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New approach to drug resistance in aggressive childhood cancer discovered

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Researchers at Oregon Health & Science University Doernbecher Children's Hospital have identified a promising new approach to overcoming drug resistance in children with an extremely aggressive childhood muscle cancer known as alveolar rhabdomyosarcoma. Their findings are published online this week in the journal *Molecular Cancer Therapeutics* and will be featured on the cover of the journal's print edition next month.

Rhabdomyosarcoma accounts for more than 50 percent of all soft-tissue cancers in children. Even after extensive therapy, the survival rate among alveolar rhabdomyosarcoma patients with advanced disease is less than 20 percent. Dismal outcomes such as these are what keep researchers in the Pediatric Cancer Biology Program at OHSU Doernbecher working around the clock toward a breakthrough.

"Despite our best efforts, outcomes for metastatic alveolar rhabdomyosarcoma have not improved for decades. That's why our findings are significant. Our clinical partners now have a new method of mitigating resistance to the current treatment for childhood muscle cancer," said Jinu Abraham, Ph.D., lead author and senior research associate in the Pediatric Cancer Biology Program at OHSU Doernbecher, and a member of the OHSU Knight Cancer Institute.

Previous studies led by Charles Keller, M.D., leader of the Pediatric Cancer Biology Program at OHSU Doernbecher, have shown an important relationship between increased growth factor signaling

through the insulin-like growth factor receptor (Igf1r) and decreased survival in children with alveolar rhabdomyosarcoma, a rare form of muscle cancer that typically occurs in the limbs, chest or abdomen of children and adolescents. Growth factor signaling is required for normal development but impairment of this pathway causes abnormal cell growth.

In the current study, Abraham and colleagues tested whether the non-chemotherapy drug NVP-AEW541 could stop Igf1r signaling in a novel mouse model genetically engineered so that alveolar rhabdomyosarcoma tumors begin and expand in the same places they are found in children. Their results showed the non-chemotherapy drug blocked tumor progression in 33 percent of mice with tumors, but most of the mice developed resistance to the drug.

To uncover the reason for resistance, the researchers conducted additional experiments that showed Igf1r partners with another tumor surface enzyme known as Her2, which fueled the tumor growth despite the growth factor-inhibiting drug.

"Fortunately, when we treated resistant rhabdomyosarcoma cells with a combination of the Igf1r inhibitor and the Her2 inhibitor Lapatinib, there was a significant increase in tumor cell killing compared with either drug alone," explained Abraham. "Our study has shown that targeting both Igf1r and Her2 may be a very promising approach in preventing resistance to Igf1r-inhibiting drugs in rhabdomyosarcoma."

"Understanding why some rhabdomyosarcoma tumors are resistant to Igf1r inhibitors is vital to studying these drugs in the clinical setting. This discovery in the lab gives us an option for trying to overcome this resistance and will guide how we combine these new targeted therapies to treat patients with cancer," said Suman Malempati, M.D., co-author of the current study and principal investigator for the first national clinical

trial using an Igf1 receptor inhibitor in combination with chemotherapy for metastatic rhabdomyosarcoma.

The Children's Oncology Group (COG) trial, now taking place at OHSU Doernbecher Children's Hospital and several other COG sites, is the first in North America to incorporate a molecularly targeted drug into a clinical trial for childhood muscle cancer.

Provided by Oregon Health & Science University