Bellwether Magazine

Volume 1
Number 68 *Spring 2008*

Article 9

Spring 2008

Alumni Profile: Albee Messing, V'78, GR'82

Nancy West
University of Pennsylvania

Albee Messing, V'78, GR'82

Research Leads to Breakthrough in Neurologic Disorder

BY NANCY WEST

Albee Messing was always more interested in human disease than animal disease. In fact, he readily admits that he was somewhat intimidated by any animal larger than a mouse. So why did he end up at Penn Vet? Always a researcher at heart, he recognized that Penn's Veterinary Medical Scientist Training Program would provide him with the best broad-based integrated training in medicine to support the research he wanted to do in neuropathology.

"Penn was a great place to study comparative neuropathology with people like Nick Gonatas, MD, professor, Department of Pathology and Laboratory Medicine, at the medical school, and the late **Jack McGrath, V'43**, at the veterinary school, who was one of the leading neuropathologists of that generation," notes Dr. Messing, who received an undergraduate degree in biology from Yale University. "The exceptional flexibility of the combined degree program enabled me to focus on neuropathology and develop it as my clinical specialty."

After receiving his veterinary medicine degree summa cum laude and completing his doctorate in experimental pathology, Dr. Messing pursued a post-doctoral fellowship in neuropathology with Dr. Gonatas. During this time, he also began to collaborate with the laboratory of **Ralph Brinster, V'60, GR'64**, Richard King Mellon Professor of Reproductive Physiology at Penn Vet, on brain tumors and peripheral nerve research involving transgenic models, a collaboration he continued after accepting a position as assistant professor of pathology at the University of Wisconsin–Madison School of Veterinary Medicine in 1985.

In his lab at Wisconsin, Dr. Messing eventually shifted the focus of his research to the central nervous system when he began to study a gene that makes glial fibrillary acidic protein (GFAP). This protein is found in the astrocyte, a type of glial cell that supports and nourishes neurons in the brain and spinal cord. If these nerve cells are injured through trauma or disease, astrocytes react by rapidly producing more GFAP. Through manipulation of the GFAP gene expression, Dr. Messing made transgenic mice, some with too much GFAP and some with none. "We were curious about how this would affect astrocyte function because scientists generally blamed astrocytes for the inability to recover following a CNS injury," he explains.

Dr. Messing's transgenic mice led to a breakthrough discovery. "The mice with too much GFAP formed abnormal aggregates of protein in the astrocytes called Rosenthal fibers," he relates. "That's where the value of my combined degree training became very apparent. I had learned about Rosenthal fibers in diagnostic neuropathology. You see them sporadically in a number of diseases, but when you see them abundantly and throughout the CNS, it's really diagnostic of only one disease in neuropathology—a rare disorder called Alexander disease."

Alexander disease, a leukodystrophy, is a progressive and usually fatal neurological disorder in which the destruction of white matter in the brain is accompanied by the formation of Rosenthal fibers. The most common type of Alexander disease is the infantile form, which typically has an onset during the first two years of life. Usually there are several types of developmental delays, both mental and physical, followed by loss of milestones, an abnormal

increase in head size, and seizures. The juvenile form, which has an onset between ages 2 and 13, is less common, and adult onset forms are even more rare.

"Alexander disease had been presumed as a genetic disorder but no one had any clue what gene was responsible for it," explains Dr. Messing, who is now faculty core director, Rodent Models Core, and professor, comparative biosciences, at the University of Wisconsin's Waisman Center. "Because we had essentially recreated one of the hallmark features of the disease simply by changing expression of the GFAP gene, we put that forward as a candidate for the gene responsible for the disorder."

During the ensuing four years, Dr. Messing's lab assembled the world's largest collection of Alexander disease samples, and found that greater than 90 percent of patients with the disorder have mutations in the GFAP gene. For a time, his lab was the world resource for genetic testing for Alexander disease. With such striking results, the testing quickly moved from the lab into standard clinical practice.

"I'm very gratified that we discovered something that's really made a contribution to this disorder and a difference in people's lives," Dr. Messing reflects. "Alexander disease takes over the world of these patients and their families.

> "The exceptional flexibility of the combined degree program enabled me to focus on neuropathology and develop it as my clinical specialty."

Getting a clear diagnosis really matters to these parents. Ultimately, we hope to develop a treatment, and we've already started working toward that challenging goal."

Going forward, Dr. Messing's research may have implications for a broader spectrum of neurologic and neurodegenerative disorders, including epilepsy, Alzheimer's disease and Parkinson's disease. "Astrocytes are increasingly viewed by the scientific community as central players in a variety of neurologic disorders," he emphasizes. "We'd like to learn how astrocyte dysfunction contributes to Alzheimer's and Parkinson's, as well as Alexander disease, and ultimately, how to modulate and possibly improve astrocyte function and protect these cells from injury."

Penn Vet Alumnus Part of Major Stem Cell Breakthrough

James Thomson, V'88, developmental biologist and anatomy professor at the University of Wisconsin–Madison, was part of a team of researchers who discovered how to turn human skin cells into what appear to be embryonic stem cells without having to create or destroy an embryo. The finding is a critical scientific accomplishment that potentially will make human embryos unnecessary in obtaining blank-slate stem cells capable of becoming any of the 220 cell types in the human body.

In the new study—the results of which appear in the December 21, 2007 issue of *Science*—Dr. Thomson and his colleagues introduced a set of four genes into human fibroblasts (skin cells easy to obtain and grow in culture) to induce the skin cells into a pluripotent state, a condition essentially the same as that of embryonic stem cells. In addition to eliminating ethical and political issues from the stem cell debate, using reprogrammed skin cells allows for customization to the patient.

"The induced cells do all the things embryonic stem cells do," explains Dr. Thomson. "It's going to completely change the field."

Although Dr. Thomson is encouraged that the new cells will speed up new cell-based therapies to treat disease, more work is required, he says, to refine the techniques through which the cells were generated to prevent incorporation of the introduced genes into the genome of the cells. In addition, to ensure their safety for therapy, methods to remove the vectors—the viruses used to ferry the genes into the skin cells—must be developed.

Dr. Thomson, who studied in the laboratory of **Dr. Ralph Brinster** while at Penn Vet, also was the first scientist to coax stem cells from human embryos in 1998.