Concise Review: Stem Cell-Based Treatment of Pelizaeus-Merzbacher Disease

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ABSTRACT

Pelizaeus-Merzbacher disease (PMD) is an X-linked disorder caused by mutation in the *proteolipid protein-1* (*PLP1*) gene, which encodes the proteolipid protein of myelinating oligodendroglia. PMD exhibits phenotypic variability that reflects its considerable genotypic heterogeneity, but all forms of the disease result in central hypomyelination, associated in most cases with early neurological dysfunction, progressive deterioration, and ultimately death. PMD may present as a connatal, classic and transitional forms, or as the less severe spastic paraplegia type 2 and PLP-null phenotypes. These disorders are most often associated with duplications of the *PLP1* gene, but can also be caused by coding and noncoding point mutations as well as full or partial deletion of the gene. A number of genetically-distinct but phenotypically-similar disorders of hypomyelination exist which, like PMD, lack any effective therapy. Yet as relatively pure CNS hypomyelinating disorders, with limited involvement of the PNS and relatively little attendant neuronal pathology, PMD and similar hypomyelinating disorders are attractive therapeutic targets for neural stem cell and glial progenitor cell transplantation, efforts at which are now underway in a number of research centers. STEM CELLS 2016; 00:000–000

SIGNIFICANCE STATEMENT

Human neural and glial progenitor cells are capable of generating myelin-producing oligodendroglial cells, that have proven capable of regenerating myelin after transplantation into the brains of myelin-deficient animals. These cells may therefore be appropriate to treat childhood diseases in which myelin does not form properly, such as Pelizaeus-Merzbacher disease, an otherwise untreatable and often deadly pediatric genetic disorder.

Pelizaeus-Merzbacher disease (PMD; OMIM 312080) is a progressive and unremitting congenital disorder of myelin formation, that results in severe neurological disability across a variety of modalities, and for which there is no treatment. PMD was first described in young boys presenting with nystagmus, spastic quadriparesis, ataxia, and cognitive impairment [1, 2]. It is an X-linked disorder, such that boys inherit the PMD mutation from their mothers, who are themselves typically unaffected, though a maternal carrier state phenotype has been described [3]. While pathologists long ago established that PMD was associated with deficient myelination, only later did linkage studies reveal that PMD mapped to the *proteolipid protein-1 (PLP1)* locus at Xq21.3-q22 [4, 5]. A series of subsequent studies then established that PMD was indeed causally associated with mis-expression or mutation of *PLP1*, one of the major constituents of central myelin [6].

PMD is a rare disorder that severely affects patients and their families. Its overall prevalence ranges from 1:200,000 to 1:500,000 in the United States, with international incidence ranging from 1:90,000 to 1:750,000 live births, depending upon the demographic [7]. Yet clinically, PMD comprises a relatively broad spectrum of disorders, whose cardinal shared feature is the dysregulation of PLP1 expression and/or structure. In its prototypic form, PMD is characterized by pendular nystagmus, head tremor, and systemic hypotonia; with time, affected patients manifest some combination of mental retardation, choreoathetosis, dystonia, cerebellar ataxia and long tract signs, especially corticospinal dysfunction. There are a number of clinical phenotypes of PMD, most associated with significant disability and typically resulting in premature death [8].

Clinically, PMD has been classified into three major subtypes, according to the age of

presentation [9]. *Connatal PMD* (aka severe/early-onset) is the most aggressive of PMD phenotypes. These patients can present at birth with nystagmus and respiratory distress, often requiring ventilation, as well as extrapyramidal signs, laryngeal stridor, feeding difficulties, and optic atrophy. These infants are characterized by extreme neonatal hypotonia, that may be so severe as to mimic spinal muscular atrophy [10]. They rarely if ever achieve ambulation or develop speech, and their survival is typically limited to the teen-age years. In addition, these patients may develop seizures, though these are typically responsive to antiepileptic agents. *Classic PMD* presents before the first year of age, with a failure to achieve motor milestones, followed by manifestation of many of the same features as connatal PMD. Relative to the connatal form, the cognition and speech of children with classic PMD may develop to a limited extent, and many children achieve the ability to ambulate with assistance. The progression of disease slows by the end of the first decade, and the life spans of affected patients vary from adolescence to young adulthood. *Transitional PMD* combines clinical features of both the classic and connatal forms [11, 12]. Two other less severe phenotypes were subsequently described, including the spastic paraplegia syndrome and PLP1-null disease. *Spastic paraplegia type 2* [13] is of later onset than the classic PMD, and is characterized by spasticity of the lower extremities that may coexist with varying degrees of cognitive impairment, nystagmus, ataxia, and dysarthria. The *PLP1 null* phenotype comprises the mildest of described PLP1-associated syndromes, and is characterized by spastic paraplegia and a mild to moderate demyelinating peripheral neuropathy [14–16]. Importantly, the clinical heterogeneity of PMD reflects its genetic heterogeneity, in that *PLP1* amplifications, exonic and intronic deletions, and point mutations, have all been associated with the disease.

Besides PMD, a number of other disorders have been described which share similar patterns of congenital hypomyelination, but arise from mutations in genes other than *PLP1* (reviewed in [17, 18]). The clinical and radiological distinctions among these disorders remain subtle and differential diagnosis challenging, despite recent significant improvements in their recognition. Ultimately, genetic analysis has clarified and continues to unravel the nature and heterogeneity of these congenital hypomyelinations. Individually rare, these disorders include the PMD-like disease associated with mutations in the gap junction protein connexin 47 *GJC2* gene (OMIM 608803) [19–21], hypomyelination with atrophy of the basal ganglia and cerebellum caused by mutations in the dystonia-associated ß4-tubulin *TUBB4A* gene (OMIM 602662) [22], *SOX10*-associated hypomyelination (OMIM 602229), and others; altogether, 14 hereditary hypomyelinating leukodystrophies have thus far been classified as such in a phenotypic series (OMIM PS312080 [17]. While these conditions have been described as principally or entirely disorders of central nervous system (CNS) myelin, most are sufficiently rare as to remain relatively uncharacterized. As such, the extent to which these hypomyelinating disorders may exhibit either peripheral or autonomic nervous system involvement is unclear, an issue with significant therapeutic implications, as CNS-directed cell replacement therapy may prove limited in its utility for those diseases with significant peripheral nervous system (PNS) pathology, absent effective concurrent treatment of the latter. Similarly, some of these disorders may be associated with significant extra-neurological and systemic manifestations, which will ultimately require treatment approaches beyond cell replacement.

INDUCED PLURIPOTENT STEM CELL AND MOUSE MODELS OF MUTANT PLP1-ASSOCIATED OLIGODENDROGLIAL DYSFUNCTION

PMD can be caused by *PLP1* mutations resulting in copy number amplifications and over-expression as well as loss-of-function. Different animal models have been developed which reflect its heterogeneous genetics and pathology; these include mice expressing supernumerary copies of the PLP1 gene [23–25], missense mutation with a HSP-like phenotype [26, 27], and PLP1 deletion [28]. Despite the limitation of murine models—among which is that they may be too short lived to allow the proper assessment of cell-based therapies—they nonetheless provide useful platforms within which to test the efficiency of a broad range of putative treatment strategies.

Induced pluripotent stem cells (iPSCs) have evolved as a new tool to assess pathological mechanisms and therapeutic responses on a patient-specific basis. iPSCs and their derived glial progenitors and oligodendrocytes may be produced from affected patients, and used to study the effect of different mutations in vitro and in vivo. In fact, iPSCs generated from PMD patients with missense mutations have been successfully differentiated into oligodendrocytes with recapitulation of PMD pathology [29]. In particular, these oligodendrocytes have manifested endoplasmic reticulum (ER) stress and progressed to apoptotic death, validating the hypothesis derived from mouse models that protein misfolding-associated ER stress accompanying *PLP1* gain-of-function mutations might trigger oligodendroglial loss in PMD [30–32]. This in turn has led to studies of agents that might rescue oligodendroglial phenotype, by mitigating unfolded protein response-mediated cell loss. As such, a variety of small molecule-based treatment strategies to this end have been proposed, that have been variably directed at lowering PLP1 expression [33], supplementing the diet with cholesterol to promote PLP incorporation into the cell membrane [34], and enhancing the ability of the endoplasmic reticulum to clear misfolded proteins [35]. While several of these strategies have shown promise in preclinical models, none of these disease-modifying strategies based on targeting PLP1 clearance or trafficking have yet advanced to clinical trials. More broadly, different small molecule-based therapeutic approaches would presumably be required to treat different PMD phenotypes, since clinically-significant disease can result from *PLP1* depletion, as in the PLP1 null syndrome, just as well as from gain-of-function and protein misfolding. As a result, and to establish a more universally-applicable, genotype-independent platform for treating this rare disorder, a number of investigators have focused on the potential utility of cell-based therapeutics for replacing diseased PMD oligodendrocytes with their wild-type and/or genetically- corrected counterparts.

CELL THERAPEUTIC STRATEGIES FOR THE TREATMENT OF PMD

Since endogenous oligodendrocytes are genetically defective in PMD, their replacement with exogenous, wild type cells would seem a potentially effective therapeutic strategy. In particular, intracerebral transplantation of glial progenitor cells has developed

as an attractive strategy for restoring lost or deficient myelin in PMD patients. This approach attempts to rescue the disease phenotype outright, by replacing mutant cells in principle with either allogeneic or genetically corrected iPSC-derived autologous oligodendrocytes carrying a normal copy of the *PLP1* gene. The ability of human oligodendrocyte progenitor cells (OPCs), derived from either second trimester fetal brain tissue [36, 37] or pluripotent cells [38], to rescue the shiverer model of congenital hypomyelination suggested the feasibility of using human OPC transplants to treat the hypomyelination of PMD [39–41], as well as a broader range of myelin diseases [42, 43]. Yet despite their attractiveness as therapeutic reagents, OPCs have not yet progressed to the clinic. Their proliferative potential seems limited in vitro [44], and treatments using purified OPCs require either predictable sources of human fetal tissue—an increasing rarity in today's sociopolitical environment—or pluripotent cell sources, the clinical use of which pose technical and regulatory challenges yet to be surmounted.

As a more practical alternative, human neural stem cell (NSC) grafts have been assessed as a potential cellular substrate for replacement in PMD on the basis of their production of oligodendrocytes in vivo in *shiverer* mice [45–47]. The availability of clinical-grade NSCs provided the basis for a first-in-man phase 1 open-label study (NCT01005004) of direct NSC transplantation into the brain of four connatal PMD patients who ranged from 9 months to 5 years of age [48]; all carried missense mutations in transmembrane (TM) domains, two in TM2 and two in TM4. This trial was designed primarily to assess the safety of intracerebral delivery of banked, serially-passaged human fetal brain-derived NSCs. Each boy received two intracerebral injections on each side of the brain into the forebrain white matter, for an intended total of total of 3×10^8 cells per child. The transplanted boys were immunosuppressed after transplant using tacrolimus for 9 months. The children were then followed for at least a year, with serial magnetic resonance imaging (MRI) and spectroscopy, and both neurological and neurophysiological exams.

The trial investigators reported a favorable safety profile at 1-year after transplantation, by both clinical and radiological evaluation [48]. They also reported some evidence of local and durable changes by MRI in the transplanted regions. Using diffusion tensor imaging, radial and axial diffusivity fell, while fractional anisotropy rose, suggesting diminished freedom of water movement in the plane of axonal fascicles. This result is suggestive of and consistent with myelin ensheathment of axons, but it is not in itself definitive; the patients' lack of clinical deterioration during this period and mild increase in MRI-assessed myelination were well within the range of the natural development of PMD children [49], the clinical variability among whom is significant. As such, the donor-derivation of any new myelin in these subjects, and hence the myelination competence of NSC allografts in humans, remains to be established - ultimately via post-mortem histological analysis. In the meantime, these index patients will continue to be monitored to establish the safety of their grafts, using clinical, radiographic, and neurophysiological outcome measures, all of which will be assessed for at least 5 years after transplant in a long-term follow up study (NCT01391637). Assuming an acceptable safety profile at 5 years, progression to a phase 2 efficacy study is a possibility. While such a study would ideally comprise an observational control arm matched as closely as possible to age and genotype, this level of precision will be difficult to achieve in an ultra-rare disorder. Such a study would need to be

able to deliver much higher numbers of NSC (e.g., 10^9), wider cell distribution and measures of donor-derived myelin such as enhanced nerve conduction in transplanted regions. Challenges to a phase 2 study of NSC in PMD include the scarce patient population and difficulties of transporting severely disabled children, high costs of the procedure hospitalization and short- and long-term monitoring. Indeed, are NSC the "best" cells to transplant in PMD, or might more lineage-restricted glial OPCs be more suited to the task? This topic is the source of much debate, but needs to be addressed in future preclinical and ultimately clinical studies that directly compare human purified NSCs and OPCs, as well as hESC- and hiPSC-derived cells to define the optimal cellular vector, stage at administration, and dose range, for treating PMD or other myelin disorders.

NON-NEURAL CELL THERAPEUTICS FOR PMD: A CAUTIONARY NOTE

Other proposed cell-based therapies for PMD must similarly be based upon strong mechanistic footings, and be grounded in rigorous, peer-reviewed preclinical studies. However, in an age where there is optimism about the potential benefits of "stem cells," broadly defined, centers in the United States and other countries are offering untested and often unfounded procedures to affected PMD children and their often desperate parents. These include autologous or allogeneic hematopoietic stem cell (HSC) and umbilical cord-derived cell infusions (UCSC) [49]. Although such HSC and UCSC grafts may provide benefits in selected enzymatic disorders of myelin [50–53], there is scant rational basis for their use in structural disorders of myelin formation and processing, like PMD. Indeed, no credible or appropriately-controlled data exist that such non-neural phenotypes mediate CNS cell replacement. Given their lack of either rational mechanism or credible preclinical data, along with the real risks of myeloablation and CSF infusion, the financial burdens placed upon already stressed families, and the human tragedy intrinsic to the delivery of false hope to vulnerable parents, we believe that such approaches lack medical justification.

TOWARD FUTURE CELL-THERAPIES USING PLURIPOTENT ESC- OR iPSC-DERIVED MYELINATING CELLS

As noted, the use of fetal tissue-derived NSCs and OPCs is problematic, given the difficulty in sourcing and qualifying these cells, and hence of expanding their availability to significant number of patients. As a result, it seems likely that future efforts in CNS cell replacement will focus on the use of hESC and hiPSC-derived NSCs and OPCs. Pluripotent cell sources have the theoretical advantages of extensive expansion capacity, homogeneity and predictability. In addition, iPSCs allow for targeted genetic correction using new nuclease-mediated targeted gene editing technologies, such as CRISPR/Cas9 [54]. Patient-derived iPSCs in particular will enjoy the distinct advantage of permitting genetic editing and correction of underlying mutations—in this case correction of *PLP1* point mutations or excision of supernumerary *PLP1* copies. As such, genetic correction of mutant patient derived iPSCs followed by their glial induction and intracerebral transplantation may

permit autologous transplantation, and may prove an attractive option for these disorders [55].

That said, there are many practical barriers to be overcome. First, iPSCs show line-to-line heterogeneity, and require extensive screening, necessitating significant expenditures in both time and resources for their derivation. While iPSCs have unlimited growth potential, the cells can accumulate genetic mutations such as single base pair mutations, and even gross karyotypic abnormalities [56–58]. Defined media will have to be developed that optimally support iPSC survival and growth, to minimize the preferential selection of genetically abnormal cells. Second, the science of precise and safe genetic correction of human cells remains a work-in-progress, and the regulatory environment surrounding such genetically modified and reprogrammed lines remains uncertain, in particular when high efficiency targeted nucleases are employed that have potential off-target effects. Third, hESC and hiPSC-derived cells may have more tumorigenic potential than tissue-derived NSCs or OPCs, and preparative protocols need to ensure that transplanted pools not include undifferentiated or incompletely differentiated cells, that might become neoplastic after injection. As a result, despite the long-term advantages of using pluripotent cell-derived NSCs and OPCs, clinical progression in the treatment of PMD and similar myelin deficiencies in the near-term may yet still include human CNS-derived allografts of myelinogenic cells, whether of NSCs or OPCs.

More broadly, PMD and other early disorders of central myelin formation and maintenance share a lack of normally myelinogenic oligodendroglia, and a dearth of available treatment options. As a result, these disorders may serve as especially attractive proofs-of-principle for establishing the clinical efficacy of cell-based therapy for myelin repair in the human brain. To capitalize upon this broad translational opportunity though, further research is needed to understand the genetic basis, precise phenotypes and natural histories of these hypomyelinating leukodystrophies, as well as the optimal cell types that might be used for their rescue. If successful in this limited but challenging patient population, then we might anticipate the broader adoption of this strategy across the entire range of disorders for which white matter failure or loss is causally involved, pediatric and adult alike.

AUTHOR CONTRIBUTIONS

M.J.O., D.H.R., P.T., M.W., M.S.W., and S.A.G.: Collaborated in the drafting of this review.

DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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