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Research interests: Cancer-induced bone diseases, preclinical models of cancer-induced bone diseases, small animal imaging

The goal of the research in our laboratory is better understanding of the molecular mechanisms mediating growth and progression of multiple myeloma and translation of the new insights into new therapeutic strategies. Multiple myeloma is a plasma cell neoplasm associated with extensive bone destruction. It is the second most common adult hematological malignancy. The high morbidity and mortality rates in myeloma are due to complications arising, in part, from the overall bone loss. In addition to the osteolysis, impaired bone formation in now recognized to contribute to the overall bone deficit in myeloma bone disease. Osteoblast function becomes progressively and severely impaired in patients and bone defects do not heal, even during tumor remission. Dickkopf 1 (Dkk1), an extracellular antagonist of the Wnt signaling pathway has been implicated in the impaired osteoblast differentiation and bone formation response in myeloma. We have shown that bortezomib (Velcade™), a first-in-class proteasome inhibitor that causes remarkable reductions in tumor burden in myeloma patients, exerts an anabolic effect on bone in ex vivo rodent organ cultures by inhibiting Dkk1 expression. The overall objectives of our current studies, which utilize molecular and cellular biology techniques as well as novel imaging techniques in a well established and characterized preclinical mouse model of myeloma bone disease, are to understand (i) how Dkk1 exerts its deleterious effects on osteoblast differentiation in vivo; (ii) whether bortezomib can reverse the bone deficit in myeloma; (iii) whether such a reversal involves modulation of Dkk1 expression in vivo.

Our lab also focuses on refining preclinical models of cancer-induced bone disease to facilitate translational studies. For example, we established a technique for non-invasive whole body optical fluorescence imaging for tracking myeloma tumor temporally in situ (Oyajobi et al. 2007). We have also begun to adapt ^{99m}Technetium methylene diphosphonate (^{99m}Tc-MDP)-single photon emission computed tomography (SPECT) for imaging in mouse models. Because of its extreme sensitivity, skeletal scanning using ^{99m}Tc-MDP has long been used clinically to assess changes in skeletal metabolism since its uptake is dependent on functional rather than structural changes and is largely related to rate of bone remodeling. However, there has been only limited application of this technology to the field of cancer-induced bone diseases. Recent availablility of 'state-of-the-art' micro-SPECT scanners dedicated to small animals, makes multiple, direct assessment of organ and tissue function feasible in mouse models and the advent of even newer hybrid-cameras combining microSPECT with computed tomography (CT) means unprecedented precision is achievable by co-registration of functional and anatomic data. In collaboration with Drs. Beth Goins and Bill Philips in the department of Radiology, we are validating the use of micro-SPECT for assessing osteoblastic activity and bone formation in a murine model of myeloma bone disease in vivo by comparing with 'gold-standard' histomorphometry and high resolution (<12µm) micro-CT. On-going studies also aim to use ^{99m}Tc-MDP-SPECT to evaluate whether bortezomib can reverse the bone deficit in myeloma.

Oyajobi, B.O., Muñoz, S., Käkönen, R. et al. (2007) Molecular Cancer Therapeutics **6**(6): 1701-1708.