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RESEARCH GOALS: The primary goal of our research is to elucidate the molecular mechanisms responsible for breast and kidney cancer homing to and growth in the bone environment in order to develop novel preventative and therapeutic modalities for bone metastasis. The secondary goal of our research is to develop and test experimental therapeutics for primary musculoskeletal tumors including osteosarcoma and chondrosarcoma.

RESEARCH SUMMARY AND SIGNIFICANCE: Bone is the most common site of cancer metastasis, causing severe pain, decreased mobility, neurologic compromise, and pathologic fractures. Unfortunately, by the time of diagnosis these lesions are frequently incurable. The mechanisms allowing cancer cells to flourish in the bone environment and cause excessive bone destruction or formation remain unclear. To investigate this area we have generated individual breast cancer cell lines that display a preference for metastasis to the bone or liver. By comparing gene expression in these cell lines using microarray analysis we have identified genes unique to cancer cells that metastasize to bone. The functional role of these genes is currently being explored using a novel mouse model of breast-bone metastasis developed in the laboratory. This information will then be used to generate new diagnostic and therapeutic modalities.

Using genome-wide cDNA microarray analysis to compare gene expression in primary RCC and patient-matched bone metastasis, we identified macrophage inflammatory protein-1 δ (MIP-1 δ) as being elevated in RCC metastasis to bone (RBM). Interestingly, our studies have shown that MIP-1 δ enhances osteoclast formation in cell culture models and we are currently investigating its role in RBM-induced osteolysis and pathological bone destruction in general.

CURRENT PROJECTS:

4. Characterization of the Role of the Transcriptional Co-activator Cited2 in the Establishment of Breast Cancer Bone Metastasis and Resultant Osteolysis.
5. Characterization of the Role of Macrophage Inflammatory Protein-1 δ in Renal Cell Carcinoma Bone Metastasis and Resultant Osteolysis.

RECENT PUBLICATIONS:

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2. **Kominsky SL**, Torres BA, Hobeika AC, Lake FA, and Johnson HM. Superantigen enhanced protection against a weak tumor-specific melanoma antigen: implications for prophylactic vaccination against cancer. *Int. J. Cancer* 2001; 94: 834-841.
3. **Kominsky SL**, Argani P, Korz D, Evron E, Raman V, Garrett E, Rein A, Sauter G, Kallioniemi O-P, and Sukumar S. Loss of the tight junction protein Claudin-7 correlates with histological grade in both ductal carcinoma in situ and invasive ductal carcinoma of the breast. *Oncogene* 2003; 22: 2021-2033.

4. **Kominsky SL**, Vali M, Korz D, Gabig TG, Weitzman SA, Argani P, and Sukumar S. Clostridium perfringens enterotoxin elicits rapid and specific cytolysis of breast carcinoma cells mediated through tight junction proteins claudin 3 and 4. *Am. J. of Pathology* 2004; 164: 1627-1633.
5. Murata S*, **Kominsky SL***, Vali M*, Zhang Z, Garrett E, Korz D, Huso D, Baker SD, Barber J, Jaffee E, Reilly RT, and Sukumar S. Ductal access for prevention and therapy of mammary tumors. *Cancer Research* 2006; 66(2): 638-645.
6. **Kominsky SL** and Davidson NE. A “Bone” Fide Predictor of Metastasis? Predicting Breast Cancer Metastasis To Bone. *J. Clinical Oncology* 2006; 24(15): 2227-2229.
7. **Kominsky SL**. Claudins: emerging targets for cancer therapy. *Expert Rev. Mol. Med.* 2006; 8(18): 1-11.
8. **Kominsky SL**, Doucet M, Brady K, and Weber KL. TGF- β Promotes the Establishment of Renal Cell Carcinoma Bone Metastasis. *J. Bone and Mineral Research* 2007; 22(1): 37-44.
9. **Kominsky SL**, Tyler B, Sosnowski J, Brady K, Doucet M, Nell D, Smedley JG, McClane B, Brem H, and Sukumar S. *Clostridium perfringens* Enterotoxin As A Novel Targeted Therapeutic For Brain Metastasis. *Cancer Research* 2007; 67(17): 7977-7982.
10. Weber K, Doucet M, **Kominsky S**. Renal Cell Carcinoma Bone Metastasis-Elucidating the Molecular Targets. *Cancer Metastasis Reviews* 2007; 26(3-4): 691-704.
11. **Kominsky SL**, Abdelmagid SM, Doucet M, Brady K, and Weber KL. Macrophage Inflammatory Protein-1 δ : A Novel Osteoclast Stimulating Factor Secreted by Renal Cell Carcinoma Bone Metastasis. *Cancer Research* 2008; 68(5): 1261-1266.
12. **Kominsky SL**, Doucet M, Thorpe T, and Weber KL. MMP-13 Is Over-expressed In Renal Cell Carcinoma Bone Metastasis and Is Induced by TGF- β 1. *Clinical and Experimental Metastasis* 2008; 25(8): 865-870.
13. Lau WM, Weber KL, Doucet M, Chou Y-T, Brady K, Kowalski J, Tsai H-L, Yang J, and **Kominsky SL**. Identification of Prospective Factors Promoting Osteotropism in Breast Cancer: A Potential Role for CITED2. *International Journal of Cancer* 2009 (in press).