Reply to Rosser Et Al.

Roger L. Albin, MD[1,2,3,4]

Jeffery H. Kordower, PhD[5,6]

[1]Neurology Service & GRECC, VAAAHS, Ann Arbor, MI, USA

[2]Dept. of Neurology, University of Michigan, Ann Arbor, MI, USA

[3]University of Michigan Parkinson's Foundation Research Center of Excellence, Ann Arbor, MI, USA

[4]Michigan Alzheimer Disease Center, Ann Arbor, MI, USA

[5]Dept. of Neurological Sciences, Rush University Medical Center, Chicago, Ill, USA

[6]Department of Neurosurgery, Rush University Medical Center, Chicago, Illinois, USA

Address correspondence to: Roger L. Albin, MD, 5023 BSRB, 109 Zina Pitcher Place, Ann Arbor, MI, 48109-2200, USA; ph – 734-764-1347; fax – 734-763-7686; email – ralbin@med.umich.edu

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We're pleased that our Editorial provoked discussion of research priorities in Huntington disease.[1] Rosser et al., however, misrepresent our comments. Rosser et al. allege a "categorical rejection of cell therapy as a regenerative treatment option for HD on the basis of a single phase II study of foetal cell transplantation."[2] This statement indicates that we regard MIG-HD as a definitive test of the value of cell transplantation. As was stated clearly in our Editorial, one of our major criticisms of the MIG-HD study is that it failed to test the efficacy of engrafting fetal tissues and could not inform discussion of whether the general approach of cell therapy for HD is appropriate. Indeed, after over 30 years of cell replacement strategy experiments, we were left with a clinical trial in which no graft survival was evident.

Our skepticism about the value of cell transplantation for HD rests on the fact that HD is a multi-focal neurodegeneration and the slender preclinical evidence base for these kinds of interventions. Rosser et al. cite Reidling et al. as an example of promising preclinical data but the results of this work underscores our concerns.[3] These were well executed experiments using the R6/2 transgenic fragment and Q140 knock-in murine genetic models. R6/2 has been the test bed for numerous potential therapies, some translated to clinical trials, and all translated interventions without success in trials. How does success in a model without predictive validity support proceeding to clinical experiments? Q140 may be a better model. The conventional but crude behavioral outcome measures employed, however, are not likely to be informative of what happens in humans. To reinforce one of our points, regardless of the source of cells

engrafted, the benefits of grafting will have to be substantial to compensate for the risks of surgeries. There should be substantial and convincing preclinical evidence of benefits before proceeding to trials. Newer therapeutic approaches designed to address the root pathology of HD, mutant huntingtin expression, have out-paced cell replacement therapy for HD. These newer approaches have a far greater chance of addressing all major symptomatic features of HD, including cognitive and behavioral deficits. HD participants undergoing cell transplantation experiments will be ineligible for other clinical trials.

Rosser et al. describe a consortium aimed at developing “best practices in the field.” We suggest moving the focus away from relatively narrow technical considerations to critical thinking about the justification for these kinds of experiments.

1) Albin RL, Kordower JH. A failed future. Mov Disord 2020;35:1299-1301.

2) Rosser AE, Busse M, Aron-Badin R, et al. Cell therapy for Huntington's disease: learning from failure. Mov Disord 2020;in press.

3) Reidling JC, Relaño-Ginés A, Holley SM, et al. Human Neural Stem Cell Transplantation Rescues Functional Deficits in R6/2 and Q140 Huntington's Disease Mice. Stem Cell Reports 2018;10:58-72.

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