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"Developing targeted therapy for Ewing sarcoma metastasis"

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SCIENTIFIC ABSTRACT
Ewing sarcoma is a pediatric cancer of bone and soft tissue. Despite aggressive treatment, patients with metastases have a 5-year survival rate of 20-30%. The failure to treat Ewing sarcoma is due to the lack of understanding of the molecular pathways that regulate metastasis. Although the cellular origin of Ewing sarcoma remains unknown, reports suggest that Ewing sarcoma could be traced back to neural crest cells. Neural crest cells migrate throughout the body to form bone, neurons, and soft tissues during embryogenesis. The extensive cell migration shares similarities with tumor cell invasion and metastasis. Our studies show that the Twist1 transcription factor, a key regulator of neural crest formation, is a negative prognostic marker for overall survival in Ewing sarcoma patients. TWIST1 is detected in significantly higher percentage of patients with metastatic disease than localized disease. , Knocking down TWIST1 suppressed lung metastasis In Ewing sarcoma tumor xenografts in mice and inhibited cell migration and invasion in culture.

We hypothesize that reactivation of the neural crest developmental pathway contributes to Ewing sarcoma metastasis. We propose to study the downstream transcriptional targets of Twist1 and their roles inEwing sarcoma metastasis. PDGFRα is a direct transcription target of Twist1 and is required for the ability of Twist1 to promote invasion. The proposed study explores whether therapeutic targeting of PDGFRα is a viable approach to treat metastatic Ewing sarcoma.

LAY ABSTRACT
Ewing's sarcoma is a malignant tumor that commonly appears in a bone. It usually occurs between 10-20 years of age. About 25% of patients present with clinically detectable metastatic disease. Because of the possibility of undiagnosed metastatic disease, chemotherapy, surgery and radiation therapy are applied for all patients. Despite aggressive therapy, almost no improvement has been seen in patients with metastatic disease (80% mortality). The failure to stop Ewing's sarcoma metastasis is due to the lack of understanding about the molecular pathways that regulate its spreading. To address this unmet need, we hypothesize that a group of genes that regulate the generation and function of a specialized group of embryonic stem cells (neural crest cells) are reactivated to allow Ewing's sarcoma cells to metastasize. Our previous study show that expression of one such gene (Twist1) is associated with metastasis and poor survival in Ewing's sarcoma patients. Therefore, we propose to examine Twist1 and other genes regulated by Twist1 in Ewing sarcoma metastasis and to test whether drugs targeting these genes will block metastasis with higher specificity and fewer side effects than conventional therapy.

In the short term, the proposed research provides new prognostic markers to identify high-risk Ewing sarcoma patients for personalized treatment options. In the long term, the proposed research could lead to novel therapeutic regimens that reduce morbidity from ineffective conventional therapies and save the lives of countless children affected with metastatic Ewing's sarcoma.