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EDITORIAL

Cell-Based Therapies for Disorders of the Brain and Spinal Cord

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The explosive growth of stem cell biology over the past decade has led to a broader consideration of the potential for cell-based approaches for treating disorders of the central nervous system. These approaches most directly include cell transplantation, for both congenital and acquired diseases of the CNS, and take advantage of a host of newly developed cellular sources for tissue repair. Both fetal and adult human tissues, as well as somatic stem and progenitor cells derived from those tissues, and their analogues derived from either human embryonic stem cells or reprogrammed somatic cells, are all under therapeutic development. In addition, cell-based therapeutics also includes strategies for the mobilization of endogenous neural stem and progenitor cells, whether by pharmacological approaches or gene therapeutics. Indeed, the panoply of approaches under development both inform and overlap one another, so that the lines between gene therapy and cell therapy have become blurred, and are destined to become even moreso. Overall, these various approaches capitalize upon our growing understanding of the types of resident stem and progenitor cells of the nervous system, their lineage potential, and their regulatory control.

Even as the availability of appropriate cellular substrates for neurological repair has so rapidly increased, our understanding of disease pathogenesis and physiology has improved, so that the challenge becomes pairing specific diseases with the most appropriate cell-based treatment strategy. This volume of Neurotherapeutics will thus focus on a spectrum of neurological diseases, which have in common the identification of one or more cell-based strategies appropriate for their potential treatment. As such, we will cover a broad swath of neurology, that includes the degenerative, motor neuronal and movement disorders, myelin disease, the lysosomal storage disorders, spinal cord injury, and the epileptic disorders. As different as these disorders are, they share dysfunction of a single phenotype, or of a discrete set of phenotypes, the replacement of which might be sufficient for disease amelioration. As such, they comprise those disease targets potentially most amenable to cell transplantation or directed induction. By the same token, our list of potential disease targets excludes those such as stroke, that involve such a complex panoply of distinct neuronal phenotypes and synaptic interactions, that cell-based structural repair remains a challenging goal. Contrasted with disorders of single or restricted phenotype, such as midbrain dopaminergic neuronal loss in Parkinson's, one can readily understand the greater efforts made on behalf of the latter.

Cell transplantation as a treatment strategy for neurodegenerative disease was indeed first explored in depth in animal models of Parkinson's Disease; these early studies were deemed sufficiently exciting to justify clinical trials of human fetal cells and tissue in medication-refractory Parkinson's. This volume thus begins with reviews by the authors of some of these seminal studies. Olle Lindvall and Anders Björklund will review the state of cell therapeutics in treating Parkinson's disease, one of the first and best-studied targets of neural cell transplants, while Curt Freed and colleagues will provide a specific perspective on the use of fetal tissue grafts in Parkinson's, both past and

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present. Historically, these studies of cell therapeutics in Parkinson's were closely followed by analogous studies in Huntington's disease (HD), which has similarly been a target of both extensive animal studies, and some initial clinical assessments. Anselme Perrier, Marc Peschanski and their colleagues discuss cell transplant strategies in HD, while Abdel Benraiss and one of us (SG) will then discuss the mobilization of endogenous neuronal progenitor cells as a potential treatment for HD. Genevieve Gowing and Clive Svendsen will then round out these reviews of cell-based therapy of neurodegenerative disorders, by discussing the role of stem cell-based therapeutics in the motor neuron disorders.

Cell-based therapeutics are hardly limited to neuronal diseases; to the contrary, in many respects the disorders of glia are even more appealing as potential therapeutic targets, since the precise wiring specificity required of a restored neural network is not needed for effective astrocytic or oligodendrocytic cell replacement, provided the underlying neuronal substrate remains viable. As a result, the myelin disorders in particular, both pediatric and adult, have been active targets of cell-based therapeutic approaches. Ian Duncan, Yoishi Kondo and Su-Chun Zhang begin by discussing the major categories of myelin disease, the experimental models for their assessment, and the use of stem and progenitor cell-based strategies in their treatment. Tamir Ben-Hur then reviews the more specific role of stem cell-based grafts in the treatment of multiple sclerosis (MS), approaching the issue from the dual standpoints of glial progenitor cells for myelin repair, and both neural and mesenchymal grafts as immune modulators. The latter point is the focus of the review of David Gosselin and Serge Rivest on the clinical application of autologous hematopoietic stem cells grafts in MS. Robin Franklin and colleagues extend the discussion by focusing on the mobilization of endogenous stem and progenitor cells for purposes of myelin repair, extending the theme of endogenous progenitor induction to the myelin disorders. Lamya Shihabuddin and Seng Cheng then discuss the use of neural stem cell grafts, and potentially those of glial progenitors as well, in the lysosomal storage disorders, focusing on the use of engrafted cells for enzymatic replacement rather than direct structural repair.

Unlike neurodegenerative diseases of restricted phenotypes, or glial disorders of largely astrocytic of oligodendrocytic phenotype, spinal cord injury involves the loss of both segmental neurons and glia at the level of injury, and often the distant deafferented targets of transected neurons. For that and many other reasons, it is an especially difficult therapeutic target, and yet simpler by degree and complexity than higher cerebral structures. As such, it has been an active target for cell-based therapies, increasingly so over the past several years. Hideyuki Okano and colleagues broadly consider spinal cord injury as a cell therapeutic target, focusing on the use of human embryonic stem cells and induced pluripotential cells for structural repair. Mark Noble and colleagues then discuss the specific attributes of astrocytes as therapeutic vectors in cord injury. Mark Tuszynski and Edmund Hollis II then review the role of neurotrophin support of both endogenous and engrafted cells, and in doing so highlight the synergistic value – and ultimately need – of multimodal strategies for cell-based spinal cord repair. Michael Fehlings and Reaz Vawda then summarize the state of current and planned clinical trials in SCI, and directly address several of the more contentious issues in this nascent field.

This fine set of reviews closes with two that explore two of the most promising new CNS targets of cell-based therapy, the epilepsies and primary retinal diseases. Ashkok Shetty reviews the potential use of cell grafts in seizure control, and in suppressing epileptogenesis in vulnerable foci, whether of developmental or acquired etiology. Jeff Stern and Sally Temple then review the use of stem cell-derived phenotypes in treating retinal disorders, in particular the use of stem cell-derived retinal pigment epithelia in ameliorating retinal loss in the macular degenerations. This latter work in particular has recently gone to clinical trials, and speaks to the speed with which cell populations of potential therapeutic interest can be brought to the clinic when justified by promising preclinical data. Finally, and as a natural follow-up to that point, Arlene Chiu and Mahendra Rao close by reviewing the regulatory issues surrounding that path to the clinic, with an important discussion of both the means and potential impediments to clinical translation. Theirs is an appropriate wrap-up to a fine set of articles spanning the current state of CNS cell therapeutics, and a harbinger of things to come in a rapidly moving field that promises a new neurology ahead.