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addition, other stem cells, for example, neural or hematopoietic stem cells, appear to reside in perivascular locations in situ (Hirshi and D'Amore, 1996). Since MSCs isolated from different tissues exhibit distinct sensitivities to inductive bioactive molecules in culture, it follows that this reactivity reflects the tissue of origin. Most well studied are the adult marrow-derived MSCs, which are often used as the standard. The inductive conditions for marrow MSCs are quite different from those required by fat-derived MSCs (Estes et al., 2006), as may be expected due to the diverse microenvironments present on the tissue side of the vasculature in which the pericytes reside. The MSCs from marrow and fat are both multipotent, but the inductive stimulus, TGF-β, for chondrogenesis for marrow MSCs must be supplemented with BMP-6 for fat MSCs. Clearly, such variation in inductive requirements must be taken into account when designing expansion and differentiation protocols for use in future therapeutic applications.

Although my colleagues and I have been working with marrow MSCs for over 20 years and have published on markers of MSCs, their perivascular localization in human skin, their multipotency, and their secretion of bioactive factors (Caplan, 2007), we and others have never performed a comprehensive and detailed comparison of the in situ and in vitro traits of MSCs and pericytes. The team led by Bruno Péault provides a solid set of observations that clearly links the MSC and pericyte. There will be a number of exceptions, but my suggestion is that all MSCs are pericytes, and this manuscript gives a formal context to better understand, in both embryos and adults, how the MSC/pericyte contributes to the formation, maturation, and homeostasis of all vascularized tissues.

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The Center of the Spinal Cord May Be Central to Its Repair

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A recent *PLoS Biology* report from Meletis et al. (2008) strongly suggests that ependymal cells are a key source of endogenous stem cells in the spinal cord. Advances in understanding endogenous neural stem cells may facilitate repair of the injured central nervous system.

Repair of the injured spinal cord is one of the "holy grails" of medicine. The development of strategies to protect and repair the injured spinal cord has been facilitated by the identification of key mechanisms of secondary injury, by the characterization of extrinsic barriers to axonal regeneration, and by the discovery of neural stem cells within the adult central nervous system (CNS) (Rossignol et al., 2007).

Complex and interrelated secondary injury processes are now increasingly understood, and they provide many potential targets for therapeutic intervention. Also critical has been the discovery that central axons are capable of regenerating but are prevented from doing so by inhibitory molecules expressed on central myelin and in the postinjury extracellular matrix (Rossignol et al., 2007). These discoveries have led to treatments now in early-stage human clinical trials (Figure 1) (Baptiste and Fehlings, 2008).

Neural precursor cells are emerging as another potential means to repair the injured CNS (Karimi-Abdolrezaee et al., 2006). The precise source(s) of endogenous neural precursor cells has been controversial; however, in the brain, evidence supports a role for cells in both

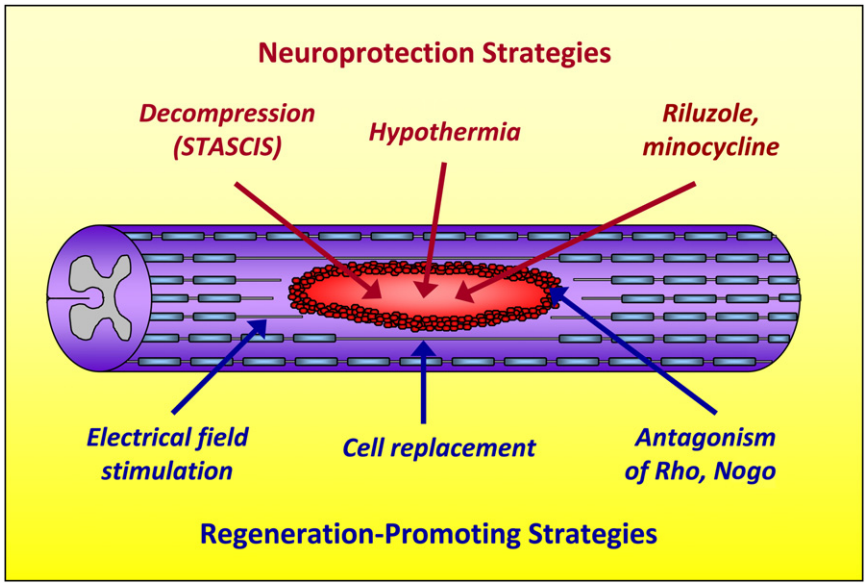

Figure 1. Strategies to Protect and Repair the Injured Cord Currently in Human Clinical Trials
Experimental therapies are grouped into those aimed to induce neuroprotection or to promote regeneration. Early decompression of the spinal cord is being examined in the Surgical Treatment for Acute Spinal Cord Injury Study (STASCIS) as well as in a study of cerebrospinal fluid drainage. Systemic hypothermia is being examined by the Miami Project to Cure Paralysis. Both decompression and hypothermia target multiple secondary injury mediators. Pharmacological approaches include riluzole, which targets excitotoxicity as well as sodium dysregulation, and minocycline, which targets apoptosis and neuroinflammation. Electrical field stimulation aims to promote axonal regeneration. Cells such as bone marrow stromal cells and olfactory ensheathing cells are being transplanted into the injured spinal cord in centers outside of North America. Antagonists of CNS axonal growth inhibitors include ATI-355, which sequesters the myelin inhibitor Nogo, and Cethrin, which inhibits Rho, a downstream molecule involved in the signaling of all known CNS inhibitors. Thank you to Derek Chew for assistance in constructing this figure.

the ependymal and subependymal layers, with many favoring a predominant role of radial glial cells. The spinal cord may have a unique source of neural precursor cells, as its ependymal layer, unlike in the brain, exhibits greater proliferation than its subependymal layer (Adrian and Walker, 1962; Namiki and Tator, 1999).

A recent publication from the Frisen laboratory (Meletis et al., 2008) represents a significant advance in determining the source of neural stem cells in the spinal cord. In order to define the origin of neural stem cells in the region of the central canal of the spinal cord, Frisen's team generated two transgenic mouse lines expressing tamoxifen-dependent Cre recombinase under the control of *FoxJ1* or *Nestin* regulatory sequences. *FoxJ1* is a specific marker of cells with motile cilia or flagella, whereas *Nestin* is expressed by neural stem/progenitor cells. By labeling and characterizing spinal cord cells with motile cilia using these novel transgenic mice, Frisen's team provides convincing evidence that ependymal cells are the predominant source of endogenous spinal cord stem cells.

There are several significant implications of these findings. First, harvesting ependymal-derived neural precursor cells for subsequent transplantation into the injured cord may be preferable to other donor cell types. This hypothesis is supported by data suggesting that transplanting cells and tissue to the anatomical site from which they were isolated may yield optimal results (Shetty and Turner, 2000). Perhaps specific cell populations are best equipped to survive and function in their original microenvironments. Second, stimulating endogenous ependymal cells within the injured spinal cord may be preferred over transplanting exogenous cells, as the latter may cause injury and also require immunosuppression. Future research will need to explore both possibilities, and the transgenic animals developed by Meletis and colleagues are ideally suited for such experiments.

Also important is the finding that, following injury, ependymal cells not only form myelinating oligodendrocytes but also differentiate preferentially into "astrocyte-like" cells that participate in astroglial scarring (Meletis et al., 2008). While astrogliosis restricts the spread of damage, it creates a physical and chemical barrier to axonal outgrowth. Moreover, work by Hofstetter et al. suggests that astrocytic differentiation of transplanted cells may exacerbate neuropathic pain (Hofstetter et al., 2005). Indeed, much remains to be learned about astrogliosis, and this publication corroborates emerging evidence that the function of the astroglial scar is complex. Of interest, the ependymal-derived astrocyte-like cells observed by Meletis et al. appeared to support axonal outgrowth, in contrast to other regions of scar suggesting further benefit to stimulating the proliferation of these endogenous progenitor cells.

Additional areas for future research are apparent. The transgenic animals employed in these experiments can determine if ependymal cells function as neural stem cells in the brain and also determine if they generate the more proliferative precursor cells in the brain's subependymal layer. As well, Meletis et al. (2008) suggest that novel molecules may guide the migration of the ependymal progenitor cells; once identified, the migration-inducing pathways might be exploited to promote repair.

It is important to place the work of Meletis et al. (2008) into a broader context. It is becoming increasingly apparent that a combination of therapies will be required to achieve clinically meaningful improvements in spinal cord function. While the stimulation of endogenous stem cells is an attractive strategy for CNS repair/regeneration, it is unclear whether sufficient cells can be mobilized to provide efficient neural regeneration. Hence, cell replacement approaches remain an attractive cornerstone for combinatorial therapies that are being considered for clinical translation. Indeed, the replacement of lost cells has shown promise in various animal models of CNS injury. Some researchers have sought and achieved neural replacement with integration of transplanted cells into functional circuits. Other groups, such as our own, have sought and achieved oligodendrocyte differentiation and remyelination (Karimi-Abdolrezaee et al., 2006). A broad array of cell types have been administered in protocols designed toward achieving

diverse goals, and benefit has been almost universally reported. The benefit, however, has also been universally modest.

The relatively modest effects of cell replacement strategies undoubtedly stem from the fact that these approaches are currently employed with insufficient understanding of the mechanisms underlying their observed benefit. Replacement of lost cells likely plays an important role, but functional improvement has also been seen in the absence of this effect. This has raised the possibility that transplanted cells may secrete trophic factors, or optimize the postinjury environment, in order to facilitate neuroprotection or enhanced plasticity of surviving, endogenous cells (Ourednik and Ourednik, 2004; Shetty and Turner, 2000). One must also consider that different donor cell types may lead to beneficial outcomes through distinct mechanisms. Studies exploring these possibilities are critically needed to advance the field of spinal repair. With improved understanding of the biology of transplanted cells and their interaction(s) with the host CNS, it may be possible to alter the exogenous cells and/or host environment in order to augment functional recovery.

Enhanced knowledge of neural stem cell biology, such as the advances provided by Meletis et al. (2008), will be key to using neural precursor cells for CNS repair and regeneration. Also key will be an increased understanding of the signaling pathways that underlie the differentiation of neural stem cells, as recently described by Whittemore's group (Cheng et al., 2007).

In conclusion, the work by Meletis et al. (2008) represents an important step forward in understanding the biology of endogenous neural stem cells in the CNS. It is fascinating to consider that the cells at the center of the spinal cord may play a central role in its repair.

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Turning Back Time: Reversing Tissue Pathology to Enhance Stem Cell Engraftment

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Histopathologic changes in diseased tissues may render them inhospitable to engraftment by transplanted stem cells. A recent report in *Nature Medicine* (Gargioli et al., 2008) demonstrates that pretreatment of dystrophic mouse muscles with tissue-modifying factors leads to reduced fibrosis, increased vascularity, and enhanced stem cell engraftment.

Stem cell transplantation holds great promise for the treatment of degenerative diseases. The success of stem cell transplantation depends not only the intrinsic properties of the transplanted cells, but also on the properties of the tissue into which the cells will be introduced. It seems to be generally true that exogenous stem cells engraft far more efficiently into tissues, whether normal or diseased, from which endogenous stem cells have been depleted. This has led to the concept that exogenous cells require a ''vacated niche'' for effective engraftment (Scadden, 2006). However, diseased tissues may pose specific barriers to cell transplantation. If the exogenous cells are introduced into an environment of necrosis, inflammation, and degenerative changes, their ability to engraft, proliferate, and differentiate into mature tissue may be severely compromised. In the muscular dystrophies, a group of diseases for which stem cell transplantation has long been considered as a potential therapeutic modality (Partridge and Sloper, 1977), the host environment is particularly relevant. The dystrophies are characterized by a progressive replacement of normal skeletal muscle with