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Targeting a transporter to treat SHH medulloblastoma

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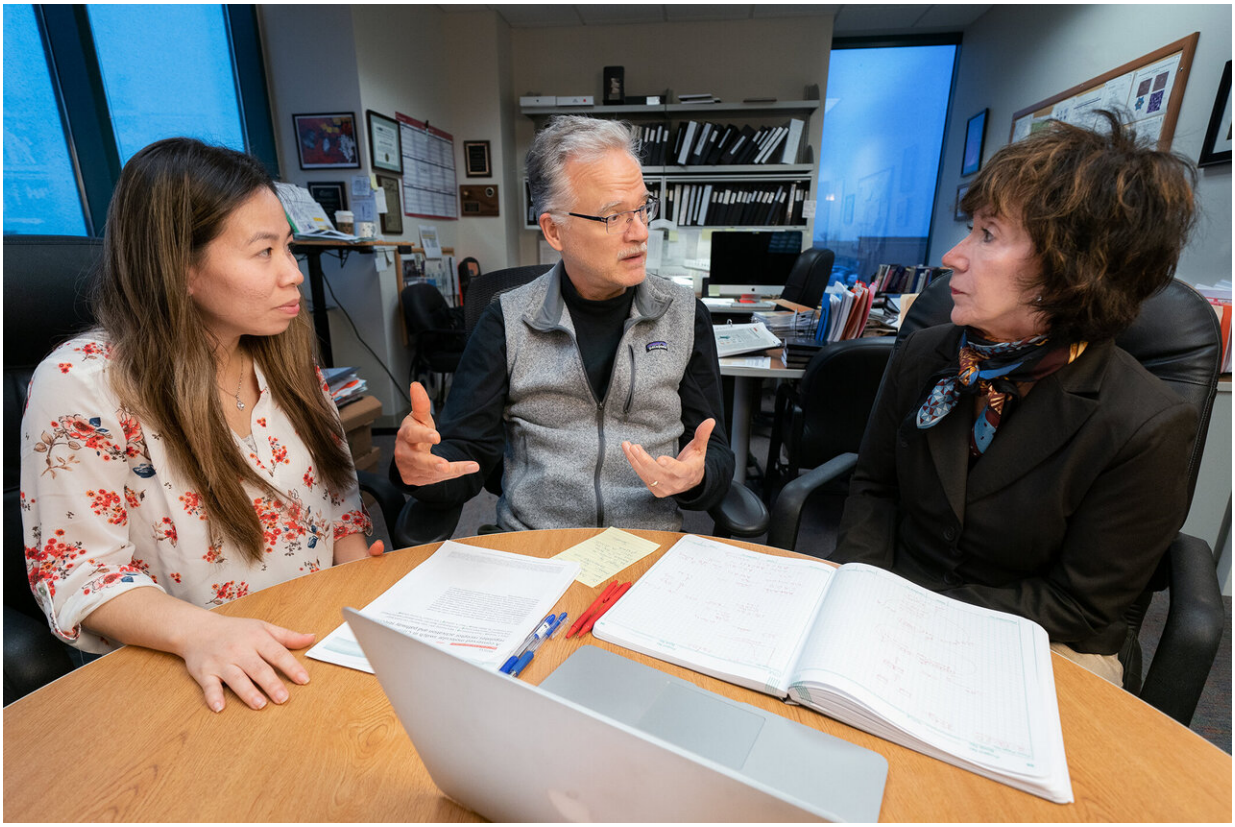

From left to right: First author Juwina Wijaya, Ph.D., and senior author John Schuetz, Ph.D., both of Pharmaceutical Sciences; and co-author Martine Roussel, Ph.D., of Tumor Cell Biology, provide research on a new target for medulloblastoma. Credit: St. Jude Children's Research Hospital

Investigators at St. Jude Children's Research Hospital have found that

the ABCC4 transporter is critical to the SHH signaling pathway in the brain tumor medulloblastoma. This work provides a rationale for development of small molecule inhibitors that target ABCC4. The findings appeared in *Cancer Research*.

Medulloblastoma is the most common malignant pediatric brain tumor. There are four genomic subgroups of the disease: WNT, SHH, Group 3 and Group 4. The SHH subgroup accounts for about 25% of all pediatric medulloblastoma cases. The five-year survival rate for SHH medulloblastoma is approximately 75%.

Transporters are proteins found on the cell membrane. They help substances enter and exit cells. The researchers found that the ABCC4 transporter is highly expressed in SHH medulloblastoma.

"We have studied the ABCC4 transporter for many years, and wanted to better understand how it interacts with critical pathways that drive tumor growth, like SHH," said senior author John Schuetz, Ph.D., of the St. Jude Department of Pharmaceutical Sciences. "By teasing apart the relationship between ABCC4 and the SHH pathway, we've identified a novel strategy for potentially treating these tumors."

The researchers built a medulloblastoma "interactome" to determine which proteins interact with and are essential to the SHH pathway. The findings showed that ABCC4 is highly expressed in the SHH subgroup and is required for optimal activation of the pathway.

The researchers found that increased expression of ABCC4 correlates with poor overall survival in SHH medulloblastoma. Targeting ABCC4 using genomic methods reduced the size of medulloblastoma tumors and extended the lifespan of mouse models.

"By following the web of interactions between different parts of key

tumor pathways, we can take a more targeted approach to cancer therapy ," said first author Juwina Wijaya, Ph.D., formerly a postdoctoral fellow in Schuetz's laboratory. "We now know another one of SHH medulloblastoma's weaknesses."

More information: Juwina Wijaya et al, An ABC transporter drives medulloblastoma pathogenesis by regulating Sonic Hedgehog signaling, *Cancer Research* (2020). DOI: 10.1158/0008-5472.CAN-19-2054

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