

RNA Interference in a Clinical Trial for Melanoma Patients

The HD community has been following RNA interference (RNAi) ever since Dr. Beverly Davidson achieved a reduction in protein expression in a mouse model for spinocerebellar ataxia in 2004 and then for Huntington's Disease in 2005. Currently there is no way to change the DNA code to make the HD protein but the idea behind RNAi is to prevent those instructions from going out.

The potential of this technique to become a virtual cure is clear but there are many challenges to be overcome and more to learn before RNA interference can become a treatment. We have reported on advances by those working in Huntington's Disease research but now there is exciting RNAi news from researchers developing a cancer treatment.

Researchers from Alnylam Pharmaceuticals have reported on a Phase I clinical trial with cancer patients with solid tumors. They used a nanoparticle delivery system which consisted of a tiny polymer, a human transferring protein (TF) targeting ligand on the outside of the nanoparticle to target the TF receptors on the surface of the cancer cells, a hydrophilic polymer to stabilize the nanoparticle, and short interfering RNA (siRNA) designed to reduce the expression of the M2 subunit of ribonucleotide reductase (RRM2) a well-established anti-cancer target.

The trial is not over but they have some important news which is of interest to the HD community. Three melanoma patients with three different dosage levels of the nanoparticles donated tissue for biopsy before and after treatment. The third patient, the one with the highest dosage, donated tissue before and after two cycles of treatment.

The researchers found nanoparticles inside cells in all of the treated tumors, at amounts corresponding with the dosage. They found reductions in both the messenger RNA of RRM2 as well as reductions in levels of the RRM2 protein. Most important they found a fragment of RRM2 messenger RNA which was cleaved exactly one would expect if the siRNA methodology was working.

This is the first study to confirm that siRNA works by the expected mechanism in humans. That is important because it is possible that a treatment might work in a different way than expected. The authors cite a mouse study which showed that the RNAi treatment for an eye disorder worked, but not through interfering with messenger RNA. If that is the case, it would make sense to discover or develop a drug to activate that other pathway instead.

This proof of principle study is encouraging because it suggests that siRNA is continuing its movement throughout the pipeline of potential treatments.

Reference:

Mark E. Davis, Jonathan E. Zuckerman, Chung Hang J. Choi, David Seligson, Anthony Tolcher, Christopher A. Alabi, Yun Yen6, Jeremy D. Heidel and Antoni Ribas
“Evidence of RNAi in humans from systemically administered siRNA via targeted nanoparticles.” Nature. 2010 Mar 21. [Epub ahead of print]

- *Marsha L. Miller, Ph.D., March 30, 2010*