



# MANHATTAN CAT SPECIALISTS

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## Gene Therapy

Gene therapy can be defined as the introduction of new genetic material into a living cell or organism for therapeutic purposes. Traditionally, we administer medication to patients in order to achieve a therapeutic response. Gene therapy, on the other hand, is a novel approach in that it allows a patient to “manufacture” its own treatment.

Before gene therapy can be applied to cats, the feline genome must be mapped. Recently, the University of Missouri selected a cat that will serve as the genetic model for all cats in the feline genome project. The cat, named Cinnamon, is the offspring of two Swedish purebred Abyssinian cats. Cinnamon has a long and well-documented pedigree. The cat's blood will be used to map the feline genetic structure, allowing for each gene's function to be studied in detail. “I'm extremely enthusiastic about the cat genome being sequenced”, says Kristina Narfstrom DVM, PhD, endowed professor of University of Missouri's veterinary school. “This will simplify the search for specific gene defects causing various forms of hereditary disease in cats”. Once it is determined which genes are responsible for specific diseases in the cat, such as blindness or cancer, affected cats and carrier cats can be detected in the cat population by performing simple blood or tissue tests. “Knowledge of specific gene defects may give rise to the next, very exciting step, that of treatment” says Dr. Narfstrom.

Cats are an excellent animal model for human genetic diseases because their genetic makeup has remained fairly consistent over time. Cats, as a species, haven't had the extensive crossbreeding that dogs have had over the centuries. In fact, scientists believe that the canine genome has been scrambled at least fourfold, as humans have deliberately modified canine behavior for uses such as herding or hunting. This is not so for cats. In fact, cats have the most highly conserved gene order of all mammals. The consistent makeup over the ages simplifies the job of sequencing the genome.

Gene therapy is a relatively new science. In 1990, the first two approved gene therapy trials were performed in the United States. Though both trials were unsuccessful, it started a wave of research and clinical trials. In 1999, the death of a young patient that was being treated for a liver enzyme deficiency was a major setback however, just one year later, the first two successful clinical trials using gene therapy were reported – one for SCID (severe combined immunodeficiency, a.k.a. the “bubble boy” syndrome) and the other for hemophilia B. Since then, there have been hundreds of clinical trials, most focusing on cancer research. In veterinary medicine, only a few successful gene therapy trials have been reported. For example: treatment of hemophiliaB in five dogs, restoration of vision in three briards with a hereditary retinal disorder, and disease regression and prolonged survival in

12 dogs with malignant melanoma. In cats, gene therapy has been used to treat genetic conditions such as mucopolysaccharidosis and lipoprotein lipase deficiency. "Hereditary diseases of the eye are especially amenable for gene therapy", says Dr. Narfstrom. "I have treated a retinal disease of dogs that have been blind since birth by using corrective gene therapy. My plan is to also perform corrective therapy in Abyssinian cats when the gene defect for PRA (progressive retinal atrophy) has been elucidated".

Genes can be transferred either by introducing them directly into a patient's cells (for example, injecting into a tumor), or by removing cells from a patient (such as bone marrow), introducing the gene, and then returning the cells back to the patient. For the gene to be transferred successfully into the patient's cells, a vector (an agent or carrier) is required. Most gene therapy clinical trials have used viruses as vectors for gene transfer. Viruses are ideal vectors because they're skillful at entering cells, traveling to the cell's nucleus, and "hijacking" the cell's genetic material so it can make more copies of its own genes. Viral vectors are currently the most efficient means of transferring genetic material into a cell.

One potential application of gene therapy that is currently being investigated is the use of viral vectors to deliver the erythropoietin gene to cats. Erythropoietin is a hormone, produced by the kidney, that instructs the bone marrow to produce red blood cells. Often, when cats are in kidney failure, their damaged kidneys produce an inadequate amount of this hormone. As a result, many cats with kidney failure become anemic. The anemia leads to weakness, lethargy, and poor appetite. The anemia can be treated with injections of human erythropoietin, however, in a significant number of cats, their immune systems recognize this protein as being foreign, and they make antibodies against it, rendering the erythropoietin ineffective. In addition, these antibodies cross-recognize the cat's own erythropoietin and neutralize it as well. When this happens, the anemia becomes immediately life-threatening and a transfusion is necessary to save the cat's life. At this point, most cat owners elect euthanasia. By devising a method of delivering more copies of the feline erythropoietin gene to cats that are deficient in this hormone, the need for frequent injections of foreign protein can be avoided. The erythropoietin gene is an ideal candidate for gene therapy because the hormone does not have to be produced at the original site (the kidney). This means that the DNA can be inserted in a more easily accessible tissue, such as muscle. And the activity of the inserted gene can be easily monitored: if the gene is working, the red blood cell count will increase. This can be measured easily and inexpensively.

Despite the promise of gene therapy, concerns about safety and efficacy remain, as relatively little is known about the durability of the transferred genes, and the practicality of repeated gene therapy treatments. There are also ethical considerations. Although there have been few clinically applicable treatments thus far, once the feline genome is completely mapped, the potential for treatment of inherited and acquired genetic disorders is limitless.