RNAi Safety Studies in Primates

As we move closer to clinical trials of gene silencing, two recently published studies offer information about the safety of RNA interference.

Dr. Beverly Davidson, University of Iowa Carver College of Medicine, and colleagues recently reported on an RNA interference safety study in primates. They used an adeno-associated viral vector to administer micro-interfering RNA (miRNA) via a stereotaxical (3-dimensional guidance system) injection to rhesus monkeys. The monkeys had normal huntingtin protein genes; they were not animal models of Huntington's disease.

The animals were followed for six months. A 45 percent reduction of the huntingtin protein was achieved in the mid- and caudal putamen. No motor deficits, neuronal degeneration, astrogliosis, or immune response were detected.

Medtronics scientist Dr. William Kaemmerer and colleagues have just published their own findings in a RNA interference primate study. A serotype 2 adeno-associated viral vector was used to deliver short hairpin-interfering RNA via a sterotaxical injection to four rhesus monkeys. Four additional monkeys received scrambled short hairpin RNA as a control. The monkeys had normal huntingtin protein genes.

The primates were followed for six months. A 30 percent reduction of the huntingtin protein was achieved in the striatum and a 45 percent reduction was achieved in the putamen of the monkeys in the experimental group. Neither group of monkeys experienced neurodegeneration. Adverse effects were not found in either group. The use of short hairpin RNA resulted in toxicity in a mouse study previously conducted by other researchers, but was not found in this primate study.

In both cases the RNA silencing sequences were non-allele specific; that is capable of silencing both a normal and a Huntington's disease gene. The theory behind non-allele specific gene silencing as a potential treatment is that a reduction in the amount of HD protein would allow the cell to better handle the pathogenic processes it causes; at the same time, the remaining amounts of HD and normal protein would be sufficient to carry out its functions.

Because the normal huntingtin protein has important functions in the cell, some researchers have argued that allele-specific gene silencing should be undertaken. As researchers such as Dr. Robert Friedlander, University of Pittsburgh Medical School, and Dr. Neal Aronin, University of Massachusetts School of Medicine, have shown in cell models, selective targeting of the HD gene can be achieved through the use of single nucleotide polymorphisms (SNPs)13 that differentiate between the normal and the HD genes. Several different SNPs have been found in the HD patient population.

Dr. Kaemmerer agrees that the concerns about reduction of the normal huntingtin protein are legitimate but finds the results of his own study to be encouraging. He does, however, point out that a small number of animals were only followed for six months, roughly comparable to 18 months in human life. It could be that side effects might show up later on or it could be that there were negative results that were too small to detect in the sample size.

Dr. Davidson points out in her article that the allele-specific strategy has not been tested in a primate model and that approximately 20 percent of HD patients do not have targetable SNPs differentiating the normal from the HD alleles.

Whether the plans go forward for allele or non-allele specific RNA interference, the Davidson and Medtronic studies provides important safety information about the reduction of the normal protein and about the methodology used that will be needed to get FDA approval for clinical trials.

Several pharmaceutical companies are working on RNA interference therapy for Huntington's disease. These include Lundbeck, Alnylam, and Prosensa, a Dutch company. Isis is developing an antisense therapy which also silences the gene.

References:

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