

Interview with Dr. Jan A. Nolta about Stem Cells

One of the most exciting potential therapeutic approaches moving through the HD research pipeline is stem cell treatment and Dr. Jan A. Nolta is in the forefront of the research. Dr. Nolta is the Director of the Stem Cell Program at UC Davis School of Medicine, and directs the new Institute for Regenerative Cures, a facility supported by the California Institute for Regenerative Medicine (CIRM).



Dr. Nolta is planning a Phase I clinical trial of mesenchymal stem cells to start at the end of 2010. The FDA has asked for a toxicology study which is now underway. After the results have been obtained, Dr. Nolta will file an Investigational New Drug (IND) application with the FDA. When approval is granted, the trial will begin.

The trial's clinical director will be Dr. Vicki Wheelock, associate professor of neurology and medical director of the UC Davis Movement Disorders Clinic. Participants will be seen in Dr. Wheelock's clinic. An external board is in the process of refining the criteria for participation and will do the selecting of volunteers.

Funding for work leading up to the trial comes from the California Institute for Regenerative Medicine and private donors. Dr. Nolta commends the Huntington's Disease community for advocacy in creating interest in the development of treatments for Huntington's Disease among CIRM officials. "HD family members attend every public meeting," Dr. Nolta said.

Mesenchymal stem cells are derived primarily from bone marrow. They will be injected into the brain using tiny catheters. Once in the brain, they act as nature's paramedics, traveling towards damaged or dying cells. They actually 'query' each cell and if a chemical signal is received indicating that the cell is in trouble, they merge with the cell and heal and protect it through neurotrophic factors which are found naturally within the stem cells. One neurotrophic factor BDNF, known to be reduced in the HD brain, is not found in the mesenchymal stem cell and Dr. Nolta is working with colleagues in Barcelona to find a way to add BDNF to these stem cells.

The mesenchymal stem cells come from healthy donors. There is no need for tissue matching since these cells shield themselves from the immune system. This is important since the reaction from the immune system was a problem in the fetal cell transplants of a decade ago.

The Phase I trials will involve just the mesenchymal stem cells. Future trials will include short interfering RNA (siRNA) to silence the HD gene. The mesenchymal stem cells will inject the siRNA into the cell nucleus using a tunneling nanotubule.

Evidence has been accumulating that the normal huntingtin's protein is needed throughout life so it does not seem prudent to use a technique which would completely

shut down production of both the normal and the mutant gene. Although the HD gene is dominant in producing the disease, both alleles express themselves. This technique reduces the expression of each protein by fifty percent or less. The idea is that lower levels of the HD protein will reduce toxicity but enough normal protein will remain in the cells to do its work.

Eventually, an allele-specific approach may be employed. This will be an individualized therapy where both copies of the individual's gene are analyzed for single nucleotide polymorphisms (SNPs). Most people with a normal and HD gene have an SNP in the HD gene but it varies from person to person. This minor genetic change is meaningless in itself but researchers have shown that siRNA can be designed to recognize and target only the HD gene based on this difference.

The mesenchymal stem cells are not expected to replace missing neurons, but Dr. Nolte and her colleagues are also working to overcome challenges so develop stem cell treatments which can.

There are two other trials involving mesenchymal stem cells injected directly into the brain. One U.S. trial is for traumatic brain injuries. A trial in Italy is for ALS. The Phase I trial was promising and Phase II is now underway.

Dr. Nolte is encouraged by the progress made so far and the future of stem cell and RNAi therapies. "What makes us so hopeful about the research going on in our lab and many other labs is that now we know what we are up against and we have incredible tools to attack this protein."

Source: interview

- *Marsha L. Miller, Ph.D., September 2, 2009*