GRANT PROGRESS REPORT REVIEW

Grant: 00976: *Investigating the Role of STAT3 Activation in Canine Osteosarcoma*

Principal Investigator: Dr. Cheryl London, DVM PhD

Research Institution: Ohio State University

Grant Amount: $44,361.00

Start Date: 4/1/2008   **End Date:** 3/31/2010

Progress Report: 24 month

Report Due: 3/31/2010   **Report Received:**   3/11/2010

Recommended for Approval: Approved

(Content of this report is not confidential. A grant sponsor's CHF Health Liaison may request the confidential scientific report submitted by the investigator by contacting the CHF office.)

Original Project Description:
Background: Osteosarcoma (OSA) is the most common bone tumor in dogs and despite aggressive treatment with amputation and chemotherapy, nearly all dogs die of their disease within 2 years of diagnosis. Unfortunately there have been no significant advancements in the treatment of OSA over the past 15 years. The researchers' laboratory has been working on defining the molecular biology of OSA and has recently identified a cellular pathway that appears to be important for OSA cell survival. This involves a protein called STAT3 that is often abnormally activated in human cancers and has not yet been investigated in canine cancers. Several canine OSA cell lines tested were found to have excessive STAT3 activation indicating that this pathway may be useful for therapeutic intervention.

Objective: In support of this information, the preliminary data demonstrates that an inhibitor of STAT3 activation is capable of killing canine OSA cell lines. The purpose of this grant is to perform a more thorough evaluation of STAT3 in canine OSA by determining the actual prevalence of STAT3 activation in canine OSA and by testing the ability of new STAT3 inhibitors developed by Columbus Children's Hospital to kill OSA cell lines. These studies will define the role of STAT3 in canine OSA and lay the groundwork for future clinical trials of STAT3 inhibitors in dogs with devastating disease.

Original Grant Objectives:
Objective 1: Evaluate STAT3 expression and phosphorylation in OSA tissue microarrays.

Objective 2: Determine the prevalence of and potential mechanism of constitutive STAT3 phosphorylation in canine OSA tumor cell lines.

Objective 3: Assess the consequences of STAT3 inhibition on canine OSA tumor cell lines.

Publications:
- Fossey SL, Liao AT, McCleese JK, Bear MD, Lin J, Li P, Kisseberth WK, and London CA, Characterization of STAT3 activation and expression in canine and human osteosarcoma, BMC Cancer, 10:81; 2009.

- Manuscript in preparation regarding the role of STAT3 dysregulation in canine OSA - activity of the new STAT3 inhibitor FLLL32 against OSA cell lines. Planned submission June 2010

- Manuscript in preparation regarding the role of STAT3 dysregulation in canine OSA - functional consequences of Oncostatin M stimulation of OSA cells, and its potential role in tumor progression. Planned submission June 2010

Report to Grant Sponsor from Investigator:
The purpose of this proposal is to characterize the role of STAT3 in canine osteosarcoma to assess whether this protein represents a novel target for future therapeutic intervention. We have made significant progress over the past 2 years, defining STAT3 as important for the growth and survival of osteosarcoma cells and identifying small molecule inhibitors capable of blocking STAT3 function. More recently we have been investigating the potential utility of a derivative of the spice curcumin that blocks STAT3. This derivative, FLLL32, was engineered from curcumin by the Medicinal Chemistry group at OSU to be more potent and more specific for targeting of STAT3 than curcumin. Work with this exciting new product is ongoing. Lastly, we have begun to identify factors that may be responsible for the observed activation of STAT3 in osteosarcoma and this will likely provide a broader range of future targets for therapeutic intervention. The overriding goal of this work is to eventually bring STAT3 inhibitors into clinical trials of dogs with osteosarcoma.