In 2012, twenty-two rhesus macaque monkeys — including r04040 — at the Wisconsin National Primate Research Center were subjects in an important trial of a promising treatment for Parkinson's disease. The study was conducted by medical physics professor Marina Emborg, and was funded by the Michael J. Fox Foundation for Parkinson's Research and the National Institutes of Health.

A protein called glial cell line derived neurotrophic factor (GDNF) protects and even repairs neurons in victims of Parkinson's disease, stroke and other brain maladies — but only when delivered directly into the brain via surgery that pierces the skull.

GDNF cannot cross the blood-brain barrier, a protective filter that keeps potentially dangerous molecules from reaching brain tissue. As a result, researchers are looking for ways to trick the blood-brain barrier into accepting GDNF, including a "Trojan horse" technique that couples the GDNF protein with another protein. In the case of this trial, that Trojan horse protein was human insulin receptor monoclonal antibody (HIRmAb).

The HIRmAb-GDNF combo was meant to fool the blood-brain barrier's insulin gateway into accepting GDNF, allowing the brain-saving protein to be delivered by IV needle. The technique had worked in experiments with rodents, but rodent insulin receptors differ from insulin receptors in primates.

The experiment r04040 was involved in showed that HIRmAb-GDNF did not fool the primate blood-brain barrier. The animals were euthanized at the end of the study, and samples showed none of the monkeys had a meaningful amount of GDNF in their brain tissue.

At the outset of the study, the monkeys were injected with a neurotoxin called MPTP. The injections damage neurons, leaving the monkeys with Parkinson's symptoms. This makes them a model for the disease in humans, allowing for research that has added to what we know about diagnosing, preventing and treating Parkinson's.

The monkeys' fine motor skills, slight tremors, slow movement and balance problems did not improve during the study, and their health went in the wrong direction.

They developed allergic reactions to the drug that required veterinary care during the study, but more serious results were uncovered during thorough examinations by a veterinary pathologist after the monkeys were euthanized. Four of the seven monkeys who received GDNF treatment had lesions on the pancreas. In humans, these lesions are a precursor to pancreatic cancer.

This result revealed the danger HIRmAb-GDNF may pose for human patients, damage it may have caused for 12 women who had volunteered for a human trial that was in the planning stages when r04040's study was done. The study's publication is a clear warning for other researchers who may have explored this avenue as a Parkinson's treatment.

It may also give new life to pancreatic cancer research. Before this study, there was no primate model for pancreatic cancer. But the unexpected results may mark HIRmAb-GDNF as a way to induce pancreatic cancer symptoms in non-human primates, giving scientists the opportunity to identify and test new methods of treatment for and early discovery of pancreatic cancer without endangering human patients in the process.

The study was published in June of 2012 by the journal PLOS ONE under the title “A Monoclonal Antibody-GDNF Fusion Protein Is Not Neuroprotective and Is Associated with Proliferative Pancreatic Lesions in Parkinsonian Monkeys.”

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