Integrated analysis finds vulnerabilities to target in a high-risk pediatric tumor

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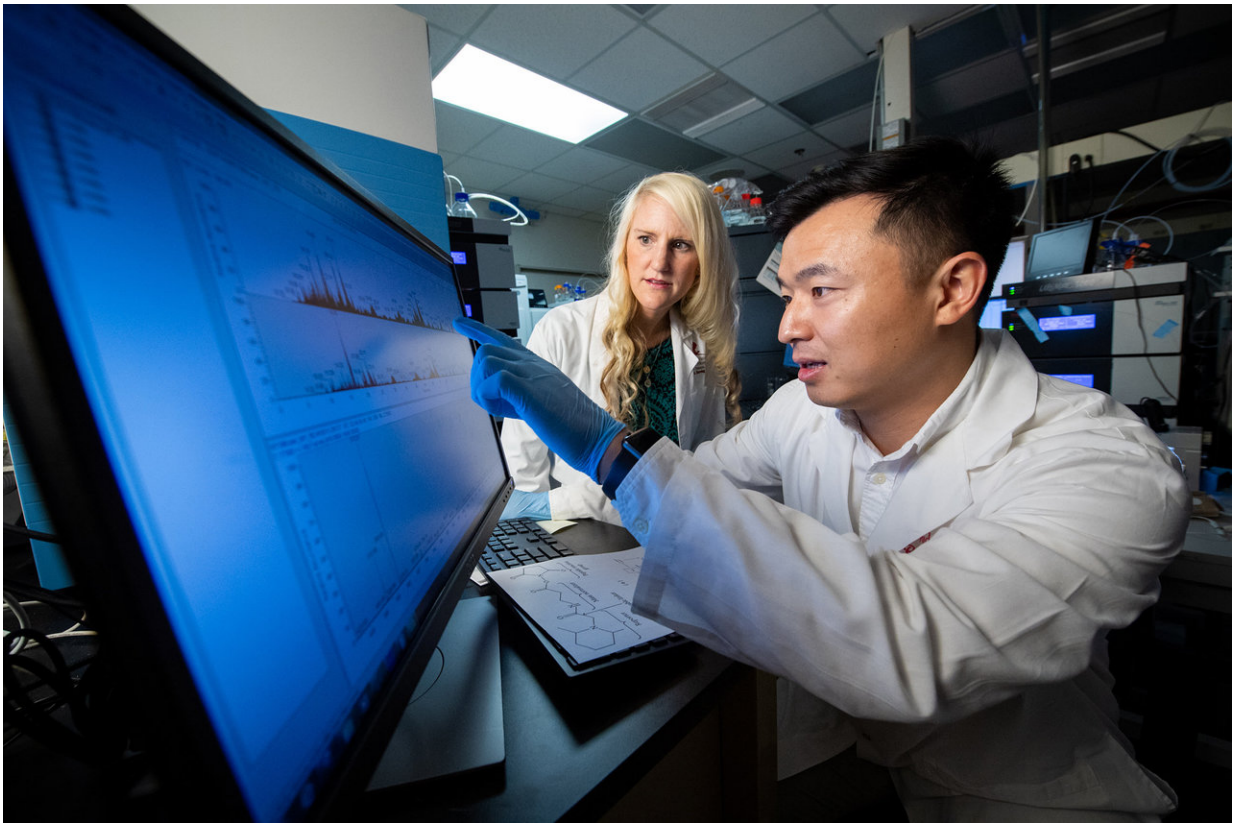

Elizabeth Stewart, M.D., and Hong Wang, Ph.D. of St. Jude Children's Research Hospital. Credit: St. Jude Children's Research Hospital

St. Jude Children's Research Hospital investigators have completed the most comprehensive analysis yet of a common pediatric solid tumor,

identifying weaknesses to target and a promising precision medicine that is now in clinical trials. The findings appear today in the journal *Cancer Cell*.

The research, part of the St. Jude Children's Research Hospital—Washington University Pediatric Cancer Genome Project, focused on the muscle and soft tissue tumor rhabdomyosarcoma. The tumor occurs in about 350 children and adolescents nationwide each year. Cure rates are 75 percent for patients whose tumors have not spread, but long-term survival is 30 percent or less for those with metastatic disease or those whose tumor returns. For these high-risk patients, overall survival has not improved significantly in 15 years.

"Recent advances in technology allowed us to extensively profile rhabdomyosarcoma to better understand its cellular origins as well as identify and prioritize vulnerabilities that extend beyond just the somatic (tumor) mutations," said Elizabeth Stewart, M.D., an assistant member of the St. Jude Department of Oncology. Stewart, Hong Wang, Ph.D., and Xiang Chen, Ph.D., of St. Jude, and Justina McEvoy, Ph.D., formerly of St. Jude, are co-first authors.

Researchers identified several signaling pathways that are disrupted in tumor cells. AZD1775, or adavosertib, inhibits an enzyme in one of the newly identified disrupted pathways. Extensive preclinical testing followed, results of which prompted the Children's Oncology Group to expand a multicenter phase I/II clinical trial of AZD1775 and the chemotherapy agent irinotecan to include high-risk pediatric rhabdomyosarcoma patients.

"This research offers a template for exploring the origins and vulnerabilities of solid tumors by looking not only at somatic mutations, but also at epigenetic changes and ultimately differences in how those changes are manifest in protein expression and activity," said senior and

corresponding author Michael Dyer, Ph.D., chair of the St. Jude Department of Developmental Neurobiology and a Howard Hughes Medical Institute investigator. "The research also highlights how preclinical models and extensive preclinical testing can help prioritize and streamline drug development."

"As genome sequencing technology improves, we continue to learn new information—not just about about the genetic alterations underlying certain cancers but about epigenetic changes and pathways disrupted by cancer," said Robert Fulton, director of technical development at Washington University's McDonnell Genome Institute. "This knowledge is critical for developing more effective drugs and treatment strategies."

Findings

The research extensively profiled cell signaling pathways disrupted in rhabdomyosarcoma, including the newly identified G2/M pathway and the unfolded protein response pathway. The analysis also confirmed previous reports that the RAS pathway is deregulated in rhabdomyosarcoma. AZD1775 inhibits an enzyme (WEE1) in the G2/M pathway, which helps regulate cell division, a process that is disrupted in cancer. In contrast, the unfolded protein response pathway is involved in protein folding, which helps maintain cellular homeostasis.

AZD1775's potential for treatment of high-risk rhabdomyosarcoma was identified through extensive preclinical testing, which began with screening more than 1,700 drug-tumor combinations.

The testing ultimately involved tracking the safety and effectiveness of several promising drug candidates in hundreds of mice with different human rhabdomyosarcoma tumors grown in the muscle. These tumors, called orthotopic patient-derived xenografts, provide a more realistic model for preclinical testing of drugs.

Along with the disrupted pathways, researchers discovered that the two main varieties of rhabdomyosarcoma—embryonal and alveolar—occurred at different developmental timepoints. "We knew embryonal and alveolar rhabdomyosarcoma involve different mutations, often occur in different locations in the body and are most common in children of different ages," Stewart said. "Now we have evidence they involve genes active at different stages of development and that alveolar rhabdomyosarcoma occurs further along the developmental program as cells become more specialized."

Challenges

The study is notable for the breadth and depth of the analysis.

Since its launch in 2010, the Pediatric Cancer Genome Project has sequenced the complete normal and cancer genomes of 700 young cancer patients, including patients with rhabdomyosarcoma.

This study expanded the project to include whole-genome bisulfite sequencing and chromatin immunoprecipitation (ChIP) to study epigenetic differences in tumor and normal tissue. The epigenome includes chemical tags like methyl groups that attach to DNA and histones to switch genes on and off to regulate protein expression.

Researchers used additional methods, including RNA sequencing, to compare gene expression and quantify protein expression (the proteome) and activity (the phosphoproteome.) "The proteomic and phosphoproteomic analysis made it possible to take a closer look at pathways that help explain tumor formation and provide insight into potential vulnerabilities," Stewart said. Wang, one of the first authors, led that effort.

Sharing

Pediatric solid tumors like rhabdomyosarcoma are rare and so are the tissue samples researchers need to better understand and treat the diseases.

Tumor tissue in this study came from orthotopic patient-derived xenografts. The samples are part of a larger ongoing effort based at St. Jude and led by Dyer and Alberto Pappo, M.D., of the St. Jude Department of Oncology. The goal is to share these orthotopic patient-derived xenografts of rhabdomyosarcoma and other pediatric solid tumors with researchers around the world to accelerate efforts that could lead to improved outcomes for patients.

The samples and related scientific data are available to researchers worldwide through the Childhood Solid Tumor Network, which is based at St. Jude. The resources come with no obligation to collaborate with St. Jude scientists.

Researchers can also access study data through the online PeCan portal developed by St. Jude.

Provided by St. Jude Children's Research Hospital