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New study finds compounds show promise in blocking STAT3 signaling as treatment for osteosarcoma

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A study appearing in the journal *Investigational New Drugs* and conducted by researchers at Nationwide Children's Hospital, discovered that two new small molecule inhibitors are showing promise in blocking STAT3, a protein linked to the most common malignant bone tumor, osteosarcoma. These small molecule inhibitors – one derived from a portion of the turmeric spice – may serve as a new, non-toxic treatment for these deadly tumors.

Osteosarcoma is aggressive and its treatment outlook has not changed significantly over the last 20 years. Treatment consists of a combination of toxic chemotherapy and aggressive surgical resection. Yet, despite these options, patients have at most a 50-to-60 percent five-year disease-free survival rate.

"The outcome for patients with advanced or metastatic osteosarcoma continues to be dismal, emphasizing the need for new therapies," said the study's lead author Jaiyuh Lin, PhD, principal investigator in the Center for Childhood Cancer in The Research Institute at Nationwide Children's Hospital. "Directly targeting STAT3 signaling represents a potential therapeutic approach to treating this type of cancer."

STAT3 is a member of a protein family that plays a role in relaying signals from cytokines and growth factors. The abnormal activation of STAT proteins is becoming more commonly associated with unrestricted

cell growth and transformation of normal cells into malignant cells. Abnormal STAT3 activation has been seen in human and canine osteosarcoma cell lines and shows cancer-causing-capabilities in cultured cells and mouse models.

"Recent experiments aimed at blocking STAT3 signaling have been successful, resulting in the inhibition of growth and the induction of death in tumors," said Dr. Lin, also a faculty member at The Ohio State University College of Medicine. "They have also shown that blocking STAT3 in normal cells is neither harmful nor toxic."

Dr. Lin and his team evaluated two newly developed compounds, LLL12 and FLLL32, to determine their ability to inhibit STAT3 activity in human osteosarcoma cells. FLLL32 is derived from the dietary agent curcumin, the principal compound in the popular Indian spice turmeric.

Findings showed that both agents were able to inhibit STAT3 activity and suppressed tumor growth in the mouse model that was developed using human osteosarcoma cells, and primary osteosarcoma xenograft provided by Nationwide Children's Hospital scientist, Peter Houghton, PhD, directly from a patient.

"This study suggests that LLL12 and FLLL32 should be suitable for targeting osteosarcoma and possibly certain types of cancer cells with persistently activated STAT3," said Dr. Lin. "This approach deserves further exploration as a potential treatment of osteosarcoma."

Provided by Nationwide Children's Hospital

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