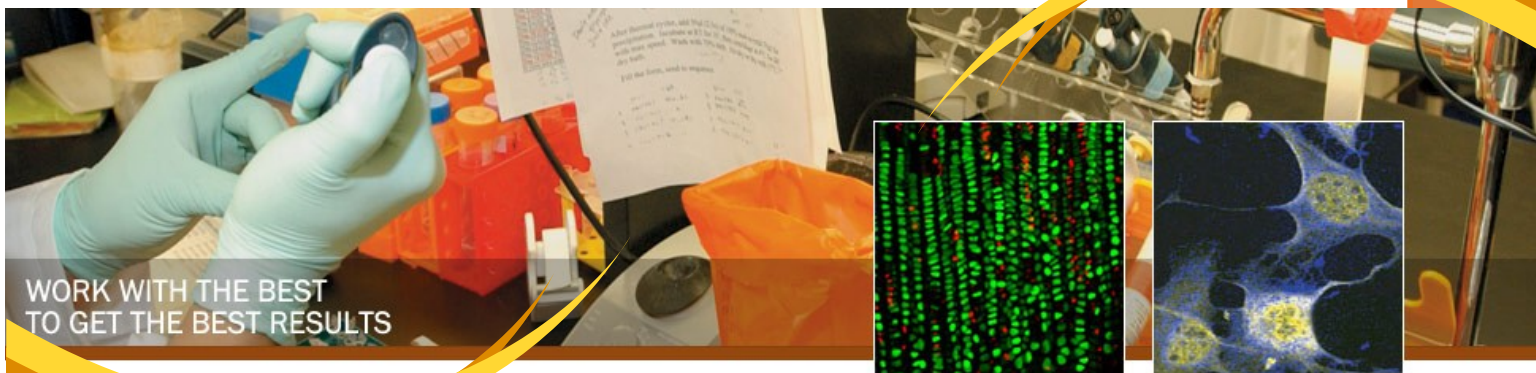




MUSCULOSKELETAL
RESEARCH CENTER
at Washington University



WORK WITH THE BEST
TO GET THE BEST RESULTS

in this issue

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Animal Model Highlight (see page 2)

Bench to Bedside



Brian Van Tine, MD, PhD
Assistant Professor
Dept. of Medicine

Metastatic and unresectable bone and muscle sarcomas are uniformly fatal. As such, the clinical management of these tumors is primarily through administration of palliative chemotherapy, which is highly toxic and only minimally beneficial. The lack of targeted therapies available to treat sarcomas is a major unmet need in the field. Argininosuccinate synthase 1 (ASS1) is the rate-limiting enzyme in the conversion of citrulline to arginine. In the absence of ASS1, arginine becomes an essential amino acid that must be delivered from the diet and/or derived from auto-

phagy, a catabolic process whereby a cell degrades its own components via lysosomal activity. We have determined that loss of ASS1 expression is a common event in sarcoma, with ASS1 expression lost in over 88% of sarcomas. This observation suggests that sarcomas may be sensitive to arginine deprivation therapy, an approach that is readily testable by administration of pegylated arginine deiminase (ADI-PEG20), an arginine – depleting enzyme. (continued on pg. 2)

Avioli Musculoskeletal Seminar Series

*BJCIH Bldg. | 11th floor
A/B Conference Room
Fridays @ 9am*

November

- 11/2 Brain Van Tine, MD, PhD
Oncology
- 11/9 Annie Schwartz
Thomopoulos Lab
- 11/16 Marja Hurley, MD
Univ. of Connecticut
- 11/30 David Burr, PhD
Indiana University

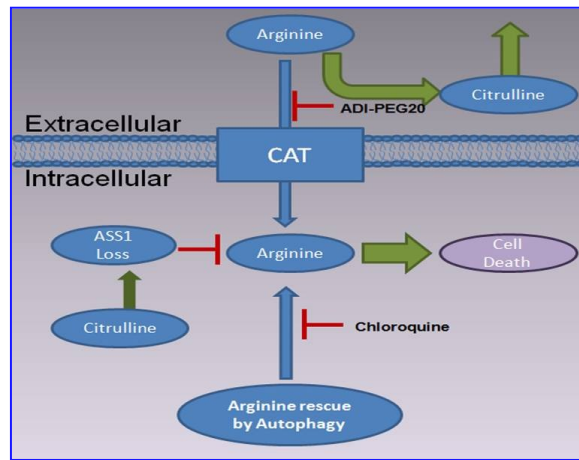
December

- 12/7 Audrey McAlinden, PhD
Orthopaedic Surgery
- 12/14 Aude-Helene Capietto,
PharmD, PhD
Faccio Lab
- 12/21 Jenna Regan, PhD
Long Lab

For more information about the MRC and the Cores, please click here:
<http://musculoskeletalcore.wustl.edu>

Please remember to include reference to support from the Musculoskeletal Research Center in your abstracts and publications.
Cite Grant # P30AR057235
from the National Institute Of Arthritis And Musculoskeletal And Skin Diseases.

(continued from pg. 1) Further experiments revealed that ADI-PEG20 induced autophagy in sensitive cell lines, which strikingly could then be triggered to undergo cell death when exposed to autophagy inhibitors. This dual treatment strategy was further validated by the successful inhibition of human sarcoma xenografts growth *in vivo*.



Animal Model Highlight

Col2-CreERT Mice

One of the mouse tools available in our Core is the Col2-CreERT^T mice developed by Susan Mackem of the NIH (*Dev. Dyn.* 2006, vol 235, 2603-2612). It can be used for the conditional deletion of cartilage-specific genes in a temporal manner via tamoxifen administration. This mouse model has been used by the Sandell laboratory to study the nature of cartilage and endochondral bone formation on Site-1 protease (Mbtsp1) ablation in postnatal mice (*J Biol. Chem.*, 2011, vol. 286, 29227-29240). Some other examples of the use of this mouse model include its application for lineage tracing of chondroprogenitor cells in the Kronenberg laboratory (*Dev. Cell*, 2010, vol. 19, 329-344) and to analyze the pathogenic mechanism of multiple hereditary exostoses in the Yamaguchi laboratory (*PNAS*, 2010, vol. 107, 10932-10937).



3rd Annual Winter Symposium

March 21, 2012

1-5pm

Eric P. Newman Educational Center

**Featured Speaker: Dr. Vicki Rosen
Harvard School of Dental Medicine**



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