

The potential for stem cell therapies to have an impact on cerebral palsy: opportunities and limitations

CRYSTAL A RUFF^{1,2,3,*} | STUART D FAULKNER^{1,2,3,*} | MICHAEL G FEHLINGS^{1,2,3,4}

1 Division of Genetics and Development, Toronto Western Research Institute, Toronto; **2** Institute of Medical Science, University of Toronto, Toronto; **3** Spinal Program, University Health Network, Toronto Western Hospital, Toronto; **4** Division of Neurosurgery, University of Toronto, Toronto, ON, Canada.

Correspondence to Dr Michael G Fehlings, Division of Neurosurgery, University Health Network, Toronto Western Hospital, 399 Bathurst Street 4WW-449, Toronto, ON M5T 2S8, Canada. E-mail: michael.fehlings@uhn.on.ca

*These authors contributed equally to this article.

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ABBREVIATIONS

ESC	Embryonic stem cell
iPSC	Induced pluripotent stem cell
MSC	Mesenchymal stem cell
NPC	Neural precursor cell
OEG	Olfactory ensheathing glia
PVL	Periventricular leukomalacia

Cerebral palsy (CP) is a chronic childhood disorder described by a group of motor and cognitive impairments and results in a substantial socio-economic burden to the individual, family, and healthcare system. With no effective biological interventions, therapies for CP are currently restricted to supportive and management strategies. Cellular transplantation has been suggested as a putative intervention for neural pathology, as mesenchymal and neural stem cells, as well as olfactory ensheathing glia and Schwann cells, have shown some regenerative and functional efficacy in experimental central nervous system disorders. This review describes the most common cell types investigated and delineates their purported mechanisms *in vivo*. Furthermore, it provides a cogent summary of both current early-phase clinical trials using neural precursor cells (NPCs) and the state of stem cell therapies for neurodegenerative conditions. Although NPCs are perhaps the most promising candidates for cell replacement therapy in the context of CP, much still remains to be understood regarding safety, efficacy, timing, dose, and route of transplantation, as well as the capacity for combinatorial strategies.

BACKGROUND

What is cerebral palsy?

Cerebral palsy (CP) is the most common pediatric developmental disability and is caused by perinatal asphyxia, infection, or preterm birth. In developed countries it occurs in approximately 2.5/1000 live births.¹ The mortality rate among affected children is higher than among their unaffected peers, and comorbid cognitive and sensory deficits, in addition to lifelong motor impairment, are frequent. A late prenatal or perinatal hypoxic-hemodynamic insult is the dominating final common pathway in the pathogenesis of CP.² Survivors of preterm birth constitute the largest etiological subgroup of children with CP,³ and periventricular leukomalacia (PVL) is the most common form of brain injury in this cohort⁴ (Fig. 1). Phenotypically, children with CP present with spastic quadriplegia (35%), spastic diplegia (21%), and spastic hemiplegia (31%), with other forms of dyskinetic CP contributing the remainder (13%).⁵ Animal models in several species provide evidence for a maturation-dependent vascular predisposition to white matter injury, with a specific sensitivity of the immature oligodendrocyte populations to ischemic and inflammatory insult.⁶ Pathologically, PVL preferentially occurs around the lateral ventricles that border the penetrating branches of the major cerebral arteries and spatially overlap descending corticospinal tracts (Fig. 1).

Relevant to this, cell replacement therapy aims to replace damaged oligodendrocytes in order to normalize function in affected neuromotor tracts.

What are stem cells?

Stem cells are multipotential cells that exist in both adult and developing tissue. Their key unifying characteristics are their multipotential capability and their ability to self-renew. Throughout development, pluripotency decreases with increased cellular differentiation (Fig. 2); differentiation is accompanied by changes in both gene expression and the epigenetic profile, leading to a mature cell phenotype. 'True' stem cells can form any tissue in the body or amnion and have virtually unlimited proliferative and self-renewal capacity. However, these cells are never used in cell transplantation paradigms, primarily because of their high mobility and propensity for teratoma formation. Instead, more differentiated cells, such as multipotent cells or fate-restricted progenitors, are the types used in preclinical studies. Furthermore, non-stem cells, usually glial cells such as peripheral Schwann cells and olfactory ensheathing glia (OEG), have also been explored for cellular therapy, and will be discussed a posteriori. Here will discuss all types of stem cells along the developmental lineage, with understanding that the cell types currently being explored preclinically primarily con-