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Leveraging biomedical informatics for assessing plasticity and repair in primate spinal cord injury

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ABSTRACT

Recent preclinical advances highlight the therapeutic potential of treatments aimed at boosting regeneration and plasticity of spinal circuitry damaged by spinal cord injury (SCI). With several promising candidates being considered for translation into clinical trials, the SCI community has called for a non-human primate model as a crucial validation step to test efficacy and validity of these therapies prior to human testing. The present paper reviews the previous and ongoing efforts of the California Spinal Cord Consortium (CSCC), a multi-disciplinary team of experts from 5 University of California medical and research centers, to develop this crucial translational SCI model. We focus on the growing volumes of high resolution data collected by the CSCC, and our efforts to develop a biomedical informatics

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framework aimed at leveraging multidimensional data to monitor plasticity and repair targeting recovery of hand and arm function. Although the main focus of many researchers is the restoration of voluntary motor control, we also describe our ongoing efforts to add assessments of sensory function, including pain, vital signs during surgery, and recovery of bladder and bowel function. By pooling our multidimensional data resources and building a unified database infrastructure for this clinically relevant translational model of SCI, we are now in a unique position to test promising therapeutic strategies' efficacy on the entire syndrome of SCI. We review analyses highlighting the intersection between motor, sensory, autonomic and pathological contributions to the overall restoration of function.

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1. Introduction

Spinal cord injury (SCI) produces a multifaceted disturbance of the CNS that impacts function and neuroplasticity at multiple levels of the neuraxis. The complexity of SCI presents a challenge for translation of therapeutics from well-controlled laboratory preparations into the heterogeneous patient population. Over the past several years there have been a number of successes within the preclinical SCI field (Dubreuil et al., 2003; Ferguson et al., 2008; Fournier et al., 2003; Freund et al., 2006; Lord-Fontaine et al., 2008; Lu et al., 2012; Maier et al., 2009; Pernet and Schwab, 2012; Simonen et al., 2003). Yet, few of these therapies have traversed the translational divide to make their way into standards of patient care (Blesch and Tuszynski, 2009; Dietz and Curt, 2012; Filli and Schwab, 2012). The challenges for translational SCI research include fundamental pipeline questions such as: (a) how do we best translate successes from well-controlled small animal studies into more heterogeneous, more complex, and larger models? (b) How do we understand the intrinsic variability in promising therapeutic interventions? (c) How do we determine the specific conditions under which a given therapy works? These questions have been discussed at great length within the research and clinical SCI community (Kwon et al., 2010, 2013) as well as within the greater biomedical scientific community (Collins and Tabak, 2014; Landis et al., 2012).

A number of recent surveys among SCI researchers and clinicians identified the need to test emerging therapeutic candidates from rodent studies in a non-human primate model prior to translation into human clinical trials (Courtine et al., 2007; Kwon et al., 2010, 2011, 2013). Parallel efforts are also underway to both standardize data collection (Lemmon et al., 2014) and integrate raw data from preclinical studies into a queryable database available to the SCI community (Nielson et al., 2014). However, variability in SCI data collection methods and models represents a challenge for both scientific reproducibility and translation. In this context, replication and translation boil down to problems of data alignment – how do we best align functional outcomes across multiple scales and multiple species to compare findings? A potential solution is to view translational model development as a 'big-data' challenge that can be addressed in part, through application of data science to SCI translational models (Howe et al., 2008; Marx, 2013; Sejdic, 2014).

In accordance with these translational goals, the California Spinal Cord Consortium (CSCC) has developed a translatable cervical SCI model in non-human primates that is clinically more relevant than small animal studies for unraveling SCI pathophysiology and preclinical trial efficacy with respect to recovery of forelimb and hand function in primates (Nout et al., 2012a; Nout et al., 2012b). The CSCC consists of a multidisciplinary team of scientists and clinicians spanning the fields of anatomy, neurosurgery, neurology, intra-operative monitoring, physiology, behavior, histopathology, bioinformatics and statistics. Our aim is to better understand the intrinsic nature of SCI in non-human primates, and to complement research being done by other groups to optimize therapeutics for clinical application in humans. Previous studies by others have assessed a wide range of important aspects of this translational model, including cortical reorganization and contribution to recovery (Chen et al., 2012; Darian-Smith et al., 2014; Qi et al., 2011), mechanisms of degeneration (Shi et al., 2009; Wu et al., 2013), and cell-therapy transplantation studies (Levi et al., 2002; Nemati et al., 2014). The overarching goal of the CSCC is to integrate as much complementary information as possible in a single translational model. Toward this end, we strive to maximize the use of each experimental subject, including multiple endpoint monitoring across multiple scales of analysis (Jindrich et al., 2011; Nielson et al., 2014; Nout et al., 2012a, 2012b; Rosenzweig et al., 2009; Rosenzweig et al., 2010).

Our research focus has been to optimize post-injury neuroplasticity and understand the relationship between this plasticity and functional recovery (Rosenzweig et al., 2010). However, there is always risk that plasticity after a lesion to the spinal cord can lead not only to beneficial recovery of motor and sensory function, but can also result in maladaptive changes like pain, spasticity, and autonomic dysfunctions (Brown and Weaver, 2012; Cameron et al., 2006; Deumens et al., 2008; Fouad et al., 2011; Weaver et al., 2006). Therefore, therapeutic interventions inducing plasticity warrant caution as beneficial effects could be accompanied by enhanced maladaptive plasticity resulting in the development of intractable sensory and autonomic malfunction (Ferguson et al., 2012; Fouad et al., 2011; Hofstetter et al., 2005). For this reason, and to promote the translational goals of the CSCC, during the course of therapeutic testing studies