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Wilmot researchers create new way to study liver cancer

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Researchers at the University of Rochester Medical Center's James P. Wilmot Cancer Center have made significant strides in the study of a primary cancer of the liver– Intrahepatic Cholangiocarcinoma (IHCC), also called biliary tract cancer. Their work has been published online and in print editions of *Cancer Research,* the most frequently cited cancer journal in the world.

Aram Hezel, M.D., an assistant professor of Hematology/Oncology in the Department of Medicine at URMC, is the corresponding author of the study that examined the role of genes commonly mutated in human cancers and their role in the growth of Intrahepatic Cholangiocarcinoma, a form of bile duct cancer.

Hezel and fellow researchers from URMC and Massachusetts General Hospital /Harvard Medical School succeeded in developing the first genetically engineered mouse model of IHCC that they hope will provide a valuable, new tool in further research of this disease. A mouse model is important to researchers as it enables them to test dozens or even hundreds of potential treatments in mice in a short span of time, accelerating the discovery process.

The model Hezel and his team created incorporates two of the most common mutations in humans – activating mutations of Kras and deletion of p53 oncogenes. An oncogene is a modified gene that increases the malignancy of a tumor cell. Some oncogenes, usually involved in early stages of cancer development, increase the chance that

a normal cell develops into a tumor cell, possibly resulting in cancer.

"This is a new model of a less common liver tumor that we have not yet had good ways to study," Hezel said. This represents the first good model that can be used as a tool to try to better understand this disease."

Intrahepatic Cholangiocarcinoma is a primary cancer of the liver. It is thought to arise from the bile ducts, a series of branching tubes within the liver that deliver bile (which is produced by the liver) to the gallbladder and small intestine. Bile breaks down fats found in foods and also helps the body get rid of waste material filtered out of the bloodstream by the liver.

The disease is diagnosed in approximately 6,000 people per year, and its occurrence is rising at a rate that makes it among the fastest growing liver cancers, for reasons scientists have not yet been able to pinpoint. Some suspect that it may be due to doctors having better tests to diagnose this type of cancer more accurately. The tumors are typically very aggressive and highly prone to metastasis at an early stage, leading to poor prognosis. To date, many aspects of IHCC's biology and genetic makeup, as well as its cells of origin, have eluded scientists.

The model provides a relevant foundation for further understanding of the earliest, precancerous stages of IHCC, a better understanding of the tumor biology, and for evaluating effective treatments. The group has found that chloroquine - a drug commonly used to treat malaria – has been effective in treating IHCC in the mouse model.

"We've not yet had good ways to study these mutations and their effects on the biliary system in humans," Hezel stated. "Among the problems with understanding this cancer is trying to get a handle on where these tumors come from and what steps lead up to them. We tend not to have lots of biopsies of the liver. Effective screening tests for other cancers

provide samples that can be studied and provide an indication of where that cancer is coming from; that's not the case with this form of cancer. We've been able to make genetic changes as seen in humans and place it in a mouse model. By studying mice, we think we can learn what cells the disease comes from. We hope we have provided step upward towards a better view of the disease, both for ourselves and for others studying it."

Provided by University of Rochester Medical Center