

NON-TECHNICAL ABSTRACT

We are proposing a gene therapy trial for Temporal Lobe Epilepsy (TLE). Although we remain ignorant of the specific cause of the vast majority of the human epilepsies including TLE, current understanding of what goes wrong in TLE has focused on a specific region in the brain called the hippocampus, which is part of the temporal lobe, hence the name TLE. We know that the main problem in epilepsy is that cells in the region of the hippocampus where the seizures start are too excitable, and can just spontaneously become active, and recruit other cells to be active with them. It is the synchronous activity of a group of cells in the brain that results in a seizure. Although this excitability can be dampened down with many of the currently available anti-epileptic drugs (AEDs), about a third of people with TLE still have frequent and disabling seizures despite the best AEDs including all combinations. This warrants the consideration of additional, potentially non-drug therapies. The approach which has shown the most promise and best efficacy to date is surgical resection, that is an operation that removes this entire brain region. In carefully selected people, this surgery can work remarkably well, with up to a 70 or even 80% success rate (defined by seizure-free status) in the first year or two, although in about 20-40% seizures do reoccur over the ensuing years. Despite the efficacy of surgery for epilepsy, this is by no means a cure, and it does come at a cost. There are significant risks associated with removing this part of the brain, not least that the majority of individuals will suffer some cognitive loss. This is more marked if the left side of the brain is removed, but even on the right (non-dominant) hemisphere, there can be some loss of memory and mental sharpness. In addition, a significant number of people cannot undergo the procedure because testing suggests that they are very dependent on that part of the brain for normal functioning. Finally, the effect as discussed above appears to wear off over time in a significant subset of people. We believe that we can achieve the same effect as removing part of the brain by delivering a gene that dampens activity in that region. Essentially, what we are proposing is to use a specially engineered harmless virus, which carries a genetic payload. This virus, called AAV, will be injected into the involved brain region, and we hope that it will reduce the excitability of the brain, thereby stopping seizures similar to surgical removal. This gene is called NPY, standing for Neuropeptide Y, and it is one of

the brain's own anti-convulsants. The major advantage of our approach compared to surgical resection is therefore that we do not have to remove a chunk of brain which contains some healthy functioning cells as well as the cells responsible for the epilepsy. Secondly, it is a simpler and much easier procedure with less surgical risks than the much more invasive resection. Finally, the protocol that we are planning is to "piggy-back" on a procedure that these individuals have already consented to. That is, this subgroup with TLE require the implantation of depth electrodes, that is electrodes which need penetrate the brain, to be able to monitor the EEG from deep sites. This is necessary because the standard EEG measuring was not able to localize the part of the brain responsible for the seizure origin in these individuals. Hence, our protocol adds minimal risk and does not require any additional surgery. The NPY gene has no known specific toxicity, nor is its increased expression likely to result in untoward complications, moreover this intervention has a major safety valve, the surgical removal of the part of the brain where the gene goes is the standard therapy for this type of epilepsy and these specific patients have already agreed to undergo this surgery as a therapeutic procedure. Hence, we believe that this study has major advantages in terms of both the potential for patient benefit regardless of the success of the study as well as minimizing risk. This will represent an important first step of gene medicine to help in the treatment of epilepsy.