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Cell Therapy for Huntington's Disease: Learning from Failure

We write in response to the editorial by Albin and Kordower,[1] "A Failed Future," which offers a perspective on the Multicentric Intracerebral Grafting in Huntington's Disease (MIG-HD) fetal cell transplantation study in Huntington's disease (HD).[2] Although MIG-HD did not achieve a positive clinical outcome, Albin and Kordower's critique of that study provides critical points of interpretation that we believe incorrect. In particular, we reject their categorical rejection of cell therapy as a regenerative treatment option for HD on the basis of a single phase II study of fetal cell transplantation. Indeed, Albin and Kordower highlight the confounds potentially caused by protocol changes during MIG-HD that emphasize the exploratory nature of this trial. Cell therapy has advanced substantially since MIG-HD was initiated; we now have fuller understanding of the cellular phenotypes and interactions that go awry in HD and thus a clearer understanding of cell-based strategies that might be used in its treatment. We suggest that Albin and Kordower make unwarranted predictions of future failure—effectively "throwing out the baby with bath water"—based on an overly broad interpretation of MIG-HD, leading them to a conclusion that is neither justified nor cognizant of the current science and does a disservice to current work in the field.

MIG-HD focused on achieving neural circuit reconstruction through transplanting striatal precursors isolated from fetal ganglionic eminence. It built on preclinical data and previous pilot human studies,[3] which constituted proof of concept that transplants can improve function and that this may not require every element of pathology to be addressed, something borne out in Parkinson's disease transplant studies where pathology also exists outside the key central nervous system target of cell therapy.[4] The limitations of fetal-derived donor cells stimulated research to derive candidate therapeutic progenitors (glial as well as neuronal[5]) from human pluripotent stem cells. Such cell products vary in their intended functions and therapeutic goals (eg, cell replacement, neuroprotection) with numerous reports of significant functional benefits (eg, Reidling and colleagues[6]). It is uninformative to lump these different products, targets, and therapeutic aims together and misleading to dismiss them all on the basis of a single phase II study initiated 2 decades ago.

We believe a more productive approach is to formulate an honest, comprehensive appraisal of foreseeable challenges to develop a rational road map for moving forward. There should be due consideration of the limitations of MIG-HD and previous studies, leading to new perspectives on the design and implementation of clinical trials of cell therapies in HD (as reviewed in Bachoud-Lévi and colleagues[7]). Indeed, publication and informed analysis of such negative data are precisely how we may best ensure future success. To facilitate this, we established Stem Cells for HD (SC4HD; https://www.sc4hd.org/), a global consortium of experts working in various areas of cell therapy. The group invites external peer review and is developing evidence-based guidance documents for the establishment of best practices in the field. We believe that this is the right process by which to assess whether the complex, but potentially powerful, strategy of cell-based therapies can have a place in the treatment of HD.

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Reply to: "Cell Therapy for Huntington's Disease: Learning from Failure"

We are pleased that our editorial provoked discussion of research priorities in Huntington disease (HD).[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 more than 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 HD being a multifocal 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 underscore 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 outpaced 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.

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