NEWSLETTER

Immune therapies....*and their translation into the human clinic*

Dr. Nicola Mason is an assistant professor in the Departments of Pathobiology and Clinical Studies Philadelphia. Nicola graduated from the Royal Veterinary College in London and performed her internship in small animal internal medicine at the University of Bristol's Veterinary School. She completed her medical residency at the University of Pennsylvania's School of Veterinary Medicine and became a Diplomate of the American College of Veterinary Internal Medicine in 1998. Having developed an interest in autoimmunity during her residency, Nicola decided to pursue a Ph.D. in immunology to better understand immune function in health and disease. Her graduate studies were performed in the laboratory of Dr. Christopher Hunter where she investigated the role of the NF-kappaB transcription factor c-Rel on innate and adaptive immune responses to the obligate intracellular parasite *Toxoplasma gondii*. At the end of her Ph.D. studies, Nicola was keen to translate the basic immunological principles learned during her thesis into a clinical setting. This desire triggered her interest in the immunotherapy of cancer; harnessing the power of the immune system to specifically target and kill malignant cells and provide long-term immunological memory against cancer antigens to prevent tumor recurrence.

After obtaining her Ph.D. in 2004, Nicola pursued her interest in cancer immunotherapy in post-

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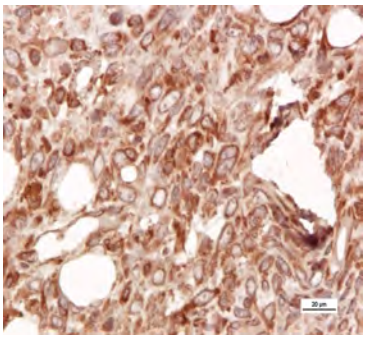
New Initiative *in the* New Year

At the last faculty meeting initial details of a school wide initiative on **host-microbial interactions** was described. The focus of this program is to build on our strong biomedical environment and clinical expertise and to develop faculty interest in the application of "omics" technologies to understand the impact of microbial communities on topics relevant to veterinary medicine. This includes but is not limited to infectious disease, inflammatory bowel disease, diabetes, nutrition and atopic disease. In the next few months there will be a series of opportunities for all faculty with general interests in this area to attend town hall meetings to provide feedback on their needs and how best to support this initiative. Faculty with initial questions may contact Chris Hunter chunter@vet.upenn.edu or Dan Beiting beiting@vet.upenn.edu .

IMMUNE THERAPIES....continued from page 1



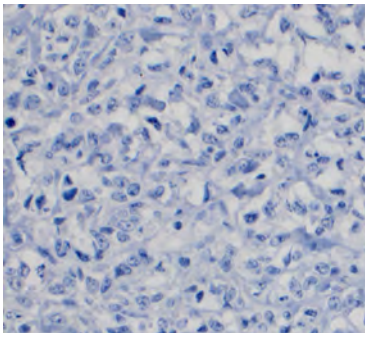


Figure 1. Her2/neu expression in canine osteosarcoma. Sections of tumor taken from two dogs with osteosarcoma were stained for the presence of Her2/neu. The top image shows tumor cells that exhibit dark brown staining, indicating the presence of Her2/neu. The bottom image shows no evidence of staining and this tumor is considered to be negative for Her2/neu expression. Only dogs positive for Her2/neu expression in their tumors are eligible to receive the targeted *Listeria* vaccine

Phil Kozak, Georges Habineza-Ndikuyeze & Kazim Panjwani

doctoral studies in the laboratory of Dr. Carl June at the Abramson Family Cancer Research Institute. In the June laboratory, Nicola worked on an approach to stimulate anti-tumor immunity based on whole tumor cells. Tumor cells themselves are incapable of directly priming an effective anti-tumor immune response as they often express low levels of MHC I molecules, required to present antigens to the immune system and they do not express the co-stimulatory molecules necessary to fully activate cognate T cells. However, by genetically modifying whole tumor cells using lentiviral vectors to stably express MHC I, co-stimulatory molecules and cytokines, these cells are capable of inducing anti-tumor T cell responses *in vitro* and can eliminate tumors in murine models. However, the translation of this approach and other immune therapy approaches into the human clinics has not proven as successful, underscoring the fact that murine models of cancer frequently fail to act as robust predictors of therapeutic success in the human clinics. This failure is in part due to the inability of many murine tumor models to accurately recapitulate the dynamic interplay between the tumor and the host's immune response that shapes the tumor's antigenicity and susceptibility to immune attack. In contrast to tumor models, spontaneous tumors that develop in an immune competent host are subject to editing or sculpting by the immune system. Cells easily recognized by the immune system are eliminated, while those that are invisible to the immune system persist. Furthermore, spontaneous tumors foster an immune suppressive environment in part by recruiting regulatory T cells and myeloid derived suppressor cells to the tumor site. Together, these characteristics present a formidable barrier to effective immune therapy. As such it has become increasingly apparent that spontaneous models of cancer, developing in immune competent animals will provide a far more robust test of immune therapy than many rodent models.

Based on this clear requirement for spontaneous models of human cancers to more accurately predict therapeutic success of immune modulation, Nicola decided to focus her own laboratory on validating canine tumors as models

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BIOMEDICAL POSTDOCTORAL PROGRAMS

Research Success Skills Workshop Series:
1) **Scientific Writing**, March 5th, 9:00-12:00pm, JMB Class of '62 Auditorium; 2) **Grant Writing** & Peer Review, March 12th, 9:00-12:00pm, JMB Class of '62 Auditorium; 3) **Lab Management**, March 19th, 9:00-12:00pm, JMB Class of '62 Auditorium and 4) ***Presentation and Public Speaking*** *Skills*, presented by Lisa Marshall, 9:00-10:30am, JMB Class of '62 Auditorium. For more information contact: Seth Freeman at freeseth@mail.med.upenn.edu

EQUINE PHARMACOLOGY LABORATORY AT NEW BOLTON CENTER

by Mary A Robinson, VMD, PhD

The New Bolton Center **Equine Pharmacology Laboratory** directed by Larry Soma VMD, DACVA, and the Pennsylvania Equine Toxicology and Research Laboratory (PETRL) at West Chester University directed by Cornelius Uboh PhD work closely together to develop and implement methods for detecting drugs illegally used during competition in race horses. In Pennsylvania, the Racing Commissions (one for harness racing, one for flat racing) mandate a zero tolerance drug policy on race day with the exception of 2 selected non-steroidal anti-inflammatory drugs (NSAIDs) and, currently furosemide (Lasix). The practical nature of a zero tolerance policy is often questioned for horses in training or at any advanced level of competition. These horses are professional athletes. Consider that professional football players often play with minor (or even moderate injuries) and are allowed the use of pain-relieving medications, such as the NSAIDs acetaminophen (Tylenol) or ibuprofen (Advil) during competition. Even intra-articular glucocorticoids are an accepted medical treatment in humans, and only need to be declared when blood and urine samples are obtained for drug testing. However, the situation for the race horse differs. Veterinarians are encouraged by the Commissions to take care of injured horses, however the horse is not allowed in competition if detectable concentrations of therapeutic medications are present in the blood or urine.

The NBC-PETRL group works to provide solutions to this difficult situation. Research studies are designed to determine the rate at which the horse eliminates the drug (pharmacokinetics), and the effect the drug has on the horse (pharmacodynamics). The PETRL group has developed methods to quantitate a large number of drugs in horse blood or urine, and performs the screening and confirmation for all PA race horse samples, amounting to more than 40,000 samples per year. Because of the strong long-standing support from the PA Racing Commissions, the NBC-PETRL group has been able to provide leadership in drug testing research. The NBC-PETRL mission is to provide accurate information to policy makers and enforcers, veterinarians, and horsemen on therapeutic and non-therapeutic drug use in race horses to help ensure the integrity of the sport, and more importantly the welfare of the horse during those intense and exciting two minutes of competition.

COMPANION ANIMAL RESEARCH FUND

Penn Vet's newly launched Companion Animal Research Fund (CARF) announced the first nine clinical and translational pilot grants for projects 1) with a potential for future extramural grant applications and 2) with translational relevance that will have an impact in the areas of diagnostics, therapeutics, prophylactics, or animal welfare. **Dorothy Brown, chair of Clinical Studies Philadelphia**, announced the following recipients to receive grants: **K. Agnello, S Volk, K Hankenson, and C Blake:** "Long term, clinical outcome of intra-articular adipose & bone marrow derived mesenchymal stem cell treatment in dogs with elbow dysplasia". **J Suran, L. Latney, and N. Wyre:** "Normal radiographic and ultrasonographic measurements in domestic companion ferrets" **L King:** "Prospective study of the use of the VetMouseTrap device to obtain thoracic CT scans without anesthesia in critically ill client owned dogs with suspected pulmonary thromboembolism". **J Lewis and A. Mexas:** "Effects of a PTP1B inhibitor (7-CBNP) on viral load & clinical signs in cats with feline immunodeficiency virus". **J Lewis and A Reiter**: "Development of a maxillofacial reconstruction clinic for companion animals" **N Mason and J Engiles:** "Evaluation of Her2/neu expression in canine osteosarcoma". **E Reineke:** "Evaluation of bupivacaine & morphine-bupivacaine caudal epidurals in cats with urethral obstruction". **J Serpell and C Siracusa**: "Influence of environmental background & behavior in clinics on diagnosis & treatment outcomes in canine behavioral medicine cases". **M Sleeper:** "Therapeutic gene transfer abrogates canine dilated cardiomyopathy".

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of human disease and on using dogs with spontaneous cancers as pre-clinical models to evaluate the safety and efficacy of immune therapies prior to their translation into the human clinic. Why Dogs? The high-quality draft genome sequence of the dog has revealed its close phylogenetic relationship with man, emphasizing the potential benefit of canine models in identifying disease genes and evaluating response to novel therapies. Unlike rodent models, many spontaneous tumors that arise in genetically outbred dogs mimic the biologic and behavioral characteristics of those that occur in man while occurring over a compressed clinical time course. In addition, privately owned dogs are subject to the same environmental influences on tumor initiation and progression as their human counterparts and most importantly, present to veterinary clinics with spontaneous malignancies that as in humans, have developed in the presence of a functional immune response. As these spontaneous canine tumors have evaded immune recognition and/or have actively suppressed anti-tumor immune responses, subsequent evaluation of immune therapies in these canine patients provides a far more robust test of their efficacy and is more likely to accurately predict response in human patients compared to current rodent models.

Nicola's laboratory is working actively and collaboratively in the translational space evaluating novel immune therapy approaches to stimulate anti-tumor immunity in dogs with spontaneous cancer. Recognizing 1) the necessity for clinically relevant large animal models of cancer for pre-clinical human immune therapy trials and 2) the increasing public demand for more effective and less toxic therapies to treat cancer in dogs, Nicola has joined forces with researchers at Penn Med to evaluate cell-based immune therapy approaches in dog with spontaneous cancers including lymphoma and osteosarcoma. In collaboration with Dr. Robert Vonderheide at the Perelman School of Medicine, Nicola first investigated the use of CD40 activated B cells as antigen-presenting cells in a cell-based vaccine approach to stimulate anti-tumor immunity in dogs. She demonstrated that canine B cells, appropriately licensed though CD40 activation, and supplied with an antigenic payload in the form of electroporated RNA can stimulate cytotoxic T cell responses *in vitro*. A clinical trial was then initiated in client owned dogs to determine whether this approach can safely and effectively induce anti-tumor immunity *in vivo* and prolong overall survival. The results were promising and Nicola's lab is now developing a second generation CD40-B vaccine that will enter clinical trials by the end of the year. The work has demonstrated for the first time that B cells can be used as alternatives to dendritic cells *in vivo* to effectively stimulate anti-tumor immune responses and that these responses can effectively prolong overall survival in the setting of spontaneous cancer.

A second approach towards anti-tumor immunity that is being investigated in Nicola's laboratory is the use of genetically re-directed T cells for adoptive immune therapy. In this approach canine T cells are being genetically modified to express a receptor specific for a target tumor antigen on malignant lymphoma cells. The modified, tumor-specific T cells are then expanded outside of the body before being adoptively transferred back into the patient. This work, pioneered by Nicola's post doctoral advisor Dr. Carl June aims to build on his recent success using this approach in human patients with Chronic Lymphocytic Leukemia. Kazim Panjwani a second year Immunology Graduate Student in Nicola's laboratory has now generated the canine constructs necessary to redirect T cells and is poised to start work optimizing this approach in the dog. This approach will represent the first of its kind to be offered for dogs with refractory B cell lymphoma and its use in the canine clinics will address important questions regarding optimal preconditioning regimes, trafficking, survival and function of these cells in a chemoresistant, solid tumor environment.

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In collaboration with Dr. Yvonne Paterson, Professor of Microbiology at the School of Medicine, Nicola is currently performing a phase I clinical trial to determine the safety and efficacy of an attenuated, recombinant *Listeria monocytogenes* expressing huHer-2/neu to elicit Her-2/neu specific T cell immune responses and anti-tumor immunity when used in an adjuvant setting in dogs with Her-2/neu positive appendicular osteosarcoma (OSA) (Fig. 1). This approach takes advantage of the potent immune stimulatory capacity of the gram positive *Listeria* bacteria. Mr. Georges Habineza Ndikuyeze, a research specialist in Nicola's laboratory and Dr. Carolyn Gross, a first year internal medicine resident are involved in the screening of these patients for trial eligibility. Demonstrating the safety and efficacy of this approach aims to accelerate its translation into the human clinic for women with Her2 positive breast cancer and adolescents with Her2 positive osteosarcoma. Furthermore, success of this approach in the canine clinic would represent the first immune therapeutic approach to prevent the recurrence of osteosarcoma in dogs and would represent a major milestone in the treatment of this disease.

As immune therapy gains traction in veterinary medicine through these cutting edge clinical trials and the translational benefit for both human and veterinary patients is further realized, it is anticipated that immunotherapy for canine cancer will be employed by an increasing number of researchers and clinician scientists. Given the anticipated demand, Nicola aims to initiate a comparative immunotherapy program at the School of Veterinary Medicine. This program will provide a facility that is dedicated to generating immune therapies and vaccines for canine cancer patients and for performing the necessary immune analysis of these patients. Furthermore, the program will provide unparalleled clinical and scientific training for qualified veterinarians who wish to specialize in immune therapy.

Nicola's work is funded by the National Institutes of Health, the Morris Animal Foundation, Canine Health Foundation, the Richard Lichter Foundation, the American College of Veterinary Internal Medicine and the Companion Animal Research Fund at Penn's School of Veterinary Medicine. Dr. Mason's office is located at 315 Hill Pavilion. See selected publications on page 7.

Feeding Cities-Food Security in a Rapidly Urbanizing World.
March 13-15, 2013
Penn Institute for Urban Research. http://www.feedingcities.com

2013
Student Research Day
Monday, March 25 at 12 noon
Hill Lobby & Auditorium

Professor **Mark Haskins,** VMD, PhD is the keynote speaker for Penn Vet's Annual **Phi Zeta Student Research Day**. Dr. Haskins will speak on "Genetic Disease: Translational Medicine--Yesterday, Today, and Tomorrow". Students are sending in their abstracts for the oral and poster presentation prizes. Registration for faculty and students online is found at:

http://survey.vet.upenn.edu/index.php?sid=62754&lang=en

Recent Papers

Bajpai P, Sangar MC, Singh S, Tang W, Bansal S, Chowdhury G, Cheng Q, Fang JK, Martin MV, Guengerich FP, **Avadhani** NG. Meta-bolism of 1-Methyl-4-phenyl-1-2-3-6-tetra-hydropyridine by Mitochondria-targeted Cytochrome P450 2D6: Implications in Parkinson's Disease. *J Biol Chem.* 2012 Dec 20. [Epub ahead of print]

Irie, T, Liu Y, Drolet BS, Carnero E, Garcia-Sastre A, & **Harty RN**. Cytopathogenesis of Vesicular Stomatitis Virus Is Regulated by the PSAP Motif of M Protein in a Species-Dependent Manner. *Viruses* 4(9): 1605-18 (2012).

Bao R, Nair MK, Tang WK, Esser L, Sadhukhan A, Holland RL, Xia D, **Schifferli DM**. Structural basis for the specific recognition of dual receptors by the homopolymeric pH 6 antigen (Psa) fimbriae of Yersinia pestis. *Proc Natl Acad Sci* U S A. 2012 Dec 31. [Epub ahead of print]

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NIH NATIONAL CANCER INSTITUTE WORK WITH VETERINARY SCHOOLS

Dr. Karen Sorenmo

Dr. Erika Krick

Drs. Karin Sorenmo and Erika Krick, Department of Clinical Studies Philadelphia, Section of Medical Oncology, were honored recently for their leadership efforts in the area of comparative oncology and their unique and noteworthy scholarly contributions to the field of cancer drug development. In 2004 the Center for Cancer Research (CCR) of the National Cancer Institute (NCI) created the CCR–Comparative Oncology Program (COP) with a goal to include naturally occurring cancers seen in pet animals complementing studies of cancer biology and therapy. The COP's Comparative Oncology Trial Consortium (COTC) is a collaborative effort that unites the NCI and extra-mural comparative oncology centers at 20 veterinary schools across the United States and Canada. The University of Pennsylvania School of Veterinary Medicine has been an integral part of this initiative for seven years. Drs. Sorenmo and Krick are currently conducting a study as part of the multi-institutional trials directed by the NCI. Their study is entitled: "*COTC007b: Preclinical Comparison of Three Indeno-isoquinolines Candidates in Tumor-Bearing Dogs*". By providing the COTC investigators access to the infrastructure of consortium, it is hoped that multi-center trials in the field of oncology will be successful and lay the groundwork for the future of translational research programs. Drs. Sorenmo and Krick are active members of the Mari Lowe Center for Comparative Oncology.

RECEPTION FOR PROFESSOR GUSTAVO AGUIRRE

Gus Aguirre

On December 10, 2012, Penn Vet faculty and staff joined in a toast to their colleague, Gustavo Aguirre, professor of medical genetics and ophthalmology in the Department of Clinical Studies Philadelphia, in celebration of his election to the Institute of Medicine in the National Academies. Dean Joan Hendricks, former deans Alan Kelly and Robert Marshak, and Dorothy C. Brown, Chair of Clinical Studies Philadelphia paid tributes to Dr. Aguirre. Phil Scott, associate dean for research and John Wolfe, professors in the Department of Pathobiology also commented on Dr. Aguirre's illustrious career in ophthalmological research. Dr. Aguirre's wife Kathleen and sons Geoffrey and David were also in attendance.

PUBLICATIONS STEMMING FROM NIH GRANT FUNDING

Under the public access policy, principal investigators **must** include **PUBMED** Central identification numbers (PMCID) when citing publications stemming from the grant for which they're reporting progress. Complete instructions can be obtained at: http://publicaccess.nih.gov/submit_process.htm
and FAQs can be found at: http://www.nihms.nih.gov/faq.html

RECENT AWARDS

Hannah Galantino Homer
Bernice Barbour Foundation
Laminitis Discovery Database
1/1/2013-12/31/2014 $100,781

Thomas Parsons
National Pork Board
Improving the Welfare of Group Housed Sows Fed Via Electronic Sow Feeding
11/1/2012-10/31/2014 $39,860

Thomas Parsons
SVF Foundation
On-hoof Conservation of Endangered Swine Breeds
1/1/2013-12/31/2013 $80,000

Pete Felsburg
Seattle Children's Hospital
Foamy virus (FV) vector-mediated gene therapy in the canine SCID-X1 model
8/7/12-7/31/13 $77,240

Nicola Mason
Morris Animal Foundation
Re-directed T cell therapy in dogs with B cell lymphoma
11/1/12-10/31/15 $281,113

Nicola Mason
AKC-CHF
Clinical advancement of RNA-transfected CD40-B cell vaccine technology for cancer therapy
1/1/13-12/31/15 $96,660

Cynthia Otto
Home Depot Charities
Agility Training Course
1/7/13--5/7/13 $2,500

Karin Sorenmo
Merial Limited
Evaluation of safety & clinical impact of chronic administration of desmopressin in conjunction with chemotherapy in hemangiosarcoma, a spontaneous tumor model--a 2-strike approach.
12/17/12-12/16/14 $97,244

Margaret Sleeper
AKC-CHF
Therapeutic Gene Transfer Abrogates Canine Dilated Cardiomyopathy
1/1/13-12/31/14 $73,387

Charles Vite
Thomas Jefferson Univ. (Legacy of Angel's FDN)Intracerebroventricular and intravenous injections of AAVrh10-GALC into the dog model of Krabbe disease
10/1/12-9/30-13 $86,729

Francis Luca
NIH
Examining the role of cbk1/NDR kinase in regulating mRNA localization
12/31/2012-11/30/2016 $1,248,000

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Selected publications from Nicola Mason's laboratory

Mason NJ, Coughlin C, Colligan T., Cohen J., Mitchell E., Overley E., Clifford C., Sorenmo K., Vonderheide R. RNA-loaded CD40-activated B cells stimulate antigen-specific T cell responses in dogs with spontaneous lymphoma. *Gene Therapy* 2008; 15(13):955-65.

Sorenmo KU, Krick E., Coughlin CM, Overley E, Gregor TP, Vonderheide RH, Mason NJ. CD40-activated B cell cancer vaccine improves second clinical remission and survival in privately owned dogs with non-Hodgkin's lymphoma *PLoS One*. 2011;6(8):e24167.

Gaurnier-Hausser A., Patel R,, Jackson K., Baldwin A., May M., Mason NJ. Nemo Binding Domain Peptide inhibits constitutive NF-κB activity in dogs with ABC-DLBCL. *Clin Cancer Res.* 2011 Jul 15;17(14): 4661-71.

Huang S., Gaurnier-Hausser A., Patel R., Kozak P., Habineza-Ndikuyeze G., Meade C., Robertson E., Mason NJ. Evidence of an oncogenic gammaherpesvirus in domestic dogs *Virology*. 2012 Jun 5;427(2):107-17

AWARD

The Council of the American Association of Immunologists has awarded **David Artis, Ph.D**. the 2013 AAI-BD Biosciences Investigator Award. Dr. Artis is jointly appointed in the Department of Pathobiology, School of Veterinary Medicine and the Department of Microbiology, Perelman School of Medicine. The award will be presented at the annual AAI meeting in Hawaii.

Publications

Ordás MC, Castro R, Dixon B, **Sunyer JO,** Bjork S, Bartholomew J, Korytar T, Köllner B, Cuesta A, Tafalla C. Identification of a novel CCR7 gene in rainbow trout with differential expression in the context of mucosal or systemic infection.*Dev Comp Immunol.*;38(2):302-11 (2012)

Shabalina SA, Spiridonov NA, **Kashina A.** Sounds of silence: synonymous nucleotides as a key to biological regulation and complexity. *Nucleic Acids Res.* Jan 4, Epub ahead of print. (2013)

Sleeper, MM, Rosato BP, Bansal S, and Avadhani NG. Mitochondrial dysfunction in myocardium obtained from clinically normal dogs, clinically normal anesthetized dogs, and dogs with dilated cardiomyopathy. *Am J Vet Res* 73 (11): 1759-64 (2012).

Biography

What is FEDS?
The **Faculty Expertise Database System** is a database in which faculty may enter biographical information that provides content for individual webpages including a *curriculum vitae (CV)*, publications, biosketch, contact information, appointments, education, and expertise statements. General information and training session information may be found on Inside.VET. at the link below. http://guides.library.upenn.edu/feds-vet. FEDS is a powerful tool that allows faculty to easily store, update and print their *curriculum vitae.*

General questions:

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Photo questions:
For questions about profile photographs and adding images to the research expertise component. Contact John Donges at
jdonges@vet.upenn.edu
215-898-4234

Publication information--can be easily pulled from PubMed or ISI. For help contact Margy Lindem, Head, Veterinary Medicine Library--
mlindem@pobox.upenn.edu

The Penn Vet Research Newsletter is distributed quarterly.

Suggestions, requests, comments, and story ideas may be directed to:

resnews@vet.upenn.edu

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Penn Veterinary Medicine

TO:

Biomedical Postdoctoral Winter Vendor Show
BRB Auditorium and Lobby
February 6, 2013 10:00am-2:30pm
Scientific Vendors. Enter a raffle to win prizes and join us for lunch!"