NF-Kappa B Signaling 

in Inflammation and Cancer....... 

Dr. Michael May is an associate professor in the Department of Animal Biology. He received a B.Sc. in Immunology from the University of Glasgow, Scotland, in 1988, and then worked as a research assistant in the Department of Immunology at the University of Manchester, England, until 1992.

After receiving his Ph.D. in Physiology and Vascular Cell Biology from King’s College London in 1996, Dr. May moved to New Haven, Connecticut where he was an Irvington Institute.

BIOMEDICAL POSTDOCTORAL PROGRAMS (BPP)

BPP’s new postdoc orientation is scheduled for April 16, 2:30 - 4:30 pm. The event is designed to give postdocs an overview of the amenities available to them at Penn. The orientation will be held in the Class of 62 auditorium in John Morgan Building. An NIH Career Development and training (K-awards) Workshop is scheduled for Monday May 5th, 9 am to 4 pm (location to be decided). NIH released the new Ruth L. Kirschstein National Research Service Award (NRSA) stipend levels for FY 2014. Here is a link to the NIH announcement:

The May lab is particularly interested in understanding how NF-κB signaling controls the pro-inflammatory function of vascular endothelial cells that line the walls of blood vessels. Notably, activation by inflammatory cytokines causes endothelial cells to express specific adhesion molecules and chemokines that coordinate the arrest and recruitment of circulating blood cells into inflamed tissue. NF-κB is a major signaling mechanism induced in endothelial cells that controls the expression of this cohort of inflammatory genes and underlies the pathophysiological role of vascular cells in inflammation. The primary focus of the research in Dr. May’s lab is to precisely determine how two distinct NF-κB signaling pathways, termed classical and non-canonical, are regulated, and to establish how selectively targeting these pathways in endothelial cells affects inflammatory disease development.

Although classical NF-κB is known to control a wide array of pro-inflammatory genes expressed in endothelial cells during disease progression, rapidly emerging evidence strongly implicates the more recently described non-canonical pathway as also contributing to pathology. Dr. May’s lab was the first to describe the functional activation of this pathway in vascular endothelial cells and they demonstrated that endothelial cell-intrinsic non-canonical NF-κB specifically regulates expression of crucial chemokines involved in lymphocyte adhesion and migration [1,2]. To explore the precise in vivo role of endothelial cell-intrinsic non-canonical NF-κB, the May lab recently generated mice conditionally lacking the major kinase required for non-canonical signaling (IKKα) in endothelial cells (IKKαEC mice). Remarkably, they found that IKKαEC animals lack all peripheral lymphoid tissues revealing an unanticipated role for endothelial cell signaling during immune development.

Ongoing studies are directed towards understanding the developmental role for endothelial cell-intrinsic non-canonical NF-κB activity. In addition, using separate genetic approaches, Dr. May’s lab is determining how ablating this pathway in vascular cells affects atherosclerosis and arthritis in mouse models of these diseases. The results of these investigations will support therapeutic targeting of non-canonical NF-κB in vascular cells for clinical use.

**Defining New Targets:** In addition to developing and employing new genetic models to study NF-κB signaling in inflammation, the May laboratory has a long-standing interest in defining the biochemical mechanisms that regulate normal and dysregulated inflammatory and immune receptor mediated NF-κB activation [3-9]. In earlier studies, Dr. May’s lab identified the signaling pathways that regulate activity of the transcription factor Nuclear Factor-kappa B (NF-κB), with a particular focus on genetically and pharmacologically targeting distinct NF-κB pathways in chronic inflammatory diseases and in cancer.

**NF-κB Signaling in Inflammation: A Tale of Two Pathways:** Chronic inflammation is a hallmark of many devastating diseases, including cardiovascular diseases such as atherosclerosis, and autoimmune diseases including rheumatoid arthritis and diabetes in both animals and humans. In addition, aberrant activation of pro-inflammatory signaling pathways such as NF-κB can drive the development of solid tumors, leukemia and lymphoma. Consequently, developing effective strategies to prevent or inhibit inflammatory cell signaling will profoundly impact human and veterinary health care.

The May lab is particularly interested in understanding how
studies, Dr. May and his colleagues identified the interaction domains between key components of the classical NF-κB pathway (NEMO and IKKβ); and by designing a small NEMO-binding peptide (NBP) to disrupt this interaction, they developed a novel but now widely used strategy to selectively inhibit classical NF-κB in vivo [10,11]. Recent studies carried out in collaboration with Dr. Reinhard Voll at the University of Freiburg, Germany, involved a novel strategy to specifically target the NBP to activated endothelial cells in vivo, thereby reducing inflammation in models of arthritis [12]. Furthermore, collaborative studies with Dr. Nicola Mason, Departments of Pathobiology and Clinical Studies, demonstrated that the NBP effectively kills canine lymphoma cells in which aberrant NF-κB signaling is a major survival signal [13]. These exciting in vitro studies led Dr. Mason and her colleagues to undertake clinical trials of the NBP in canine lymphoma at the Ryan Hospital. Current research in the May laboratory focuses on unveiling new important protein:protein interactions as amenable targets in both the classical and non-canonical NF-κB signaling pathways. By precisely defining the mechanisms controlling normal and aberrant NF-κB activation, and employing these novel peptide and endothelial cell targeting pharmacological strategies, the overarching goal is to develop new and effective clinical approaches to block pathophysiological NF-κB signaling.

Finally, the May laboratory is interested in defining the molecular “cross-talk” between the two major NF-κB signaling mechanisms. These studies are crucial for determining the overall effects of therapeutically targeting individual pathways and providing the mechanistic insight required to identify new targets for novel pathway-specific inhibitors. In pursuing these studies, the May lab provided the first demonstration [14]
The annual Phi Zeta Student Research Day was celebrated on March 11th at Penn’s School of Veterinary Medicine. The Martin M. Kaplan V40 Lecture was delivered by Charles Rupprecht, VMD, MS, PhD, from Ross University School of Veterinary Medicine. His topic was “Bats, Emerging Infectious Diseases and the Rabies Paradigm”. Phillip Scott, Vice Dean for Research and Academic Resources presented awards for the oral presentations to VMD/PhD students: Rebecca Evans (1st); Erika Lin-Hendel (2nd); Stephen Artim (3rd); and to VMD students: Ashley Klein (1st); Katelyn MacGillivray (2nd) and Chelsea del Alcazar (3rd). Competitive poster prizes were awarded to: Kelly Giffear (1st); Lauren Glowzenski (2nd) and Pierce Nathanson (3rd).

Publications


continued: Phi Zeta Student Research Day, MARCH 11, 2014

Mark your calendars for the Annual Faculty Research Retreat to be held on Friday, June 13, 2014 at the New Bolton Center campus. Garret A. FitzGerald, M.D., chair, Department of Pharmacology and director of the Institute for Translational Medicine & Therapeutics of the Perelman School of Medicine will deliver the Marshak Lecture entitled “Translational challenges in drug development”.

Link to more photos:
http://www.flickr.com/photos/pennvet/sets/72157642649663235/

Leszek Kubin, faculty poster judge talks with student Scott Pandya

Phillip Scott with student presenter Stephen Artim

Jonathan Madara at poster with alumnus Sean Maguire

Lauren Glowzenski, 2nd place poster awardee, with Dean Joan Hendricks
Dr. May continued from page 3

Carolyn Gray, Kelly McCorkell and Michael May

that disruption of tonic classical NF-κB signaling in NEMO-deficient cells affects the basal regulation of the non-canonical NF-κB pathway (Figure 1). Notably, this observation may account for the puzzling and complex phenotype observed in patients suffering from a family of inherited X-linked immune deficiencies caused by inactivating mutations in NEMO (NEMO-ID) [15]. Future studies will define the precise mechanisms controlling aberrant non-canonical NF-κB in NEMO-ID patients to establish the potential therapeutic effect of targeting this unusual pathway.

Dr. May's research is currently funded by NIH/NHLBI-R01 HL096642, and he has received previous funding from NIH/NHLBI-R01 HL080612, NIH/NIAID-NO1 A122070, the American Heart Association and the WW Smith Charitable Trust for Cardiovascular Research. His laboratory and office are located in Old Vet 200E.

References


Publications

RC Tsou, KS Rak, DJ Zimmer, & KK Bence (2014) Improved metabolic phenotype of hypothalamic PTP1B-deficiency is dependent upon the leptin receptor. Mol. Metab. in press. Commentary appears in this journal about this paper: “Relationship status update for PTP1B and LepR: It’s complicated” An elegant step in solving these questions has now been taken by the group of Kendra Bence from the University of Pennsylvania.


Penn vision scientists report that dogs, too, have an area of their retina that strongly resembles the human fovea. What’s more, this retinal region is susceptible to genetic blinding diseases in dogs just as it is in humans.


RECENT AWARDS (direct costs)

Anna Kashina
NIH/NIGMS
R01-GM108744
Regulation of actin during cell migration
4/1/14-3/31/18
$1,216,000

Anna Kashina
URF University of Pennsylvania
Protein arginylation in regulating of skeletal muscle strength
$40,000 3/1/14 to 2/28/15

Ellen Puri
NIH/NCI
R01-CA-141144-05
Fibroblast Activation Protein in the Tumor Microenvironment in Lung Cancer
7/2/13 to 1/31/15
$394,501

Ashley Boyle
Boehringer Ingelheim VetMedica
Determining optimal sampling site for strangles using loop-mediated isothermal (LAMP) PCR
1/1/2014 – 12/31/2014
$15,000

Igor Brodsky
NIH/NIAID
R21 AI109267
Role of Caspase-8 in Yersinia virulence and host defense.
1/1/14-12/31/15
$247,500

Nicola Mason
Sarcoma Pilot Grant Award (PENN)
Canine Sarcoma: Her2 and radiation
$50,000 07/01/14 to 06/30/15

Phillip Scott
NIH/NIAID R21
Resident memory T cells in leishmaniasis
4/1/14-3/31/16
$275,000

Michael May
ITMAT (UPENN)
Transdisciplinary Program in Translational Medicine and Therapeutics
Targeting Vascular Endothelial Cell-Intrinsic Non-Canonical NFkappa B
$20,000 2/1/14 to 1/31/15

Gus Aguirre
Foundation Fighting Blindness
PENN Large Animal Translational & Research Facility
4/1/14-3/31/19
$2,500,000

Leah Byrne (Beltran Lab)
NIH/NEI
F32
Optimizing Gene Therapies in Large Animal Models of Retinal Degeneration
4/1/14-3/31/17
$165,354

Mark Oyama
AKC-CHF
Genome-wide association study of myxomatous mitral valve disease in Norfolk terriers
$43,563 3/1/14-2/28/15

Cynthia Otto
Dept. of the Army
Stage 2: Maintaining Hydration of Dogs in Working Environments
$140,754 3/15/14-3/14/15

Posters Session on March 11, Student Research Day
Be on the lookout... for CHMI

The Center for Host-Microbe Interactions (CHMI) will again post a Request for Applications (RFA) for pilot projects of up to $50,000 for the duration of one year. Clinical and basic science laboratories throughout the School of Veterinary Medicine are invited to submit proposals for research projects that leverage ‘omic approaches to investigate host-microbe interactions. Funding of five projects is anticipated. A full description of the pilot program and proposal guidelines will be announced shortly.

Proposals that are cross-departmental or have a component with other Schools at Penn are strongly encouraged.

A global licensing agreement... Aratana and Advaxis have entered into an exclusive licensing agreement based on a collaboration focused on cancer immunotherapies in the treatment of several different types of cancer that commonly occur in companion animals. Immuno-oncology, an exciting advancement in treating human cancers has benefitted by an ongoing clinical study, sponsored by Advaxis, in client-owned dogs with osteosarcoma, conducted by Dr. Nicola Mason, jointly appointed in the Departments of Clinical Studies PHL and Pathobiology. In the study, dogs treated with ADXS-cHER2 immunotherapy after the standard of care (amputation plus follow-up chemotherapy), had a significant prolonged survival benefit compared with dogs that received standard care without ADXS-cHER2. The majority of the treated dogs are tumor-free. Osteosarcoma is the most common primary bone tumor in dogs, accounting for roughly 85% of tumors on the canine skeleton. Approximately 8,000-20,000 dogs a year (predominantly middle to older-aged dogs and larger breeds) are diagnosed with osteosarcoma in the United States. Advaxis has created more than 20 distinct immunotherapies based on its platform, either directly or through strategic collaborations with recognized cancer centers of excellence.

Publications


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

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