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Targeting the Tumor Microenvironment of Metastasis to Treat Metastatic Ewing Sarcoma

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Ewing sarcoma is the second most common bone tumor in adolescents and young adults. Over the years, a series of clinical trials has dramatically improved the survival of children diagnosed with Ewing sarcoma that has not spread – from 20% in the 1970's to over 75% today. During this timeframe, outcomes for patients who either present with metastatic tumors (tumors that have spread from their primary site) or who suffer a metastatic relapse have not improved at all. Currently, treatment of these patients includes intensive (and very toxic) chemotherapy, surgery, radiation, and sometimes bone marrow transplantation. Thus, there is an urgent need to understand the biology of Ewing sarcoma metastasis and to develop new, less toxic, treatments based on this understanding. Our group has developed a clinically relevant mouse model of Ewing sarcoma metastasis that we have used to study this process in the lab. We discovered that a drug that blocks the Wnt signaling pathway in Ewing sarcoma cells prolongs survival of these mice. Our collaborators have discovered a new mechanism of cancer metastasis, dubbed Tumor Microenvironment of Metastasis, or TMEM, that can be inhibited by other relatively nontoxic drugs. We have preliminary evidence that TMEM functions in Ewing sarcoma, and plan to explore ways to interfere with TMEM in our mouse models to develop novel, less toxic treatments to prevent Ewing sarcoma metastasis in patients. We will approach this problem in three ways. First, we will perform tests designed to confirm that TMEM in Ewing sarcoma functions in the same way as has been described in breast and pancreatic cancer. Next, we will use a panel of targeted therapies to determine which can interfere with TMEM function in Ewing sarcoma. These will include inhibitors of a variety of signaling pathways, all of which have been implicated in TMEM function. Each inhibitor being tested is available for administration in clinical trials. Our third step will be to test drugs that individually inhibit TMEM function in combinations to see which are able to prevent metastasis in our mouse models. Effective combinations will then be tested in clinical trials with the expectation that they will provide a relatively well-tolerated, less toxic treatment to prevent metastasis and improve survival.