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**RESEARCH GOALS:** The goals of my research are to understand the molecular mechanisms involved in cancers that involve the bone, either primarily or secondarily. The majority of work is focused on how primary carcinomas (ie. breast, kidney) interact with the bone microenvironment when they metastasize. Current activities focus on the role of novel osteoclast differentiating factors in the initiation of osteolytic tumor-induced destruction within the bone. Additional work is being done on the mechanisms involved in osteosarcoma metastasis to the lung. Specific factors are being identified that can be targeted with novel agents. Animal models are used to test molecular targeting of new agents.

**RESEARCH SUMMARY AND SIGNIFICANCE:** We have developed human bone metastasis-derived cell lines from a wide variety of cancers. We have also developed novel mouse models in which to study the function of specific genes in bone metastasis-related pathways. Specific drug therapies that target either the cancer cells or host bone cells can be tested in these models. We have shown that targeting the EGFR pathway decreases tumor growth and bone destruction in metastatic renal cell carcinoma. Other growth factors such as TGF- $\beta$  also play a major role in this particular cancer, and blockade has similar effects on abrogation of tumor growth. Recently we are characterizing an osteoclast differentiating factor, MIP-1 $\delta$  and its role in bone destruction and osteolytic metastasis. Renal cell carcinoma is a cancer with no reliably effective treatment once it metastasizes. Translational work in this area has the potential to markedly improve or extend the quality of life in affected patients. Novel drug delivery systems are being tested for potential use in patients with breast cancer bone metastasis. In osteosarcoma, a novel mouse model was developed to show that targeting the IGF-R1 pathway inhibits the development of lung metastasis.

### **CURRENT PROJECTS:**

1. Laboratory projects involving renal and breast cancer metastasis to bone (see above)
2. Assessing usefulness of ER consults (Carmen Pichard)
3. Assessing patient anxiety prior to image-guided needle biopsy of musculoskeletal tumors (Casey Humbyrd)
4. Ongoing mining of image-guided needle biopsy database

### **RECENT PUBLICATIONS:**

1. **Weber K**, Doucet M, Kominsky S: Renal cell carcinoma bone metastasis-elucidating the molecular targets. *Cancer Metastasis Rev*, 26:691-704, 2007.
2. Kominsky SL, Doucet M, Thorpe M, **Weber KL**: MMP-13 is overexpressed in renal cell carcinoma bone metastasis and is induced by TGF- $\beta$ 1. *Clinical and Experimental Metastasis*, 25:865-870, 2008.
3. **Weber K**, Damron TA, Frassica FJ, Sim FH: Malignant Bone Tumors. Instructional Course Lecture Series, 57:673-688, 2008.
4. Kominsky SL, Abdelmagid SA, Doucet M, Brady K, **Weber KL**: MIP-1 $\delta$  – A novel osteoclast stimulating factor secreted by renal cell carcinoma bone metastasis. *Cancer Research*, 68:1261-1266, 2008.

5. Frassica FJ, Papp D, McCarthy EF, **Weber KL**: Analysis of the Pathology Section of the OITE Will Aid in Trainee Preparation. *Clinical Orthopaedics Related Research*, 466:1323-8, 2008.
6. Chang DW, Satterfield WC, Son D, Neto N, Madewell JE, Raymond AK, Patrick CW, Miller MJ, Costelloe CM, **Weber, KL**: Use of Vascularized Periosteum or Bone to Improve Healing of Segmental Allografts after Tumor Resection: An ovine rib model. *Plastic and Reconstructive Surgery*, 123:71-78, 2009.