

## On the Use of “Stem Cells” for Optic Nerve Hypoplasia

American Association for Pediatric Ophthalmology & Strabismus (AAPOS) Research Committee\*

In the past few years, the medical community has seen an explosion of knowledge and has felt cautious optimism about the future use of cell-based therapies for numerous diseases—including blinding diseases of children.<sup>1</sup> In general, these potential therapies are centered around stem cells, which can be divided into 3 categories: (1) pluripotent embryonic stem (ES) cells derived from human embryos; (2) induced pluripotent stem cells, in which differentiated cells, such as skin fibroblasts, are “reprogrammed” to “de-differentiate;” and (3) somatic stem cells (SSC), derived from tissues such as umbilical cord blood and bone marrow. With the exception of limbal stem cell transplantation in corneal opacification,<sup>2</sup> the use of various forms of stem cells, for the treatment of eye disease, has only been studied systematically in animal models.<sup>3-4</sup>

Recently, novel treatments using cell-based techniques have been advocated for patients with otherwise untreatable congenital ocular malformations such as optic nerve hypoplasia. An example is a website from China.<sup>5</sup> According to the websites of those offering these regimens, children who undergo infusion of somatic stem cells, such as those derived from umbilical cord blood—often along with adjunctive therapy, such as acupuncture and physical therapy—are reported to have improvements in their visual behavior. Most often, these procedures are performed in countries where government oversight of medical consumer safety is limited.

The practice of marketing cell-based therapies for optic nerve hypoplasia concerns us for several reasons. First, we are concerned about its safety and efficacy. The use of biologic material in the treatment of human disease in the absence of regulated quality control of reagents places patients at risk for adverse events. Possible adverse events may include untoward immune reactions and transmission of infectious agents. A PubMed search of “optic nerve hypoplasia” and “stem cells” reveals no peer-reviewed articles supporting safety or efficacy—even in principle—of this technique.<sup>6</sup> The information provided on websites for such therapies typically relies on anecdotes and patient/family testimonials. Because visual function assessment in young children is particularly susceptible to effort, learning, mood, suggestion, and the placebo effect, the visual function data provided by the advocates of these cell-based therapies are currently insufficient to justify patient treatment.

Second, these cell-based therapies target a vulnerable population (children) who are unable to legally provide

informed consent according to the Declaration of Helsinki<sup>7</sup> and whose families are often desperate for any intervention that might improve vision. Such families may pursue treatment despite the high cost of the procedure and the unknown risks. We believe it is unethical to target such patients/families with therapies that have not undergone rigorous study, and which are advertised as established medical treatment. Given that these approaches have not been approved by the Food and Drug Administration, they would not be legal to perform in the United States absent regulatory waivers. In addition, we see an inherent conflict of interest for those who profit financially by advancing unstudied technologies on patients.

Third, the biologic plausibility of such “therapies” is not apparent. These stem cells are delivered by injection into the peripheral blood. In order to “treat” optic nerve hypoplasia effectively, peripherally administered “stem cells” presumably would have to enter the eye and enter the ganglion cell layer of the retina. The cells would have to extend axons in a precise retinotopic manner through the mature optic nerve head—a task that has not been accomplished even in optimized animal models. These neurons would then have to synapse with the correct partner cells in the lateral geniculate nucleus and code for information in a way that could be interpreted by higher cortical centers. The individuals offering such “treatments” have yet to demonstrate in peer-reviewed literature that the methods used accomplish any of these tasks.

Lastly, we agree with the statement by Blight et al<sup>8</sup> that the “risks and costs of untested therapies are not limited to the individuals who pay for such treatments.” As these authors point out in the case of cell-based therapies for spinal cord injury, individuals receiving such regimens are likely to be excluded from future, controlled clinical trials for which they might otherwise qualify. Use of “stem cells” in unregulated and uncontrolled ways also undermines the legitimate science being done across the globe to better the lives of patients.

We stress that we *are* cautiously optimistic that cell-based therapies will eventually have a role in treating blinding diseases of adults and children. The burden of proof, however, remains with those proposing such treatments. Solid, peer-reviewed animal studies should precede use of these treatments in humans, followed by well-designed, clinical studies with appropriate data and safety monitoring, and, ultimately, randomized clinical trials.

### References

1. Jeganathan VS, Palanisamy M. Treatment viability of stem cells in ophthalmology. *Curr Opin Ophthalmol* 2010;21:213–7.
2. Kolli S, Ahmad S, Lako M, Figueiredo F. Successful clinical implementation of corneal epithelial stem cell therapy for treatment of unilateral limbal stem cell deficiency. *Stem Cells* 2010;28:597–610.

\*Research and Writing Committee Members: Brian P. Brooks, MD, PhD, Chair of Writing Committee “On the Use of ‘Stem Cells’ For Optic Nerve Hypoplasia; Graham E. Quinn, MD, MSCE, Chair, AAPOS Research Committee; Gil Binenbaum, MD; Suqin Guo, MD; Jonathan M. Holmes, MD; Mohamad Jaafar, MD; Kristina Tarczy-Hornoch, MD, DPhil; Jaime Tejedor, MD; David K. Wallace, MD; Agnes Wong, MD, PhD, FRCSC.

3. MacLaren RE, Pearson RA, MacNeil A, et al. Retinal repair by transplantation of photoreceptor precursors. *Nature* 2006; 444:203–7.
4. Jin ZB, Okamoto S, Mandai M, Takahashi M. Induced pluripotent stem cells for retinal degenerative diseases: a new perspective on the challenges. *J Genet* 2009;88:417–24.
5. China Stem Cell News. <http://www.stemcellschina.com/>, accessed March 4, 2011.
6. ONH/SOD Stem Cell Treatment. <http://opticnervehypoplasia-onh.com/>, accessed March 4, 2011.
7. Rickham PP. Responsibility in investigations on human subjects. Statements by medical research council. *Br Med J* 1964;2:178–9.
8. Blight A, Curt A, Ditunno JF, et al. Position statement on the sale of unproven cellular therapies for spinal cord injury: the international campaign for cures of spinal cord injury paralysis. *Spinal Cord* 2009;47:713–4.