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Research Briefs

Penn Launches Institute for Regenerative Medicine

In November 2007 Penn announced the launch of the cross-disciplinary Institute for Regenerative Medicine to investigate and harness the therapeutic potential of stem cells in treating cancer, diabetes, cardiovascular disease, degenerative diseases, wound healing and aging. **Ralph L. Brinster, V'60**, Richard King Mellon Professor of Reproductive Physiology at Penn Vet, and Dr. Jonathan A. Epstein, William Wikoff Smith Chair in Cardiovascular Research and chair of Penn Medicine's Department of Cell and Developmental Biology, will head the Institute. The Institute will draw on existing Penn programs in basic cell and organ biology, extensive animal modeling opportunities, practical and experiential expertise in tissue engineering, innovative translational research programs and ready access to pediatric and adult patients.

Protein Interactions in Immune-System Response Identified

A team of Penn Vet researchers, led by **Dr. Christopher Hunter**, chair of the Department of Pathobiology, has identified protein interactions involved in the immune system process that fights infection, yet, in certain inflammatory diseases, attacks friendly tissue. This signaling protein, Interleukin 10 (IL-10), plays an important role in regulating the balance between the protective white blood, or T, cell response and one that is pathological and out of control.

White and red blood cells.

While IL-10 is recognized as a major anti-inflammatory factor, what leads to its production has been poorly understood. According to the findings, messenger proteins Interleukin 27, or a combination of Interleukin 6 and another type of messenger molecule called transforming growth factor beta, induce production of IL-10. This suggests that modulating these messenger molecules could increase IL-10 concentrations that temper overactive immune responses. The study sheds light on the immune-system response and may provide directed means to intervene in severe autoimmune disease.

Agent Orange Chemical Attacks Mitochondria to Cause Cancer

Dr. Narayan Avadhani, chair of Penn Vet's Department of Animal Biology, led a team of School researchers that demonstrated the process by which the cancer-causing chemical dioxin attacks cellular machinery, disrupts normal cellular function and promotes tumor progression. The team discovered that mitochondria, the cellular subunits that convert oxygen and nutrients into cellular fuel, are the target of tetrachlorobenzodioxin, or TCDD. The research showed that TCDD induces mitochondria-to-nucleus stress signaling, which in turn induces expression of cell nucleus genes associated with tumor promotion and metastasis. TCDD, the most toxic compound in the dioxin family, is a by-product during waste incineration and paper, chemical and pesticide manufacturing. It was the toxic ingredient in Agent Orange and closed the Love Canal in Niagara Falls. The public health impact of dioxin, according to the Environmental Protection Agency, compares to that of the pesticide DDT.

The study appeared in the December 17, 2007 issue of the *Proceedings of the National Academy of Sciences*. Other Penn Vet researchers include **Drs. Gopa Biswas**, **Satish Srinivasan** and **Hindupur Anandatheerthavarada**. Research was supported by the National Cancer Institute and the National Institutes of Health.

One Shot of Gene Therapy Spreads Through Brain in Animal Study

In the September 12, 2007 issue of the *Journal of Neuroscience*, **John H. Wolfe, V'82 GR'86**, professor of pathology and medical genetics and director of the Walter Flato Goodman Center for Comparative Medical Genetics, and researchers from the Children's Hospital of Philadelphia show that, in a mouse study, a single gene therapy injection to one location in the brain can deliver a beneficial gene throughout the brain, provided the initial injection site is sufficiently well connected. If these results can be replicated in humans, it could prove a potent weapon against neurological disorders such as Tay-Sachs disease. The researchers targeted a well-connected area of the brain using a neutralized virus for a delivery vehicle. The virus was carried along neural pathways throughout the brain, delivering the enzyme-producing gene. One benefit was that each corrected cell produced a "sphere of correction" where it provided the enzymes to neighboring cells as well. Given the results, the possibility exists for future cases to need a limited number of treatments for a full recovery, but the possible use of this treatment on humans is years away.

Researchers Learn More about How Herpes Virus Invades Cells

Penn researchers have uncovered an important step in how herpes simplex virus (HSV-1) uses cooperating proteins on its outer coat to gain entry into healthy cells and infect them. The researchers believe they have demonstrated the effectiveness of monitoring these protein interactions using biomolecular complementation. Participating in the study were **Dr. Roselyn Eisenberg**, professor of microbiology at Penn Vet; **J. Charles Whitbeck, GR'93**, and **Brigid Reilly, V'09**, of the Department of Pathobiology at Penn Vet; Gary Cohen, professor of microbiology at Penn Dental; and Doina Atanasiu and Tina M. Cairns of the Department of Microbiology at Penn Dental. The study was supported by the National Institute of Allergy and Infectious Diseases and the Merck Summer Research Fellowship Program at Penn Vet.

The findings, published in the *Proceedings of the National Academy of Sciences*, provide a better understanding of the mechanism that viruses use to conquer healthy cells.

Silencing Small but Mighty Cancer Inhibitors

Researchers from Penn Vet and Johns Hopkins University have uncovered another reason why one of the most commonly activated proteins in cancer is so dangerous. As reported in *Nature Genetics* in December 2007, the Myc protein can stop production of at least 13 microRNAs, small pieces of nucleic acid that help control which genes are turned on and off.

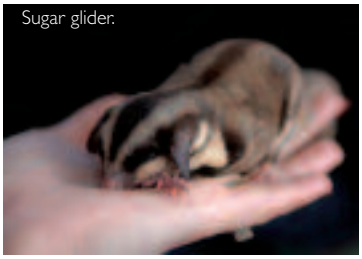
Also, in several instances, re-introducing repressed microRNAs into Myc-containing cancer cells suppressed tumor growth in mice, raising the possibility that a type of gene-therapy approach could be effective for treating certain cancers.

From Penn Vet were **Dr. Andrei Thomas-Tikhonenko**, associate professor of pathology, and **Dr. Duonan Yu**, from the Department of Pathobiology. The research was funded by the National Institutes of Health.

Students recently participated in Penn Vet Student Research Day; abstracts from their presentations can be found at www.vet.upenn.edu/research/students.

Work by Penn Vet Researchers Selected for Faculty of 1000 Biology

The paper "The Sugar Glider (Petaurus breviceps): A Laboratory Host for the Nematode Parastrongyloides trichosuri"—coauthored by the Department of Pathobiology's **Dr. Thomas J. Nolan**, adjunct associate professor of parasitology, and professors **Dr. Gerhard A. Schad, HON'77**, and **Dr. James B. Lok**, along with X. Zhu, J. Cole and W. Grant—was selected for Faculty of 1000 Biology. Launched in 2002, Faculty of 1000 Biology is an award-winning on-line service that highlights and evaluates the most interesting papers published in the biological sciences, based on recommendations of more than 2,000 of the world's top researchers. The paper appeared in the October 2007 issue of the *Journal of Parasitology*.


Sugar glider.

Oxygen Levels Affect Immune System Response

Dr. Cindy Otto, associate professor of critical care, was part of a team of researchers that discovered a signaling pathway involved in the body's responses to infections and other damaging stimuli. Drugs or other treatments that alter this signaling potentially could help either improve the effectiveness of the immune response or reduce the damage that results when the immune system gets overactive, as in autoimmune diseases or sepsis (overwhelming infection). The team found that activated macrophages immediately stop making nitric oxide (NO) when oxygen is removed, and this effect is reversed as soon as oxygen is reintroduced into the environment. This rapid and reversible control of NO production occurs at levels of oxygen found in many disease states, suggesting that regulation of NO production by oxygen may be important in patients.

The findings were published in the article "Physiologic and Hypoxic O2 Tensions Rapidly Regulate NO Production by Stimulated Macrophages," which appears in the on-line version of the *American Journal of Physiology–Cell Physiology*.