Researchers unveil experimental compound to block therapeutic target in blood cancer

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Blossom Damania, PhD, Jason Wang and a team of UNC Lineberger researchers report in PNAS they have discovered a hyperactive cell signal that contributes to tumor growth in primary effusion lymphoma, an aggressive blood cancer. Credit: UNC Lineberger

Researchers at the UNC Lineberger Comprehensive Cancer Center have

discovered a hyperactive cell signal that contributes to tumor growth in an aggressive blood cancer. They also developed an experimental therapeutic to block the signal and slow tumor growth.

The researchers reported in the journal *Proceedings of the National Academy of Sciences* they identified a novel therapeutic target for primary effusion lymphoma, a type of non-Hodgkin lymphoma caused by infection with the Kaposi's sarcoma-associated herpesvirus, also known as human herpesvirus-8.

"We found a protein called Tyro3 that's highly upregulated and expressed in a subtype of non-Hodgkin lymphoma, called primary effusion lymphoma," said UNC Lineberger's Blossom Damania, Ph.D., vice dean for research in the UNC School of Medicine, the Cary C. Boshamer Distinguished Professor of Microbiology and Immunology, and co-director of the UNC Lineberger virology and global oncology programs. "We also developed a compound that targeted Tyro3, and we found that it killed primary effusion lymphoma cells and tumors."

Primary effusion lymphoma is a highly aggressive subtype of non-Hodgkin lymphoma, a type of blood cancer involving abnormally growing white blood cells.

"Patients with primary effusion lymphoma have a poor prognosis with a median survival time of approximately six months post-diagnosis," said Jason Wong, the paper's first author and a graduate student in the UNC School of Medicine Department of Microbiology and Immunology. "Since current treatment options can be ineffective, finding new therapeutic targets is a high priority.

In their recent study, Damania and her colleagues searched for cell signals called kinases that were hyperactive in primary effusion lymphoma, as well as in other types of non-Hodgkin lymphoma. They

collaborated with UNC Lineberger's Gary Johnson, Ph.D., Kenan Distinguished Professor in the UNC School of Medicine, to characterize the activity of the kinase signals in the cancer cells. Kinases help to control cell signaling, telling cells to grow and divide. Their studies showed that Tyro3 kinase was uniquely hyperactive in primary effusion lymphoma cells compared with normal cells, and they found it could activate a pathway that promotes the cancer's survival.

When they treated the cells with a compound they developed, UNC3810A, they saw a dose-dependent activation of cell death and significant suppression of tumor growth. The compound was developed in the lab of UNC Lineberger's Xiaodong Wang, Ph.D., research associate professor in the UNC Eshelman School of Pharmacy and medicinal chemistry director of the UNC Center for Integrative Chemical Biology and Drug Discovery.

"UNC3810A was used as an in vivo tool compound to understand the biological roles of Tyro3 in primary effusion lymphoma in this study," Wang said. "The work towards optimizing UNC3810A to preclinical candidate will be continued in my lab."

"We identified a new target in a subtype of non-Hodgkin lymphoma, and this target is also upregulated in other types of cancers besides lymphomas, and so potentially the drug we developed can be used for multiple cancers," Damania said.

More information: Jason P. Wong el al., "Kinome profiling of non-Hodgkin lymphoma identifies Tyro3 as a therapeutic target in primary effusion lymphoma," *PNAS* (2019). www.pnas.org/cgi/doi/10.1073/pnas.1903991116