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Research Briefs

Ralph Brinster to Receive Gairdner Foundation International Award

Dr. Ralph L. Brinster, V'60, the Richard King Mellon Professor of Reproductive Physiology, will be awarded the Gairdner Foundation International Award on October 26, 2006 in Toronto. Dr. Brinster is receiving the award for his "pioneering discoveries in germ line modification in mammals."

First awarded in 1959, the Gairdners are among the most prestigious international awards in medical research, recognizing outstanding contributions by medical scientists whose work will significantly improve the quality of life. Among the 279 Gairdner winners during the past 46 years, 65 have gone on to win the Nobel Prize.

Dr. Brinster's research career is noted for many achievements in the field of reproduction, genetics and stem cell biology. In particular, Brinster has been a leader in the biology of germ cells. Early in his career, he established techniques to grow and manipulate eggs, and later used these methods to generate genetic changes in mice and other animals. More recently, Dr. Brinster has created a technique of altering genes in spermatagonial stem cells.

"Ralph Brinster is truly a trailblazer in the field of gene modification in animals," said **Dr. Joan Hendricks, V'79, GR'80**, dean of the School. "His early findings helped usher in the era of transgenic research and its many medical and scientific benefits, while his current work is at the forefront of stem cell medicine."

Dr. Brinster is the sixth Penn faculty member—and the first from the School of Veterinary Medicine—to win a Gairdner, a list that includes Clay Armstrong (2001), Baruch S. Blumberg (1975), Britton Chance (1972), Daniel J. McCarty (1965) and John H. Gibbon (1960), all from the School of Medicine.

"Bubble Bassets" Cured of Genetic Disorder

Researchers from Penn Vet have found a way to cure basset hound puppies of a deadly immune disorder, a victory that could eventually change the way the disease is treated in humans.

The disease, X-linked severe combined immunodeficiency, or XSCID, first received public attention with "Bubble Boy" David Vetter, a victim who could survive only in an isolated, germ-free environment. Today, the disease affects one in every 100,000 boys and often proves fatal before the age of one year.

Although XSCID has been treated in the past through a gene therapy technique in which bone marrow is taken out of a patient, treated with the corrective gene, then placed back in the body, the Vet School team used a different approach, injecting the corrective gene directly into the bloodstream of the pups.

"Although ex-vivo gene therapy has been shown to be capable of restoring normal immune function in XSCID boys, there are several potential problems with this approach," said **Dr. Peter J. Felsburg, V'69**, professor of immunology, who led the team that included researchers from the National Institute of Allergy and Infectious Disease. "The number of gene-corrected bone-marrow stem cells that can be transplanted back into the patient is limited to correcting the potentially low number of bone-marrow stem cells harvested from the patient. In addition, the manipulation and culturing of the cells outside the body may alter their ability to provide for long-term generation of new immune cells."

This procedure, the team says, could prove to be both a more effective and more efficient treatment of the disease in years to come.

By Air—and Water

A recent discovery of five fossils in northwestern China provides an important link between ancient and modern birds. The fossils indicate that early birds probably evolved

rosettes&ribbons has moved on-line!

Effective this issue, *Rosettes & Ribbons*, which highlights faculty and staff accomplishments, is now being offered on-line. We are very excited by this new format, which allows us enhanced content flexibility, more up-to-date listings and a wider reach. Be sure to check it out at **www.vet.upenn.edu/bellwether/rosettes.shtml!**

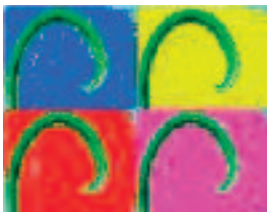
Reconstruction of the Early Cretaceous amphibious bird *Gansus yumenensis*, in a lake in China. *Gansus* demonstrates that the ancestors of today's birds may have been semiaquatic in habit. *Illustration by Mark A. Klingler/CMNH.*

in a watery environment and were similar to modern-day ducks or loons. The bone structure and webbed feet of the specimens—called *Gansus yumenensis* for the province in which they were found—indicate that they swam and took flight from the water. Though no skulls were found, it seems likely that that these duck-like early birds ate fish, insects and the occasional plant.

"*Gansus* is very close to a modern bird and helps fill in the big gap between clearly non-modern birds and the explosion of early birds that marked the Cretaceous period, the final era of the Dinosaur Age," said **Dr. Peter Dodson**, professor of anatomy, who discovered the fossils with three former students.

A Jekyll-and-Hyde of Cytokines: IL-25 Promotes and Limits Inflammatory Diseases

The same signal responsible for promoting the type of immune responses that cause asthma and allergy can also limit the type of inflammation associated with debilitating diseases like inflammatory bowel disease, arthritis and multiple sclerosis, according to Penn Vet researchers. The team discovered how IL-25, a signaling protein known as a cytokine, prevents destructive inflammation and promotes immune responses associated with asthma and allergic responses.



The findings, which appear in the April 2006 *Journal of Experimental Medicine*, suggest that manipulating IL-25 could provide a method to treat a wide variety of chronic inflammatory diseases.

"It appears that IL-25 has a Jekyll-and-Hyde personality: it can be helpful or hurtful depending on how it interacts with T helper cells, a subset of immune cells that influences inflammatory responses," said **Dr. David Artis**, assistant professor of parasitology and senior author of the study. "These studies show that IL-25 promotes type-2 T helper cells that drive the type of response required for eradicating worm infections and causing asthma. Importantly, IL-25 can simultaneously limit destructive inflammation caused by inflammatory T helper cells commonly found in diseases like inflammatory bowel disease, arthritis and MS."

These results also support the notion that the immune response that causes allergies and asthma is an evolutionary hangover resulting from mankind's historical fight with parasitic worm infections. That is, a type-2 response once useful in fighting worm infections has now become a dangerous menace, causing inflammatory responses to commonly encountered environmental antigens. About 30 percent of Americans suffer from the negative effects of type-2 inflammation: asthma and allergies, which result from an inflammatory response to factors encountered in the environment, whether industrial air pollutants or peanut-oil molecules.

Funding was provided by the National Institutes of Health, the Crohns and Colitis Foundation of America's William Shelby Modell Family Foundation Research Award, the Irvington Institute for Immunological Research Postdoctoral Fellowship and Schering-Plough Biopharma.

New Treatment at Ryan Veterinary Hospital for Feline Saddle Thrombus

In July 2006, the Matthew J. Ryan Veterinary Hospital Emergency Service, in tandem with Ryan's Interventional Radiology Service, began offering rheolytic thrombectomy for the treatment of certain blood clots encountered in veterinary patients. The AngioJet Thrombectomy Device historically has been used to remove blood clots in humans. Recently, rheolytic thrombectomy was described for the treatment of feline distal aortic thromboembolism, with encouraging initial results. This procedure involves placement of a specialized catheter through the carotid artery and into the saddle thrombus using fluoroscopic guidance. Once in place, the thrombus is fragmented and evacuated, restoring perfusion to the limbs.

Saddle thrombi secondary to heart disease in our feline patients is a frustrating disease historically associated with extreme patient discomfort and a grave prognosis. The researchers' current study will focus on aggressive, rapid removal of these thrombi as soon as possible with concurrent management of the underlying cardiac disease and anticipated reperfusion injury to maximize outcome in these patients. These techniques can be used in dogs with certain thromboembolic manifestations as well.

Researchers Find Role for MicroRNAs in Oxygenation, Nourishing of Colon Tumors

Researchers at Penn Vet have identified how molecules of microRNA are responsible for the growth of blood vessels in a model for human colon cancer. The process, called angiogenesis, results in the ability of ravenous cancer cells to recruit blood vessels and receive a steady supply of nutrients and oxygen.

The findings, which appear in the on-line version of *Nature Genetics*, suggest these microRNAs might also be a good target for future therapeutics to slow the growth of cancer cells.

"These findings also uncover a new role for a well-known cancer-causing gene called MYC," said **Dr. Andrei Thomas-Tikhonenko**, associate professor of pathobiology. "We have discovered that, within a tumor cell, one of the tasks of MYC is to turn loose a particular set of microRNAs, which then becomes responsible for promoting the growth of new blood vessels that nourish the tumor."

The researchers discovered the role of microRNAs in angiogenesis while studying what makes MYC unique among other cancer-causing genes. In particular, they were curious why cells with hyperactive MYC do not accumulate particularly fast in Petri dishes yet grow explosively in animal models for the disease.

The MYC protein is known to have a role in determining how certain genes are transcribed into messenger RNAs. To understand the role of MYC in angiogenesis, the researchers used microarray technology to screen MYC-positive and -negative cancerous cells for the presence or absence of 192 known pro- and anti-angiogenesis molecules. They found that, while MYC did not lead to excessive amounts of pro-angiogenesis molecules, it did seem to depopulate an entire family of anti-angiogenesis molecules related to the thrombospondin-1 protein. MYC effectively disabled the brakes that slow angiogenesis.

Also participating in this study were **Asal Homayouni**, **Duonan Yu** and **Cinzia Sevignani** from the School of Veterinary Medicine; Greg H. Enders, Emma E. Furth, William M. Lee and Danielle Murphy from Penn's School of Medicine; and Erik Wentzel from Johns Hopkins University. Funding for this research was provided by the National Institutes of Health and a grant from the University of Pennsylvania Research Foundation.