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Kelly *et al.* reply: Walczak and colleagues[1] state that the neonatal desensitization approach that we reported for long-term human xenograft survival in rats[2] is not universally successful. Our model was validated in 19 separate experiments using almost 200 host animals (Sprague-Dawley rats) and with a range of human donor cells (primary fetal central nervous system cells of both cortical and striatal origin, as well as embryonic stem and fetal progenitor–derived neural cells and non-neural fetal cells). We have since found good xenograft survival following desensitization in Lister hooded rat hosts (unpublished data), but we have had more inconsistent results in Black 6 and CD1 mice. We have had reports from others of similar effective immunoprotection by neonatal desensitization in rat models of stroke (B. Onteniente, personal communication), ocular[3] and Parkinson's disease (E. Torres, personal communication). We have successfully used the approach in rat models of Huntington's disease (V.R., unpublished data). However, we know of one other group that has had difficulty replicating these results in the mouse host. It is therefore clear that neonatal desensitization can work, but we need to understand the precise conditions and mechanisms required for robust application of the model. To this end, a systematic characterization will be required to evaluate the following issues: the number and types of cells and route of administration that can induce neonatal desensitization; the number of cells for adult CNS grafting and required degree of similarity to the inoculating cells; the mechanism of desensitization, including the fate of desensitizing cells after inoculation in the neonate; the features of the host environment that permit desensitization and/or enhance rejection; and the specific donor-host species pairings that facilitate or inhibit desensitization. We are actively pursuing some of these questions. For example, for successful transplantation in the mouse, it is necessary to significantly increase the number of inoculating cells beyond that used for transplant in rats (V.R. *et al.*, unpublished data). Fully understanding the mechanisms underlying this phenomenon, and defining its practical limits, is a larger task than can be undertaken by one group. In this respect, we would like to emphasize that it is critical for such work that careful attention is paid to the appropriate use of positive controls. In particular, there must be demonstration that the cells grafted into the adult brain of an animal that has undergone neonatal desensitization are capable of surviving for the same period of time using another effective immunosuppression regime in the same animal model.

COMPETING FINANCIAL INTERESTS
The authors declare no competing financial interests.

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