NEWSLETTER

Are defective viral genomes the ultimate trigger for anti-viral immunity?

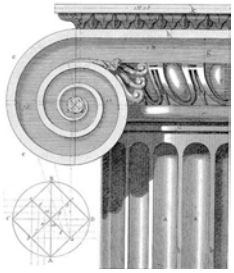
Dr. Carolina B. López is an Assistant Professor in the Department of Pathobiology. She received a B.S. (1992), a M.Sc., and a professional title of Biochemist (1995) from the Pontificia Universidad Católica de Chile, Santiago, Chile. During this period Dr. López studied the immune response to *Litre*, the Chilean version of *poison ivy*. After emigrating to the United States she worked as a Research Assistant at New York University and completed her Ph.D. in Biomedical Sciences (2002) at

continued on page 2

As the new academic year begins we welcome investigators from the **Wistar Institute,** those who are already here, and those in the process of moving into laboratory space in Hill Pavilion and Rosenthal Building while renovations of their facilities are completed. Many of the Wistar faculty have long been collaborative partners with their counterparts at **Penn Vet** and their presence enhances and invigorates the biomedical research environment. The interchange of information and ideas will strengthen our collaborations and is compatible with Penn Vet's broad multidisciplinary approach to science. Penn Vet will welcome Wistar investigators at a reception on November 7th.

"Between animal and human medicine there is no dividing line—nor should there be. The object is different but the experience obtained constitutes the basis of all medicine."
Rudolf Virchow (1821–1902)

YOU MAY REUSE SOME TYPES OF APPLICATIONS



Normally you cannot submit the same research project more than once, but there are exceptions. If your application does not succeed, you can submit the same application to NIH if you wish to:

- Submit an investigator-initiated application after responding un-successfully to an RFA.
- Respond to an RFA after unsuccessfully submitting an investigator-initiated application.
- Submit an unsuccessful application as a different activity code (e.g., R01, R03, R21).

When resending the same application, always create a new application, not a resubmission.

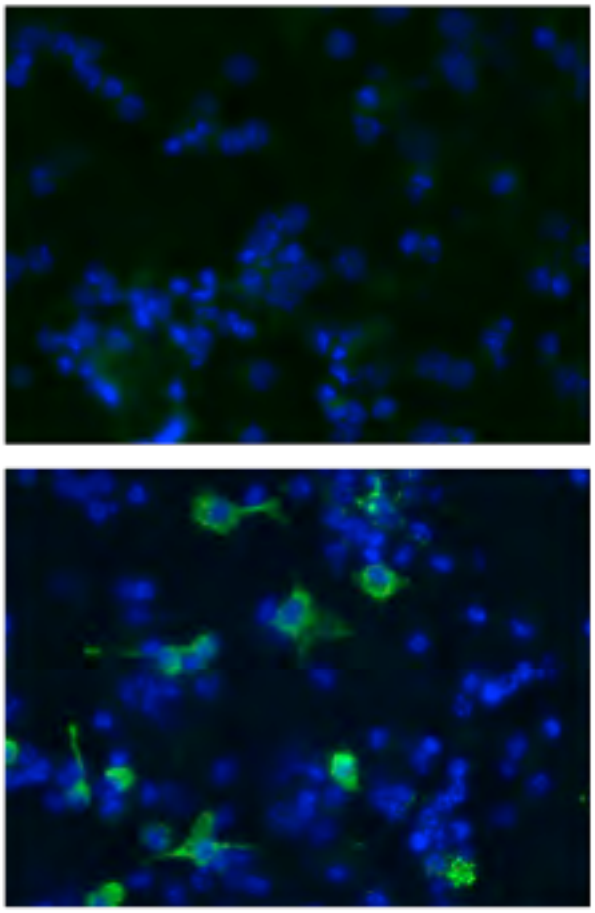
- You'll have to revise to meet the requirements of the new announcement. Be sure to check the "New" box on the face page.
- Do not refer to it as a resubmission.

Dr Lopez *continued from page 1*

the Mount Sinai School of Medicine in New York. She continued at Mount Sinai as a post-doctoral fellow and was promoted to non-tenure track Assistant Professor in 2005. She joined the Department of Pathobiology at Penn Vet in September of 2010. Dr. López's research centers on understanding the processes that lead to the generation of the immune response against viruses. In particular, her group studies early events following virus-host interaction that determine the successful transition from the less specific initial innate immune response to the more specific and persistent adaptive immune response.

Are defective viral genomes the ultimate trigger for anti-viral immunity?

Following infection, pathogen-induced stimulation of dendritic cells promotes their migration from the tissues to the draining lymph nodes, enhances the production of pro-inflammatory molecules, and permits effective antigen presentation to T cells, thereby inducing the transition from a fast but unspecific immune response to a long-term protective and specific adaptive immune response. Identification and characterization of viral elements capable of triggering dendritic cell maturation will not only provide essential insight into the requisites for triggering effective immunity during infection, but may also identify potential novel adjuvant molecules to be used in vaccination.



Bone marrow-derived dendritic cells mock treated (upper panel) or infected with Sendai virus (lower panel) and stained with anti-SeV NP protein (green) 20 h post-infection (40x).

While investigating the viral components required for the efficient triggering of dendritic cell maturation, Dr. López's group discovered that defective interfering viral genomes (DIVGs) that are generated during the normal replication of viruses are potent stimuli for the activation of dendritic cells. DIVGs for a large number of animal and plant viruses have been characterized *in vitro,* but the mechanism for their generation as well as their role during the virus life cycle remain speculative. Dr. López reported that DIVGs activate dendritic cells through a unique mechanism that is different from that utilized by standard viruses and, moreover, is capable of overcoming the viral-encoded antagonist

continued on page 3

SEARCH VET SCHOOL PUBLICATIONS

Penn Vet's Atwood Library has developed a web page that dynamically displays most recent articles published by authors affiliated with Penn's School of Veterinary Medicine. The list is retrieved from Scopus, one of the world's largest scientific, technical, and medical databases. Find the link under Vet Library News at: http://gethelp.library.upenn.edu/guides/vet/scopusfeed.html. If searching off campus, you will be prompted for your PennKey.

continued from page 2

of immune activation found in mature viruses [1, 2]. Her group is now using a reverse genetics system that allows for the recovery of mutant DIVGs to characterize the viral motifs responsible for the potent stimulatory activity of DIVGs. The goal of this project is to identify a minimal stimulatory motif from DIVGs to be eventually harnessed as an adjuvant for vaccination. In addition, Dr. López's group is investigating the generation and role of DIVGs during the course of natural viral infection to test the hypothesis that DIVGs are critical for triggering the anti-viral response *in vivo*.

What is the cellular machinery involved in the detection and response to viruses?

Anti-viral responses are initiated following recognition of "danger" signals by the infected host. Viral molecular motifs denoting danger are normally present in the virus genome and are exposed during viral replication within the host cell. A number of cellular sensors of viral genomic motifs have been identified, including members of the Toll-like receptor and RIG-I-like helicase families. These sensors localize to different cellular compartments and are partially redundant in their specificity. The signaling initiated by the binding of pathogen-specific molecular motifs to the sensors is critical for the initiation of the immune response. However, despite the presence of high levels of viral danger signals, pathogenic viruses replicate to high titers in the host. In studies designed to understand how pathogenic viruses evade the host immune response, Dr. López and collaborators observed that it takes more than two days before the host response to influenza or parainfluenza virus infection can be detected in mice [3]. The delay in the onset of anti-viral immunity is presumably due to the presence of viral-encoded antagonists that counteract immune recognition by blocking detection and/or signaling by cellular sensors so that the virus can grow and spread successfully.

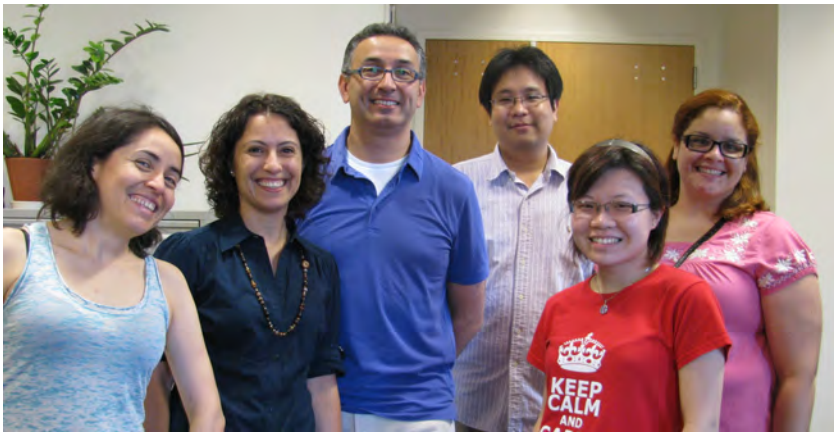
Dr. López's group seeks to understand the cellular mechanisms that overcome viral antagonism of immune responses to pathogenic respiratory viruses, such as influenza, parainfluenza, and respiratory syncytial virus. The group is currently assessing the cellular response mediated by the viral sensors RIG-I and MDA5. Challenging the current paradigm, the group has shown that both proteins are involved in the response to parainfluenza virus [2] and they are currently investigating the specific role of each of these molecules in immune recognition and response to virus infection, as well as in overcoming viral immune antagonism. Dr. López is particularly interested in investigating cellular molecules that are involved in the efficient response to DIVGs.

Lung-Bone Marrow Axis: Essential role in anti-viral immunity.

Upon viral recognition and sensing of the infecting virus, infected cells produce cytokines and chemokines that promote the recruitment and activation of immune cells. Dr. López lab has shown that soon after a respiratory infection, molecules produced in the infected lung are transported through the blood to signal cells located in the distal bone marrow [4, 5]. Cells instructed in the bone marrow become resistant to virus infection and respond more efficiently to viral cues when recruited to the lung, thereby enhancing the innate immune response and facilitating the clearance of the virus. Dr. López group identified type I interferons as critical mediators of lung-bone marrow communication during viral infection [5, 4]. The group is currently interested in characterizing other mediators of the lung-bone marrow axis and in determining their role during the initial anti-viral response. In addition, they are investigating the specific effects of these signals in specific bone marrow cell populations.

continued on page 4

LOPEZ LABORATORY continued from page 3



Dr. López's research is currently funded by the NIH/NIAID (R01 AI083284 and R21 AI083481). Her laboratory is located at 337 Hill Pavilion and her office is in Suite 318.

References:

1. Yount, J.S., *et al.*, A novel role for viral-defective interfering particles in enhancing dendritic cell maturation. *J Immunol*, 2006. **177**(7): p. 4503-13.

2. Yount, J.S., *et al.*, MDA5 Participates in the Detection of Paramyxovirus Infection and Is Essential for the Early Activation of Dendritic Cells in Response to Sendai Virus Defective Interfering Particles. *J Immunol,* 2008. **180**(7): p. 4910-8.

3. Moltedo, B., *et al.*, Cutting edge: stealth influenza virus replication precedes the initiation of adaptive immunity. *J Immunol*, 2009. **183**(6): p. 3569-73.

4. Hermesh, T., *et al.,* Antiviral instruction of bone marrow leukocytes during respiratory viral infections. *Cell Host Microbe,* 2010. **7**(5): p. 343-53.

5. Lopez, C.B. and T. Hermesh, Systemic responses during local viral infections: type I IFNs sound the alarm. *Current opinion in Immunology,* 2011. **23**(4): p. 495-9.

Biomedical Postdoctoral Announcement

Garnett Powers-Postdoc Insurance enrollment sessions:

November 15 TRC (Translational Research Center): Main Auditorium 9:00-10:30am & 3:00-4:30pm

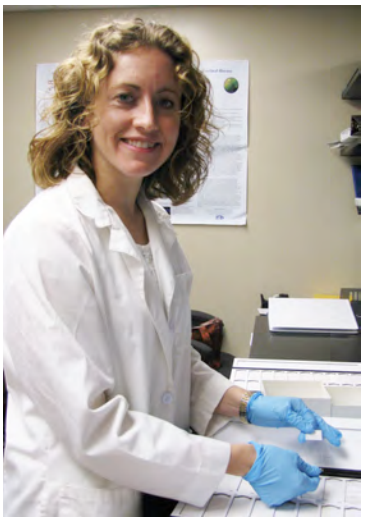
November 16 TRC (Translational Research Center): Main Auditorium 9:00-10:30am & 3:00-4:30pm

Biomedical Postdoc Research Symposium: Wednesday, October 12th 12:30-5:30 pm
BRB Auditorium & Lobby

http://www.med.upenn.edu/postdoc/

Penn Vet's **Tracy Bale** Earns Endocrine Society's Richard E. Weitzman Memorial Award—The award is presented annually to a young investigator in recognition of meritorious accomplishments in the field of endocrinology. University of Pennsylvania School of Veterinary Medicine's Tracy Bale, Ph.D., Department of Animal Biology was named recipient of the 2011 Richard E. Weitzman Memorial Award."My research is my passion," said Dr. Bale. "To be recognized by a group of peers such as those within the Endocrine Society is a true honor and I am humbled to have been named the 2011 Weitzman Memorial Award honoree". *see page 7*

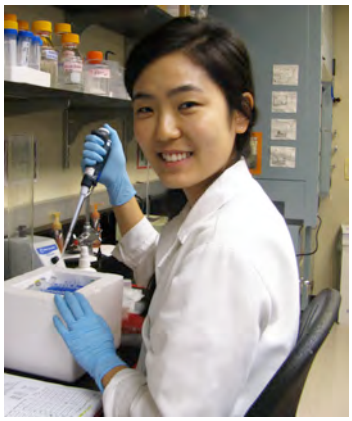
SUMMER MENTORING IN RESEARCH AT PENN VET



Kristin Gardiner, Merial Program, Gus Aguirre Laboratory

Penn Vet faculty opened their laboratories to introduce students to research during the summer of 2011. Students arrived from a variety of programs designed to expose students to biomedical research—this includes the development of research ideas, experiments, presentation of research results, and simply, to learn about life in a research laboratory. Some are high school students, others are veterinary students in their first or second year of veterinary school, and some are college undergraduates who are exploring fields of study in hopes of graduate training in the future. Summer students were part of an official program or volunteered to gain valuable experience for a future in scientific research.

The **NIH/Merial Summer Research Program**, as one example of summer opportunities is funded by Merial and by a National Institutes of Health (NIH) training grant. Other sources of support include funds from the office of the dean, the four departmental chairs and centers. Since its inception, the Merial program has funded 331 awards to 300 different students to perform biomedical research in the laboratories of 131 different faculty members at the University of Pennsylvania. *Link to program.*



Annie Oh, Merial Program, Andras Komaromy Laboratory

Another program is the **STEMPREP Project,** headquartered at Southern Methodist University (SMU), Dallas, Texas and the non-profit Distance Learning Center (DLC) in Philadelphia. In 1990, the DLC invented the STEMPREP (science-technology-engineering-math) Project to find and train a national pool of minority 7th grade trainees who have expressed a desire and talent for a STEM career. *Link to program.*

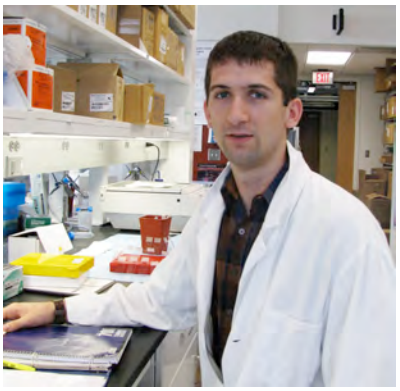
Penn's Summer Undergraduate Internship Program (SUIP) is a source of summer trainees who have joined Penn Vet labs for the summer. A program of the Biomedical Graduate Studies at Penn, the SUIP provides an intense research experience to students interested in graduate study in the biomedical and biological sciences. *Link to program.*

Michael Adu, Virginia Tech, Penn's SUIP program, Carolina Lopez Laboratory

"I am so grateful for the opportunity provided by the Aguirre laboratory and the NIH-Merial Fellowship program to have spent the summer engaged in meaningful veterinary ophthalmology research."

Kristin Gardiner

Frazly Alexander, University of the Virgin Islands, Nicola Mason Laboratory



Sam Mason, University of Pittsburgh, Phil Scott Laboratory

RECENT AWARDS

David Artis
NIH U01 [AI-095608-01]
Regulation of protective immunity following enteric viral infection
7/25/2011 – 6/30/2016, $225,000

Gustavo Aguirre
Foundation Fighting Blindness
"Retinal remodeling in canine models of LCA/Early onset retinal degeneration.
7/1/11-6/30/12, $56,443

Margret Casal
Int. Soc. of Vet. Dermatopathology
Molecular Characterization of Ichthyosis in the Labrador Retriever
7/1/11-6/30/12, $5,000

Gregory Griffeth (VCIC)
Schering Plough Animal Health (Merck).
Clinical Effectiveness of 13.64% w/w CBPI Flavored Chewable Tablets for Dogs Against Fleas: A Multi-Center Pivotal Field Trial
7/1/11-7/31/12, $38,800

Cynthia Otto
American Kennel Club
AKC Companion Animal Recovery
Detection Dog DNA Bank
10/1/11-9/30/12, $100,000

Cynthia Otto
American Kennel Club
2011 Penn Vet Working Dog Conference-Defining, developing and documenting success in working dogs
8/1/11-11/30/11, $2,000

Cynthia Otto
American Kennel Club
Defining, developing and documenting success in working dogs
5/1/11-12/31/11, $10,000

Mark Oyama (VCIC)
IDEXX Laboratories, Inc.
Feline SNAP Cardiopet Field Trial Pilot
6/30/11-10/31/11, $17,188

Emily Thomas, Resident
Amer Col. Vet Emergency & Crit. Care.
The effect of methylnaltrexone on gastrointestinal complications in dogs treated with opioids in the intensive care unit 8/1/11-7/31/12, $8,274

Ashley Boyle
American Quarter Horse Association
Verification of a *S. equi* detection assay for equine nasopharyngeal and guttural pouch wash samples
10/01/2011-09/30/2012 $16,751

Sue McDonnell
Schering-Plough Animal Health
Zylkene Behavior Trials
07/22/2011-09/30/2011 $10,620

Thomas Parsons
PA Lions Hearing Research Foundation--Temporal Precision of Information Transmitted by the Auditory Nerve
07/01/2011-06/30/2012 $20,000

Thomas Parsons
University Research Foundation
The role of neural refractoriness in the temporal coding of conspecific calls.
08/01/2011-07/31/2012, $29,413

Ralph Brinster
St. Baldricks Foundation
Translating the Science of Testicular Tissue Cryopreservation
7/1/2011-6/30/2014 $156,000

Serge Fuchs
NIH Role of HOS in Cell Transformation and Apoptosis.
8/8/2011-7/31/2016 $1,288,410

Nicola Mason
Morris Animal Fdn. "Development of a CD20-specific antibody fragment for targeted therapy of canine B cell lymphoma. 9/1/11-8/31/13 $108,527

Igor Brodsky
McCabe Fund Pilot
Mechanisms of *Salmonella* immune evasion--9/1/11-8/31/12 $24,918

Igor Brodsky
Mari Lowe Center Comparative Oncology--Pilot. Role of calcium signaling in inflammsome activation
8/1/11-7/31/12 $20,000

Igor Brodsky
Ctr for Molecular Studies in Digestive & Liver Diseases. Pilot: Mechanisms of *Salmonella* immune evasion.
7/1/11--6/30/12 $20,000

Igor Brodsky
University Research Foundation
Role of calcium signaling in inflammasome activation. 3/1/11--2/29/12 $25,000

SOME RECENT PAPERS

Siracusa MC, Saenz SA, Hill DA, Kim BS, Headley MB, Doering TA, Wherry EJ, Jessup HK, Siegel LA, Kambayashi T, Dudek EC, Kubo M, Cianferoni A, Spergel JM, Ziegler SF, Comeau MR, **David Artis,** TSLP promotes interleukin-3-independent basophil haematopoiesis and type 2 inflammation (2011) *Nature*, 477(7363):229-33.

John B, Ricart B., Harris TH, Tait ED, Randall L, Weninger W, Hammer DA, **Hunter CA**. 2011. Analysis of behaviour and trafficking of dendritic cells within the brain during Toxoplasmicencephalitis. (2011) *PloS Pathogens*, 7(9):e1002246

Guziewicz KE, Slavik J, Lindauer SJ, **Aguirre GD**, Zangerl B. Molecular consequences of BEST1 gene mutations in canine multifocal retinopathy predict functional implications for human bestrophinopathies. *Invest Ophthalmol Vis Sci.* 2011 Jun 23;52(7):4497-505.

R J. Whitmarsh, CM. Gray, B Greggi, DA Christian, M J May, PJ. Murray, and **CA Hunter** A critical role for SOCS3 in innate resistance to *Toxoplasma gondii. (2011) Cell Host. Microbe,* 10(3):224-36.

Prenatal stress can program effects of grand offspring

Previous studies have shown that stress during pregnancy produces negative outcomes for the offspring, both in humans and laboratory animals. A new study from the University of Pennsylvania demonstrates that in mice this increased stress sensitivity can be passed on from father to sons of the second generation. The finding, published in the *Journal of Neuroscience last week*, is an example of transgenerational programming that likely involves epigenetic changes: the study of how genes are affected by the environment. The new study by **Tracy L. Bale**, an Associate Professor of neuroscience in the **Department of Animal Biology at Penn's School of Veterinary Medicine** and graduate student Christopher P. Morgan subjected pregnant mice to a variety of stressors early in gestation. These first generation offspring were then bred to produce grand offspring in order to determine if the fathers' stress-sensitivity could be passed on to their sons. Male mice are not involved in taking care of the young. "If fathers can pass the

effect on to their sons, then we know some epigenetic mark has to be found in their sperm," said Bale. Similar to their fathers, the sons showed the same patterns of behavioral and physiological stress measures. Interestingly, the changes in these males seemed to be in the direction of what females normally look like. Indeed, other programming cues that are predictably masculine also seemed to be in the feminine direction. These results suggested that the normal production of signals responsible for developing a typical 'male' brain were somehow disrupted by the stress their grandmother had experienced during pregnancy. In their examination of important genes involved in the brains of these mice, the authors found that the hundreds of microRNAs (small RNAs that do not code for proteins but are important in regulating expression of other genes) had a very distinct pattern of expression that was also affected by these same signals. Understanding the gene targets that these microRNAs regulate can provide valuable insight into what disrupted processes may be altering the ability of the brain to appropriately cope with stress.

Early Prenatal Stress Epigenetically Programs Dysmasculinization in Second-Generation Offspring via the Paternal Lineage. *J. Neurosci,* 2011,31(33):11748-11755

RECENT PUBLICATIONS

Vite CH, Wang P, Patel RT, Walton RM, Walkley SU, Sellers RS, Ellinwood NM, Cheng AS, White JT, O'Neill CA, & Haskins M. Biodistribution and pharmaco-dynamics of recombinant human alpha-L-iduronidase (rhIDU) in mucopoly-saccharidosis type I-affected cats following multiple intrathecal administrations. (2011) *Mol Genet Metab.* 103(3):268-74.

KU Sorenmo, E Krick, CM Coughlin, B Overley, TP Gregor, RH Vonderheide, & **NJ Mason CD40**-

activated B cell cancer vaccine improves second clinical remission and survival in privately owned dogs with Non-Hodgkin's Lymphoma. (2011) *PLoS one* 6(8): 1-8

Bish LT, **Sleeper MM,** Forbes SC, Morine KJ, Reynolds C, Singletary GE, Trafny D, Pham J, Bogan J, Kornegay JN, Vandenborne K, Walter GA, Sweeney HL Long-

Term Systemic Myostatin Inhibition via Liver-Targeted Gene Transfer in Golden Retriever Muscular Dystrophy. (2011) *Hum Gene Ther.*, Aug 30. [Epub ahead of print]

C Lopez, Tamar Hermesh (2011) Systemic responses during local viral infections: type I IFNs sound the alarm. *Current Opinion in Immunology* 23(4): 495-499.

Administrative tasks occupy 42% of scientists' time…

By Leszek Kubin, Ph.D.,
Research Professor of Physiology, Department of Animal Biology and Penn Vet's representative to the *Office of Research Services Advisory Committee*

A survey conducted in 2007 among approximately 6000 investigators from major American universities indicated that they devoted **42%** of the time allocated to research to administrative tasks. A new government-initiated survey of administrative burdens will be distributed among selected PIs later this year. If you receive it, fill it out and make your voice heard.

The issue of administrative burdens on the conduct of research has been discussed at recent meetings of the Office of Research Services (ORS) Advisory Committee. The committee was formed by Dr. Steve Fluharty, the SeniorVice Provost for Research, three years ago and is chaired by Dr. Steven Albelda of Pulmonary and Critical Care Division at the School of Medicine. We meet bimonthly to discuss technical and administrative issues related to research administration in a forum comprising a group of central research administrators and researchers from all biomedical schools at Penn.

Among the issues tackled by this forum are:

- a proposal to alter the use of direct costs so that some could cover "administrative and compliance activities conducted by faculty or staff when those activities can be specifically identified to individual projects."
- a draft of new instructions for the IACUC with more rigid requirements to enforce the regulations.
- In the pipeline is a more elaborate tool to list our potential conflicts of interest that will be collected, periodically updated and kept in a central database to avoid conflicts in the design of new research proposals.

Interested readers may find my earlier report on the ORS Advisory Committee that has been posted under 'Research-Research Services Advisory Committee' on the Inside.Vet page (http://inside-wlbs.vet.upenn.edu/).

"Agreed. We fund only those proposals we can understand."

World Leadership in Animal Health

On September 14, 2011, the Penn Vet **World Leadership Award** was given to **Ilaria Capua, DVM, PhD,** director of the Department of Comparative Biomedical Sciences at the Istituto Zooprofilattico Sperimentale delle Venezie, Legnaro, Italy. She is involved in cutting edge research on influenza viruses and viral zoonoses. This award, along with the Student Inspiration Award, were established through a gift from the Hill Family Foundation and they are the largest prizes in veterinary medicine.

Penn Veterinary Medicine

The **Penn Vet Research Newsletter** is distributed quarterly. Suggestions, requests, comments, and story ideas should be directed to:
resnews@vet.upenn.edu

Office *of the* Associate Dean
for Research
Phillip Scott, Ph.D.
University of Pennsylvania
School of Veterinary Medicine
(215) 898-9793
380 S University Avenue
Suite 310B Hill Pavilion
Philadelphia PA 19104-4539