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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 TGF- β -induced factors in the initiation and growth of cancer cells 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.

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- β also play a major role in this particular cancer, and blockade has similar effects on abrogation of tumor growth. 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 are investigating the potential of a new drug treatment to prevent local tumor growth and metastasis in chondrosarcoma and osteosarcoma.

FUTURE DIRECTIONS/AVAILABLE RESEARCH PROJECTS: Basic molecular research: There are multiple ongoing projects available for residents interested in a basic science experience. For those without prior molecular backgrounds, drug-related experiments in animal models would be ideal in addition to work with human tissue samples. Ideally this work could start in the PGY2 year so that a good publication would result from completion of the entire project.

Clinical research: We are in the process of retrospectively developing a tumor database that includes all of Dr. Frassica, Weber, and Leitman's cases for the past 12 years. Prospective data is also being collected. Retrospective studies are available in the area of musculoskeletal oncology and prospective studies can be done if started in the PGY2 year.

RECENT PUBLICATIONS:

1. Weber KL, Lewis VO, Randall L, Lee A, Springfield D: An Approach to the Management of the Patient with Metastatic Bone Disease. Instructional Course Lecture Series, 53:663-676, 2004.
2. Weber KL: Specialty Update: What's New in Musculoskeletal Oncology. Journal of Bone and Joint Surgery, 86:1104-1109, 2004.

3. Chang DW and Weber KL: Segmental Femur Reconstruction Using an Intercalary Allograft with an Intramedullary Vascularized Fibula Bone Flap, *Journal of Reconstructive Microsurgery*, 20:195-199, 2004.
4. Weber KL: Specialty Update: What's New in Musculoskeletal Oncology. *Journal of Bone and Joint Surgery*, 87:1400-1410, 2005.
5. Hammoud S, McCarthy EF, Weber K: Tumoral Calcinosis in Infants: A Report of Three Cases and Review of the Literature. *Clinical Orthopaedics and Related Research*, 436:261-264, 2005.
6. Bhattacharya B, Dilworth HP, Iacobuzio-Donahue C, Ricci F, Weber K, Furlong MA, Fisher C, Montgomery E: Nuclear β -catenin Expression Distinguishes Deep Fibromatosis from Other Benign and Malignant Fibroblastic and Myofibroblastic Lesions, *Am J Surg Pathol*, 29(5):653-659, 2005.
7. Hammoud S, Weber K, McCarthy EF: Unicameral Bone Cysts of the Pelvis: A study of 16 cases, *Iowa Orthopaedic Journal* July, 2005.

PAST RESIDENT RESEARCH PROJECTS:

Alden K, Weber K, Hungerford M: Periprosthetic Thyroid Metastasis after Total Knee Arthroplasty: A Report of Two Cases and Review of the Literature