Bellwether Magazine

Volume 1
Number 55 *Winter 2002*

Article 2

Winter 2002

# First Successful Multi-Organ Gene Therapy

Stephen Bradt
*University of Pennsylvania*

School of Veterinary Medicine
UNIVERSITY OF PENNSYLVANIA

# Bellwether

No. 55 • Winter 2002

THE NEWSMAGAZINE OF THE UNIVERSITY OF PENNSYLVANIA SCHOOL OF VETERINARY MEDICINE


## Inside

4 A Glimpse into the Future
10 Mitochondria Stress
14 Phosphorus Management
16 2002 Huidekoper Society Dinner
19 Rosettes and Ribbons
24 CDC Veterinarians
26 V.M.D. Notes


21 Twin degrees


31 Open House

*Cover Story*

# Gene therapy treats a disease affecting multiple organ systems

*By Stephen Bradt*

For the first time, researchers have successfully used gene therapy to treat a disease that affects organs throughout the body of a large animal.

The study, led by **Dr. Mark E. Haskins, V'69,** of the School and Dr. Katherine Parker Ponder of the Washington University School of Medicine in St. Louis, involved dogs with a rare disorder in which an enzyme deficiency causes clouding of the corneas, cardiac disease and bone abnormalities leading to loss of mobility by six months of age. Newborn dogs treated with hepatic gene therapy maintained near-normal mobility throughout the 17-month study and showed little evidence of the other debilitating signs normally associated with the disease.


**Dogs with the genetic disease mucopolysaccharidosis VII and a diagram of the retroviral vector used in intravenous neonatal gene therapy. The untreated 5 month-old dog on the right is unable to stand. The 17 month-old dog on the left, treated at 3 days of age, can stand and run and has not developed most signs of the disease.**

Cover photo and this photo by James E. Hayden, RBP, FBCA, Bio-Graphics.

"While gene therapy has been used previously in dogs, this is the first use to treat a disorder affecting multiple organ systems throughout the body," said Haskins, professor of pathology and medical genetics at the School. "Previous applications of gene therapy in dogs have targeted disorders affecting a single bodily function, such as vision or blood clotting. Like many diseases that we might eventually like to treat with gene therapy, this one has complex, multisystemic effects."

The experiments involved seven dogs with mucopolysaccharidosis VII, a disorder in which the enzyme β-glucuronidase is deficient in activity. Also known as Sly syndrome, MPS VII is among a constellation of lysosomal storage diseases; in humans, such disorders include Tay Sachs disease and Gaucher disease.

"In theory, the approach should be applicable to other lysosomal storage diseases, with the exception of those that affect the central nervous system," said Ponder, associate professor of medicine and assistant professor of biochemistry and biophysics at Washington University. "We're hopeful that the approach might also be applicable to hemophilia."

Lysosomal storage diseases such as MPS VII can be treated through enzyme replacement therapy, but that approach requires regular intravenous injections and is prohibitively expensive. Bone-marrow transplantation is another option but is risky, and compatible donors are often unavailable.

MPS diseases affect 1 in 27,000 live births among humans, but the disease is debilitating for patients and emotionally wrenching for their families. Human symptoms include growth retardation, mobility problems, facial deformities, corneal clouding, liver and heart valve abnormalities and mental retardation, among others. Most patients die in childhood.

"The gene therapy research of Drs. Haskins, Ponder and collaborators involving MPS VII dogs has significant implications for all MPS disorders," said Barbara Wedehase, executive director of the National MPS Society, an organization of parents of children with MPS. "Their current and ongoing research will provide new insights into the treatment of individuals affected with these devastating disorders."

In these experiments, two- to three-day-old dogs with MPS VII received four injections of a retroviral vector expressing canine β-glucuronidase. The vector used was made from the Moloney murine leukemia virus with a liver-specific promoter; at several days of age, canine liver growth is so rapid that transduction occurs readily and β-glucuronidase is secreted continuously into the bloodstream.

The enzyme's activity was subsequently found at normal, stable levels for up to 14 months in the treated dogs; one dog has produced 60 times normal enzyme for 17 months. Unlike other dogs with MPS VII, the treated dogs gained weight normally, attaining nearly 90 percent the weight of their unaffected littermates, and avoided the serious side effects normally associated with lysosomal storage diseases. The β-glucuronidase gene does not appear to have been inserted into the germ line.

Haskins and Ponder were joined in the research by **Drs. John R. Melniczek, V'92**, **Margaret A. Weil**, **Thomas M. O'Malley**, **Patricia A. O'Donnell**, **Van W. Knox**, **Hamutal Mazrier**, **N. Matthew Ellinwood**, **Meg Sleeper, V'93**, **Susan W. Volk, V'95**, **Jean Zweigle** and **John H. Wolfe, V'82** of Penn's School of Veterinary Medicine; Albert M. Maguire of Penn's School of Medicine; Lingfei Xu and Robert L. Mango of Washington University's School of Medicine; and **Gustavo D. Aguirre, V'68** of Cornell University's College of Veterinary Medicine. The work was funded by the National Institutes of Health.