ISSCR INTERNATIONAL SOCIETY FOR STEM CELL RESEARCH

PROGRESSIVE MULTIPLE SCLEROSIS

INTRODUCTION

Multiple Sclerosis (MS) is a chronic disease in which myelin, the insulating substance of the brain and spinal cord, is attacked by the immune system. The resultant demyelination is accompanied by loss of oligodendrocytes, the myelin-producing cells of the central nervous system. This leads to disruption of neuronal signal conduction, and, ultimately, to visual, sensory, motor, and cognitive deficits. MS is one of the more common causes of neurological disability, especially in younger people, and affects several million individuals worldwide; no clear cause has yet been identified. In general, MS proceeds from a phase of recurrent self-limited episodes, designated relapsing-remitting MS (RRMS), to a more chronic phase of demyelination-associated neurodegeneration, progressive MS, which is characterized by the consolidation of permanent disabilities.

There are a number of immune modulators that are routinely and successfully used for the treatment of RRMS. However, treatment-refractory cases of RRMS are not uncommon, and these may be treated via reconstitution of the immune system using hematopoietic stem cell transplantation. While this latter strategy may be curative, its risks limit its use to only the most severe cases of RRMS. Beyond these, among cases treated with immunomodulators alone, about a third of RRMS cases will ultimately advance to progressive MS (PMS). During that phase of the disease, progressive neuronal loss is superimposed upon stable demyelination leading to atrophy and attendant worsening disability. Patients with PMS seem to lose their ability to remyelinate affected regions of the brain and spinal cord, whether by the depletion or inactivation of their resident glial progenitor cells (GPCs), which leads to the inexorable loss of neurons, which require myelin for their support as well as for their long-distance communication. There are currently limited treatment options available for PMS, and none that effectively stabilize disease or restore lost function.

RATIONALE AND EXPERIMENTAL EVIDENCE OF CELL-BASED THERAPIES FOR PMS

Given the dearth of effective treatment options for the progressive myelin and neuronal loss of PMS, cell replacement is under investigation as a means of treating this condition. To that end, multiple groups have now used transplanted glial progenitor cells to treat animal models of acquired demyelination. Both human tissue-derived and pluripotent stem cell-derived glial progenitor cells have significantly increased – and often rescued - the lifespans of congenitally dysmyelinated mice, with effective remyelination of the host brains, and recovery of lost neurological functions. Similarly, transplanted human GPCs have repaired experimental white matter lesions in toxin-induced demyelinating lesions in a variety of animal models of adult demyelination, all intended to model the pathological features of PMS.

WHAT IS THE CLINICAL STATUS OF CELL-BASED THERAPIES FOR PMS?

The provision of new, healthy glial progenitor cells, which give rise to new myelin-producing oligodendrocytes, is under development as a potential treatment strategy, with the tandem goals of stabilizing disease by preventing further neuronal loss and restoring function by remyelinating demyelinated neuronal axons. In preclinical work thus far, methods have been developed for producing large numbers of homogeneous, deliverable human glial progenitor cells from pluripotent human stem cells, including both embryonic and induced pluripotent stem cells. These cells have proven effective at remyelinating white matter lesions in a variety of both postnatal and adult animal models of acquired demyelination; their potential use as cellular reagents for treating PMS is under review by the FDA.

WHAT DOES THE NEAR FUTURE HOLD?

We may reasonably anticipate the progression of glial progenitor cell-based therapies for PMS to clinical trials in the relatively near future, pending acceptable preclinical safety data and FDA approval.

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