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Special issue: Spinal cord regeneration and repair

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Introduction

..... We may thus infer from what has been said that, in man as in laboratory animals, the regenerative act commences, and may even attain a certain strength, on condition that the traumatic commotion be sufficient to stir the axons out of their lethargy..... As is known, this tendency to restoration is frustrated by two negative conditions (1) the lack of substances able to sustain and invigorate the indolent and scanty growth of the sprouts; (2) the absence in the paths or systems of interrupted nerve fibres of catalytic agents capable of attracting and directing the axonic current to its destination.if experimental neurology is someday to supply artificially the deficiencies in question, it must accomplish these two objects: it must give to the sprouts, by means of adequate alimentation, a vigorous capacity for growth; and place in front of the disoriented nerve cones.....specific orienting substances. (Cajal, 1928)

What is perhaps most remarkable about this quote from Ramon y Cajal is that he recognized so early on that regenerative failure was a multifaceted problem and that, because of this, a combinatorial approach would be needed to stimulate regeneration or sprouting to a purposeful end. Some of the conditions essential for promoting regeneration, he thought, would be “almost impossible to satisfy” but the situation was not hopeless. With these thoughts, Cajal introduced and reviewed the classic experiments of his student Francisco Tello, who first documented the successful use of pre-degenerated, peripheral nerve grafts to stimulate, at least transiently, axonal regeneration of fully adult CNS axons. After nearly a century, we have come to appreciate the many particular intrinsic and extrinsic cellular and molecular limitations that occur following CNS injury to which Cajal was referring. Considering the addition of our more modern discovery that there exists a plethora of growth inhibitory molecules that actively block regeneration, and which also need to be mitigated, the question remains whether we have at hand so fundamental an understanding of the many contributors to regeneration failure that we are now in a position to devise strategies with which to move more rapidly toward a clinically efficacious therapy. The use of combinatorial tactics to promote functional regeneration has now become a major theme of modern regeneration biologists and this will be echoed throughout the various reviews and original research papers that appear within this special issue. It was my goal in choosing the various topics for discussion that they address a broad spectrum of critical, albeit sometimes controversial, issues related to regeneration, sprouting and rehabilitation after spinal cord injury. Taken in total, I hope that the readers of this compendium come to appreciate that we are, indeed, entering an era where strategies for providing functional benefit in animal models of spinal cord injury are sufficiently robust that there should be optimism for translational success.