cerebral cortex and intercortical connectivity.

It is known that after injury the preserved corticospinal connections are highly activity-dependent and can be strengthened with activity-based therapies (motor training). This modulation of neural plasticity and functional recovery can be seen with the use of robotics in neurorehabilitation reviewed by Huang et al. [11]. There is an abundance of research utilizing robotic devices to restore motor function after SCI. Many robots are dedicated to lower limb rehabilitation,

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aiming to restore gait locomotion and typically designed as wearable exoskeletons to assist with walking. Upper limb rehabilitation has also incorporated robotic therapies but to much less extent.

Damage to the corticospinal tract (CST) due to injury to the cord diminishes motor control. Therefore, the CST is an excellent target for neuromodulation/stimulation of descending supraspinal pathways, as described by Perez et al. [12], aiming to strengthen those connections. This topic is concluded with considerations regarding the developing field of biomedical engineering in SCI and “engineered” neural plasticity reviewed by Moritz et al. [13].

Plasticity is a broad phenomenon comprising both positive and negative features. It encompasses neural development, learning and recovery of function following neural damage, but can also be a maladaptive response to injury or disease, such as neuropathic pain, which is reviewed by Lee-Kubli et al. [14]. More recently, electrophysiological techniques are being used increasingly in combination with behavioral protocols with the goal to investigate the role of controlled motor activity, promote spinal cord plasticity and understand its relationship with motor recovery in individuals with SCI. In light of this, Efektar et al. [15] review reflex training as a novel approach to improve motor function, and Iddings et al. [16] discuss the use of vibration to improve spasticity and gait speed. Donovan et al. [17] conclude with a thorough review of the current state of affairs in SCI clinical trials, giving an overview of where we are currently.

This collection of papers does not hope to represent all of what is being investigated in the field of SCI therapeutics but individually represent excellent examples of the breadth and depth of the work going on and areas that have seen recent advances. SCI injury impacts molecules, biochemical pathways, cellular biology, neuronal and glial populations, neural circuits and anatomical pathways, local and remote neurophysiology, behavioral functioning, other organ systems, and the psychological responses to both loss of normal function (sensory, motor, and autonomic) and gain of pathological function (neuropathic pain, spasticity, and dysautonomia) in the nervous system and in other bodily functions controlled by the nervous system. Whole textbooks have been written about the neurological aspects of SCI [18], and yet we have far too

little to write about in terms of therapeutic interventions that markedly repair the injured nervous system to restore its function. We anticipate ongoing hard work in the area of SCI therapeutics with many more discoveries to come.

Required Author Forms Disclosure forms provided by the authors are available with the online version of this article.

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