Scientists unveil powerful resource to advance treatment of pediatric solid tumors

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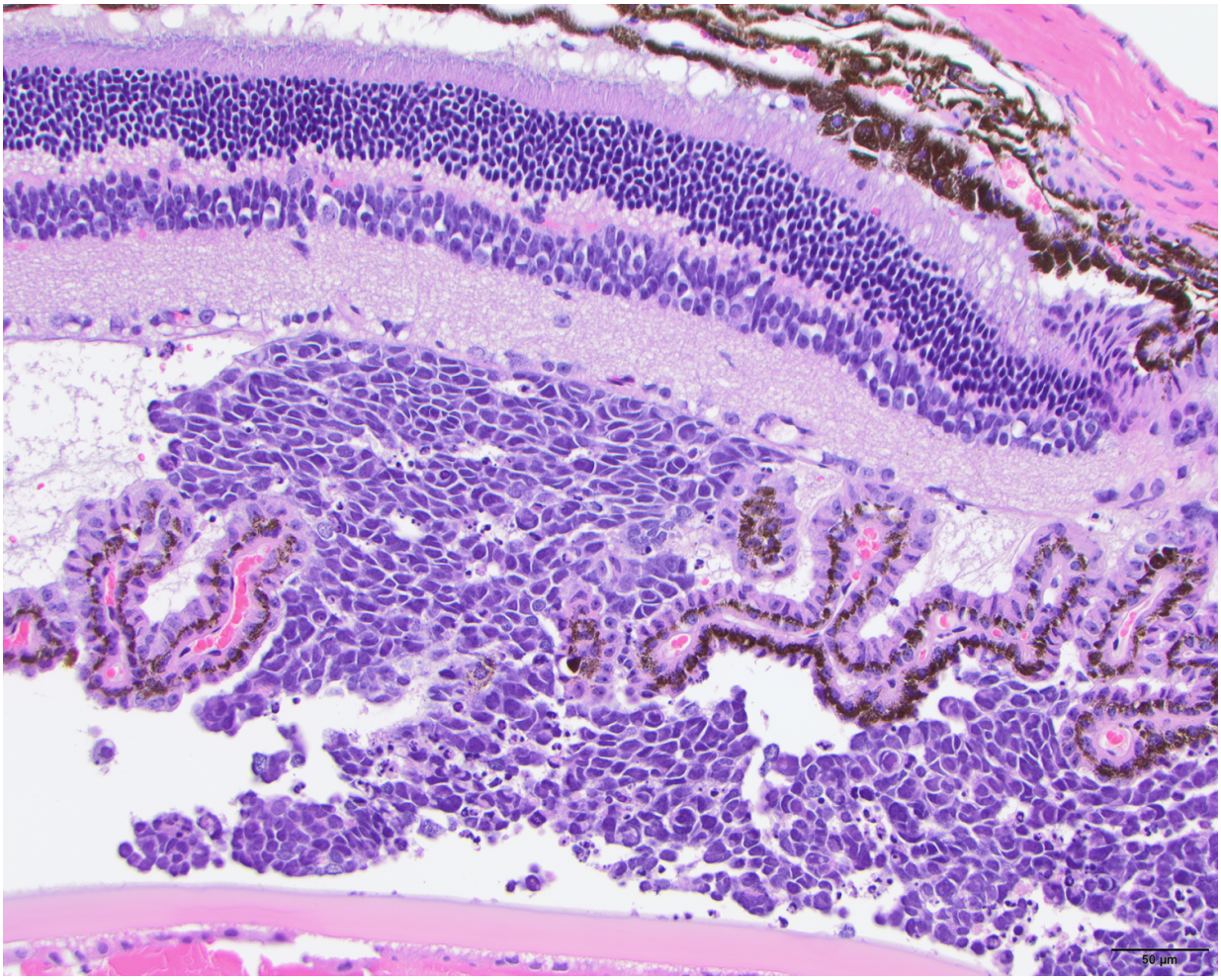


Histology image of a retinoblastoma sample taken with 20x magnification. Credit: Michael Clay, MD, St. Jude Children's Research Hospital

In an effort to improve outcomes for patients with some of the deadliest childhood cancers, St. Jude Children's Research Hospital scientists have created the world's largest collection of pediatric solid tumor samples, drug-sensitivity data and related information and have made the resource available at no charge to the global scientific community.

St. Jude and the Howard Hughes Medical Institute collaborated to create the resource, known as the Childhood Solid Tumor Network. The work is reported today as an advance online publication in the scientific journal *Nature*.

"Survival rates for children with recurrent solid tumors have not improved significantly in more than 20 years and remain below 30 percent," said corresponding author Michael Dyer, Ph.D., chair of the St. Jude Department of Developmental Neurobiology and a Howard Hughes Medical Institute investigator. "This research will change that by promoting scientific collaboration to leverage the efforts of researchers worldwide to advance understanding and ultimately treatment of pediatric solid tumors."

The project has already helped identify children with the muscle tumor rhabdomyosarcoma as the pediatric solid tumor patients most likely to benefit from combination chemotherapy that includes the experimental drug AZD1775. Planning has begun to incorporate the finding into an ongoing national clinical trial of the combination therapy for certain high-risk pediatric solid tumor patients.

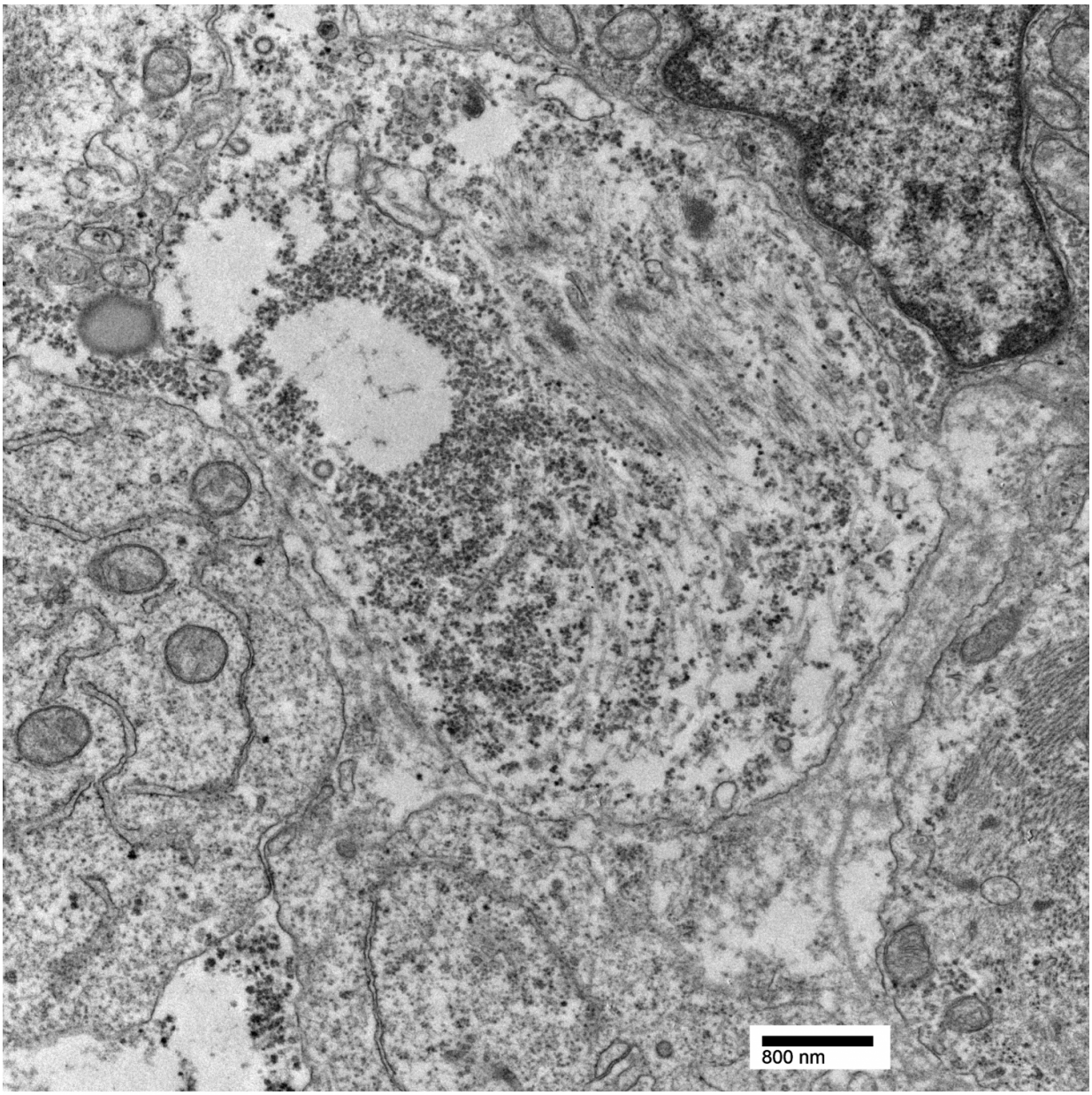
Pediatric solid tumors are rare and so are the tissue samples and other resources needed to advance their understanding and treatment. Solid tumors of the bone, muscle, kidney, eye and other organs excluding the brain account for about 30 percent of childhood cancers. While the overall cure rate for these pediatric solid tumors is 75 percent, long-term survival is much lower for the approximately 30 percent of patients

whose tumors return.

The Childhood Solid Tumor Network was created to share the patient tumor samples and other scientific resources Dyer and his colleagues have developed by learning to grow human tumors in the same organ in mice. The network now includes samples from more than 67 different patient tumors representing 12 types of pediatric solid tumors. Along with the tumor samples, information about the drug sensitivity, pharmacokinetics and the molecular make-up of the tumors is also available. Accessing the data requires no commitment to collaborate with St. Jude scientists.

The network has significantly expanded scientific resources for pediatric solid tumor research. For example, through the Childhood Solid Tumor Network, investigators studying the bone cancer osteosarcoma have an additional 20 patient tumor samples available for research to supplement five osteosarcoma cell lines now widely used to study the tumor. For the eye tumor retinoblastoma, available resources increased from two cell lines that have been widely used for research to an additional 18 retinoblastoma tumor samples.

"When the St. Jude-Washington University Pediatric Cancer Genome Project started to sequence the complete tumor and normal genome of pediatric cancer patients, we realized we needed better models to take full advantage of the discoveries," Dyer said. The genome project began in 2010 to sequence the genomes of 600 children and adolescents with some of the least understood and most difficult to treat cancers.



Cell nucleus in the upper right corner of a sample of rhabdomyosarcoma with characteristic glycogen accumulation and filaments forming early z-bands (center), and lipid, basement membrane and tight junctions also present. Credit: CTI-EM Core, St Jude Children's Research Hospital

With the consent of patients and parents, researchers developed a system

to grow St. Jude patient tumors in the same organ in mice. Such tumors are called orthotopic patient-derived xenografts. The standard approach has been to grow patient tumors in the flank of mice.

"The tumor samples were collected at diagnosis, recurrence and autopsy. Many came from patients with recurrent disease, which is important since previously we have had few models of recurrent pediatric solid tumors," Dyer said.

In the first five years, tumor samples from the biopsies and surgical specimens of 168 St. Jude patients resulted in 67 pediatric solid tumors, representing neuroblastoma, osteosarcoma, Wilms tumor, retinoblastoma, rhabdomyosarcoma and other less common tumors. Patient identification was removed.

A comprehensive analysis comparing the original patient tumor to the orthotopic xenografts showed many orthotopic patient-derived xenografts retained their "molecular fingerprint" even after being grown in successive generations of mice. That suggests the tumors maintain their molecular identity when grown in the same microenvironment in mice and provide more accurate models for tracking tumor development and drug sensitivity, Dyer said.

Along with whole-genome and whole-exome sequencing and gene-expression profiling, the analysis included the most detailed examination yet of the genomic or clonal complexity of pediatric solid tumor orthotopic xenografts. Solid tumors include subsets of cancer cells called clones that have different mutations. Understanding and addressing clonal diversity is key to obtaining better cure rates because failure to kill all the clones in a tumor leaves the door open for cells from one clone to multiply and trigger a fatal relapse.

Researchers also demonstrated the potential of orthotopic xenografts to

speed drug discovery and advance multi-drug chemotherapy. The scientists developed a new method that uses orthotopic xenografts to enhance sensitivity of drug screening to help identify the most promising compounds to move into clinical trials. The results, which include more than 500,000 data points on drug sensitivity, metabolism and related information, are available to the global biomedical research community in what is believed to be the world's only free searchable database for childhood cancer.

Drug sensitivity screening helped researchers identify rhabdomyosarcoma as particularly sensitive to AZD1775, an inhibitor of the enzyme WEE1 that is involved in cell division and expressed at high levels in a variety of solid tumors. Investigators used orthotopic xenografts of high-risk rhabdomyosarcoma to show that the tumors responded when AZD1775 was combined with the chemotherapy drugs irinotecan and vincristine, which are currently used against rhabdomyosarcoma.

"This study shows that orthotopic patient-derived xenografts can serve as a bridge connecting basic and translational research to improve outcomes for patients," Dyer said. "It serves as the gold standard for development, characterization and use of patient-derived tumors."

Efforts continue to develop additional orthotopic patient-derived xenografts. The Childhood Solid Tumor Network now includes almost 100 pediatric solid tumors. Scientists plan to expand the effort to include induced pluripotent stem cells from children who are genetically predisposed to develop cancer. These are cells that have been reprogrammed to function as stem cells, which have the potential to become any cell type in the body.

More information: Elizabeth Stewart et al, Orthotopic patient-derived xenografts of paediatric solid tumours, *Nature* (2017). DOI:

10.1038/nature23647