Cell Therapies for Parkinson's Disease Webinar
14 November 2013

Questions & Answers

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1. What do you think is the best animal model to study PD cell-based therapeutics (severe vs moderate dopaminergic neuron loss)? And are there any dependable in vitro models? In a more specific way to phrase this question: Which is the most appropriate model for preclinical poc studies? Which species?	**Dr Bryan** – From a regulatory standpoint, we don't see any specific animal model as the best model. Sponsors of INDs for PD have used the MPTP model in nonhuman primates, and the 6-OHDA model in rodents. They have used these models to provide evidence of proof-of-concept (POC). We have accepted those models to provide POC. However, the sponsor should propose which model is best for showing the activity of their product. We are flexible and consider the sponsor's proposals on a case-by-case basis. **Dr Kordower** – I think what you want is a model that reflects the disease. In a recent Brain paper that we published, by 5 years post diagnosis (which is an inclusion criteria for studies going forward), there is basically no dopamine left in the striatum and there is massive cell loss in the substantia nigra. I think the best model is the one that models that, and I think that is the MPTP monkey or the more severely lesioned 6-OHDA rat. The compound that you use is irrelevant. What is relevant is the end result. What you want is a model for which there are very few fibers left in the striatum when you are intervening so that there is no upregulation of host system that will occur at that point. One more thing, since a-syn is so important in the pathogenesis, viral overexpression of a-syn is also very important. Especially for neuroprotective studies. **Ms Osborne** – I echo Dr Kordower's sentiments. 6-OHDA rat is the most recognized model for POC studies in terms of dose ranging 6-OHDA. The value of monkey: its size and its ability to mimic the human condition and to see the cell changes that you have in terms of seeing improvement. I think there is a need for both the rat and the NHP model in terms of testing.

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2. How should we approach heterogeneous cell populations for transplantation from a regulatory perspective?	**Dr Bryan** – This is an issue with many cell therapies intended to treat various disease indications. Trying to define for the product – what are the characteristics of the cells and how many different types of cells there are and which characteristics of the cells relate to efficacy and safety – is a challenge. And so, as with the preclinical models, the question of how to define the product, how to address the issue of heterogeneous cell populations, and how to control the heterogeneity to the extent feasible, are issues that the sponsors need to come and talk to us about. The earlier that sponsors come to us and talk, the better we will be able to guide them along in the efficient development, to have a product that we can have confidence regarding what the cells are, and that the appropriate animal studies were done. **Dr Kordower** – Just be careful what you wish for. We don't know what a homogenous population is in terms of its function or its safety. You might for example, need glial cells with the dopaminergic cells to get best efficacy so while I understand the need for safety in terms of a homogeneous population, a homogeneous population might not provide you the most optimal cell type.
3. Will it be possible for individuals who have Deep Brain Stimulation (DBS) to subsequently receive a stem cell transplant procedure?	**Dr Kordower** – They will not be able to be in clinical trials. That is for sure. Because previous neurosurgical interventions will be an exclusion criteria for the clinical trials. But when a cell therapy for PD is approved down the road, there is no reason why they could not receive stem cells. **Dr Bryan** – In regard to the eligibility criteria for clinical trials, we would be worried that the previous DBS would confound the interpretation of clinical trial data. That would be a concern. I won't say that we would absolutely prohibit it. It is up to the sponsor to propose eligibility criteria and present their justification, and we will consider the proposal. But certainly a previous neurosurgery that confounds the interpretation of the clinical data would be a problem. **Ms Osborne** – I concur that these would not be appropriate patients for a clinical study.

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4. In your assessment what are the scientific mechanism of action (MOA) and regulatory hurdles for dopaminergic neurons derived from human embryonic stem cells and human induced pluripotent stem cells?	**Dr Bryan** – One of the greatest hurdles is defining the product from a manufacturing standpoint, so that you can have confidence that the doses that are administered to different patients have the same characteristics with regard to safety and efficacy. **Dr Kordower** – In my view the big safety issue is teratomas. In previous studies with hESCs, teratomas have been found; however, that is a problem that is diminishing. In recent studies by Dr. Lorenz Studer's group, they have not had teratomas, but that is the biggest hurdle from a safety point of view. From an efficacy standpoint the big hurdle is innervation. This gets back to what are the best animal models. So, in a rodent if you get lots of cells to survive because the striatum is so small you can get functional recovery that would likely never occur in non human primates or occur in humans, you have been led down a path that is not an accurate one. So I think innervation from these grafts is going to be critical and needs to be tested in large animals.
5. Are there any examples/studies outside the USA that have demonstrated stem cell transplant to Substantia Nigra to have been successful acutely and long term?	**Dr Kordower** – Certainly there are studies around the world – In many places around the world. For example, in the University of Lundt, preclinical studies in rodents have been pioneering for decades (Sweden); in France there has been work done there. There has been some recently wonderful work in Japan. There is a recent study in which they grafted stem cells (using iPSCs) from an autograft. They took the fibroblasts of a monkey and put it in the same monkey (autograft) and compared it to an allograft that they took from a monkey and put it in a different monkey and found much different immunological responses. There is excellent stem cell work being done around the world. But there is also quite dubious work being done and it is difficult (especially from what is out in the internet) to be able to discern what is real and what is not.
6. What is the optimum stage of development of the transplanted cells? Should we try to mimic the fetal tissue stage since we know that they "work"?	**Dr Kordower** – We don't know that they "work". The two double blinded studies failed to meet their primary endpoints. In some patients it appears that there is a benefit. That is quite different than "we know that they work". As far as the cells, we try to mature them in ways that mimic normal development. That is the important feature. If you grab them too early, you run the risk of teratomas. If you grab them too late, you run the risk of them not surviving very well. Recent findings from Drs. Lorenz Studer's and Ole Isaacson's group, show that getting cells to survive is not going to be the critical issue.

Questions	Answers
7. How hard has it been to recruit patients in the previously executed gene therapy trials	**Dr Kordower** – In our initial trial it was not hard at all. The fact that our initial phase 2 clinical trial failed to meet its primary end point (although it met the secondary endpoints), made the second clinical trial more difficult to recruit patients. In general, most clinical trials have difficulty enrolling patients; however, we really did not struggle to get sufficient enrollment. **Ms Osborne** – In the two clinical trials I am currently involved in – one is approved but not yet accruing (first patient should be treated either in December or January), and the other clinical trial is being conducted at the NIH center and enrollment is lagging but I don't know the specifics of why. Certainly increasing the number of sites that study is conducted at could significantly impact on enrollment. **Dr Feigal** – There needs to be a balance between number of study sites and controlling the potential for variability. **Dr Kordower** - There are a number of excellent sites for neurological and movement disorders and the variability in the trials usually come from the neurosurgical side.
8. There are no approved devices for cell delivery. Would this need to be co-developed as part of a combination product – a BLA?	**Dr Bryan** – When the Sponsor submits an application to FDA, we need to have a discussion about which catheters, or other devices, they are planning to use, and the regulatory status of those catheters or devices. With regard to whether there would be co-development, whether the product (i.e., the cells and device) would be under an investigational new drug application (IND), or an investigational device exemption (IDE), we would have to consider that in the context of the specific application.

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9. Could you comment a bit more with regards to that since some of these are going to be co-developed as a combination product?	**Dr Bryan** – There is no one single way that this is done. In some cases the development of the device or catheter can be done under the IND along with the development of the cells. In other cases we have seen where the Sponsor has a separate IDE that they have filed with the Center for Devices and Radiological Health (CDRH), FDA, for the development of the device or catheter, and then they have a separate IND for the cells. **Dr Kordower** – For our gene therapy trials we just modified the Hamilton syringe and the FDA did not have much of a problem with that. For our fetal transplant trials, it was before the FDA got involved in monitoring cell replacement. We used a modified spinal cord stylet. I got the impression that as long as you do your safety/toxicology studies with devices that you are going to use in the clinic and as long as you don't have any problems, then that is ok with the FDA. But I admit this might be an oversimplification. **Ms Osborne** – From my experience with 2 previous clinical trials that required specialized devices, we have brought up the device issues in the early consultation with the FDA. Since the majority of the regulatory issues with cell therapies lie within the Office of Cell, Tissues and Gene Therapies (OCTGT), FDA, that is where the initial contact occurred. They have facilitated consult jointly and independently with individuals at CDRH. So as we have had specific design considerations, we have had the opportunity to be advised by CDRH reviewers. The use of the devices has occurred under the IND, not a separate IDE. Essentially, all of the information that would have been supplied under the IDE including the hazard analysis and the performance control for that device was included in the IND. There is precedence and guidance on this. There is a draft guidance on combination products that dates back to early gene therapy trials. It is actually more efficient than it sounds. **Dr Bryan** –I want to emphasize that it is very important that the preclinical studies use the devices and catheters that are planned to be used in the clinical studies, if it is feasible. We understand it is sometimes not feasible because of the size of the animals. If the device is novel, then we may ask for separate studies in a large animal to evaluate the safety of the device.
10. How does the FDA regulate stem cell trials?	Many stem cell clinical trials are regulated under section 351 of the Public Health Service (PHS) Act, and require an Investigational New Drug Application (IND). However, the regulations that apply to a stem cell clinical trial depend on the specific product and indication.