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Perspective Article

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Summary – Cancer cell metastasis session

Session Chair: C.M. Bagi

Pfizer Inc., Global Reasearch and Development, Drug Safety Evalution, Groton, CT, USA

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Metastasis, the spread of cancer cells to distant sites in the body and the invasion of normal tissue by cancer cells, is the hallmark of malignancy. Our understanding of rules governing the formation of human tumor cells and metastasis is progressing rapidly. Over the past decade we have learned far more about the many steps involved in the conversion of normal cells to cancer cells, and the subsequent processes involved in establishment of metastasis. In his introductory talk **Dr. E. Keller** (University of Michigan) reviewed the multistep process of cancer metastasis and "Seed and Soil" theory proposed by Dr. S. Paget more than a century ago. Dr. Keller briefly discussed the rationale for using the metastasis suppressor genes since each step of the metastasizing process is probably controlled by a different molecular system, a failure of which would most likely render a tumor cell incapable of metastasizing. **Dr. D. Welch** (Jake Gittlen Cancer Research Institute) spoke about challenges and opportunities in cancer research, in particular breast cancer metastases to bone. Prostate and breast cancer as well as myeloma cells metastasize to bone 70-80% of the time. Dr. Welch described some of the properties of the bone microenvironment that contribute to bone metastases including the growth factors and cytokines that are stored in the bone matrix. He concluded that recent development of *in vitro* and *in vivo* models has provided the opportunity to study the earliest steps of the process of bone colonization by the cancer cells. He showed some exciting data from his laboratory using BRMS1 suppressor gene and human breast carcinoma cells. **Dr. H. Donahue** (Penn State University) described the importance of intercellular communication in breast cancer metastasis to bone. Stromal cells in the primary and metastatic target organs are important mediators of cancer cell extravasation, chemoattraction, target organ endothelium adhesion, and tumor cell growth at the site of metastasis. Dr. Donahue and his colleagues developed an *in vitro* model system to test their working hypothesis that could explain the role of altered gap junctional communication in breast cancer cell metastasis to bone. **Dr. T. Guise** (University of Texas, San Antonio) presented a comprehensive overview of the vicious cycle between cancer cells, osteoclast mediated bone resorption, and growth factors and cytokines released from the bone matrix as a consequence of PTHrP stimulated bone resorption. The emphasis was made on PTHrP stimulated bone resorption through stromal cells and RANK ligand with consequent release of TGFβ and increase of PTHrP via Smad and MAP kinase pathways. She also discussed involvment of other osteolytic factors in osteolytic bone metastsis including IL-6 and IL-11 in particular in those metastatic tumors that are PTHrP negative. Finally, Dr. Guise talked about osteoblastic metastasis and accumulating evidence suggesting a central role of ET-1 in eliciting the osteoblastic bone response. Taken together, convincing evidence exists to suggest that tumor cells selectively interact with the bone microenvironment which led to identification of novel therapeutic targets and interventions aimed at both osteolytic and osteoblastic metastases. **Dr. C. Bagi** (Pfizer, Groton) gave an overview of cancer of the prostate and implications for bone metastases. He stressed that bone metastases have severe impact on the quality of life of cancer patients and include intractable pain, fractures, nerve compressions and/or pulses, marrow suppression, and hypercalcemia of malignancy. Once established, bone metastases are more resistant to therapy than cancers in other sites. Anticancer treatment, particularly estrogen and androgen ablation in breast and prostate cancer patients also has severe impact on already compromised skeletal tissue and can cause so-called "cancer osteoporosis". Radiation therapy, cytotoxic therapy and glucocorticoid therapy along with muscular weakness and inactivity further add to bone loss and propensity for fracture. Therefore, improved treatment of the skeletal consequences of malignancy will impact the disease progression, but perhaps more importantly will improve the quality of life of patients affected with metastatic disease. Finally, Dr. Bagi presented data utilizing CWR22 human prostate cell line capable of eliciting osteoblastic response, a hallmark of metastatic prostate cancer. At the

Corresponding author: Cedo M. Bagi, M.D., Ph.D., Drug Safety (and Efficacy) Pfizer Inc., Global Research and Development, Eastern Point Road 8274-56, Groton, CT 06340, USA
E-mail: cedo_bagi@groton.pfizer.com

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end of the session **Dr. Keller** (University of Michigan) spoke about high-throughput screening methods, such as gene array and tissue microarrays and the potential of these methods to facilitate identification of putative factors important in the promotion of bone metastases.

Interest in the skeletal complications of malignancy continues to increase. There are several reasons for this growing trend including an aging population, higher incidence of cancer, improved diagnostic tools, and more effective anticancer therapy. In addition, life expectancy has been prolonged, in particular in the patient population suffering from breast and prostate cancer. The development of new therapies for metastatic carcinoma requires a better understanding of the mechanism of homing of the tumor cells to bone, liver and lungs and the factors required for their growth in these organs. Even though many questions regarding cancer metastases to bone remain to be addressed, the session covered some of the most relevant issues regarding metastatic disease with emphasis on principles of the cancer metastasis process and cell-cell communication, breast and prostate cancers and bone metastases, and finally on available high-throughput screening methods that should facilitate our understanding of metastatic process and help drug discovery efforts.