A Failed Future

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The history of invention is not the history of a necessary future…but rather of failed futures…

- David Edgerton[1]

In this issue, Bachoud-Levi et al. describe the results of the Multicentric Intracerebral Grafting in Huntington Disease (MIG-HD) study, a phase II trial of engrafting fetal ganglionic eminence tissue into the striata of subjects with manifest HD.[2] The concept motivating MIG-HD was that fetal ganglionic eminence contains striatal neuron precursors, that engrafted cells would differentiate into striatal projection neurons and reconstitute some of the striatal circuitry degenerating in HD, and that grafting would produce symptomatic improvement. Based on preclinical non-human primate experiments and single-site open label study data, the authors designed an ambitious experiment to assess target engagement, safety, and efficacy.

Prior open-label, single site studies were heterogeneous.[3] Grafting methods differed (tissue blocs versus cell suspensions and varying numbers of grafts), there was variable subject selection and outcome measures, and markedly differing approaches to immunosuppression varying from none to several different regimens. There were no actual controls in any prior study and a number of serious adverse events, notably subdural hematomas (SDHs) requiring evacuation, were reported. Outcomes were highly variable with a small number of reports of that were suggestive, but not definitive, of improvement after grafting. MIG-HD aimed to bring some order to the field with a uniform multi-center study. To address the critical issue of controls, the MIG-HD investigators chose a delayed start design with a substantial run-in period to estimate the rates of decline of all subjects. This approach allowed comparison of grafted and delayed grafted subjects and comparison also of subject clinical trajectories before and

after grafting. Tissue blocs were engrafted, the surgical approach was standardized, standard immunosuppression protocols were employed, and engraftment was measured with PET imaging and cortical evoked potential methods. This complex study had to overcome a number of obstacles and required a significant extension of the study period to accumulate the projected number of subjects.[3]

Bachoud-Levi et al. provide a clear and comprehensive description of MIG-HD outcomes.[2] Neither the primary outcome measure, changes in the Total Motor Score component of the Unified Huntington Disease Rating Scale (UHDRS-TMS), nor any of the numerous secondary/exploratory measures revealed evidence of engrafting benefits. Particularly problematic is the fact that PET studies indicated failure of the transplants to survive, in clear contrast to previous studies that demonstrated graft viability upon post-mortem assessment[4,5,6]. The hypothesis underlying this major effort could not really be tested. Furthermore, there was immunological evidence of rejection responses in numerous subjects, resulting in a midstream immunosuppression protocol alteration. Out of 53 subjects, there were 10 serious procedure related adverse events, including 1 intracranial empyema, 3 SDHs (2 requiring surgical intervention), 1 putaminal hematoma with significant sequelae, 1 seizure, 1 clinically manifest graft rejection event, and 3 intrastriatal cysts (1 requiring endoscopic surgery with cauterization of ectopic choroid plexus). Intrastriatal cysts occurred previously in grafted HD patients[7], likely caused by inadequate tissue dissection/preparation[8]. Because of SDHs, the grafting procedure was modified after the initial 29 grafting sessions by reducing the number of injection tracks. Due to evidence of graft rejection, the immunosuppression regimen was intensified for the last 20 subjects, although this did not seem to help graft viability.

What can be learned from MIG-HD? With respect to efficacy, the results are clearly negative on all measures. There was no positive evidence of successful engraftment and the significant changes in surgical methods and immunosuppression protocols in mid-trial makes the dataset difficult to interpret. Parallel efficacy and engraftment results were obtained in a single-site German study that mimicked the MIG-HD protocol (N=10).[9] The authors argue that MIG-HD results are informative in terms of other goals of phase II studies – assessing safety and study procedures. The authors argue that MIG-HD results led to a safer surgical approach and demonstrated the need for improved immunosuppression. In light of the present results, this interpretation can only be justified for a devastating and universally fatal disease such as HD.

It is unlikely that future cell-based therapy experiments will utilize fetal tissues. The implication is that the MIG-HD experience will inform future cell-based therapy experiments based on embryonic stem cells (ESCs) or induced pluripotent stem cells (IPSCs). This interpretation may be generous. Reducing the number of injection tracks may reduce surgical complications but as the goal is to reconstitute striatal circuits, reducing the number of injections may also reduce the probability of a clinical effect. Some current therapeutic gene therapy trials are delivering compounds to the putamen using a posterior to anterior approach.[10] This approach would likely be safer although any clinical trial using this approach for HD cell-based therapy should be preceded and modeled by experiments in nonhuman primates. Whether or not failure of immunosuppression was responsible for engraftment failure is difficult to assess without evidence that engraftment succeeded in at least some subjects. The authors' interpretation is problematic as intraputamenal solid tissue nigral grafts in Parkinson disease

patients survive consistently[11-15]. Ependymal cells, which are notoriously antigenic, may have been included in these tissue preparations. As the authors point out, it's likely that significant bench research will be needed to clarify the role of immunosuppression and indicate appropriate protocols. As the field moves towards cell-based therapies with individual patient derived IPSCs, immunosuppression may not be required.

One thing that is very clear is that a trial of this kind requires a great deal of effort. The costs of the MIG-HD trial should be measured partly in terms of opportunity costs. These resources, not least of which was the time and effort of numerous talented investigators, could have been devoted to more productive experiments. The MIG-HD results and this additional consideration should prompt re-examination of the rationale for cell-based therapies in HD. HD is a multisystem neurodegeneration. It is true that there is early, preferential loss of striatal projection neurons but many brain regions undergo marked neurodegeneration. In addition, the motor aspects of HD are a lower priority for therapeutic attention as personality and cognitive impairments are the major sources of disability in early to moderately advanced HD. The evidence for striatal circuit reconstitution improving these features is less compelling. There is also experimental evidence that striatal neurodegeneration in HD is partly the consequence of loss of trophic support from neocortical afferents.[16] Against this background, the idea that focal striatal engraftment will produce marked clinical effects, and they would have to be marked to justify the risks of surgery (and possible immunosuppression), seems naïve.

Scientists and physicians are avid consumers and promoters of novel technologies. Historians of industrial technologies remind us that most efforts to develop novel technologies end in failure.[1] Biomedical research, as shown by the pitiful success rate of drug candidates

entering clinical trials, is no exception. In pursuit of novel technologies, there is a constant risk that enthusiasm for innovation leads to sterile infatuations with specific approaches. The pursuit of useful therapies for HD has been frustrating. This frustration should not overpower our critical judgment and promote perseverative pursuit of approaches unlikely to succeed.

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