New biomarker-guided strategy has potential for liver cancer treatment

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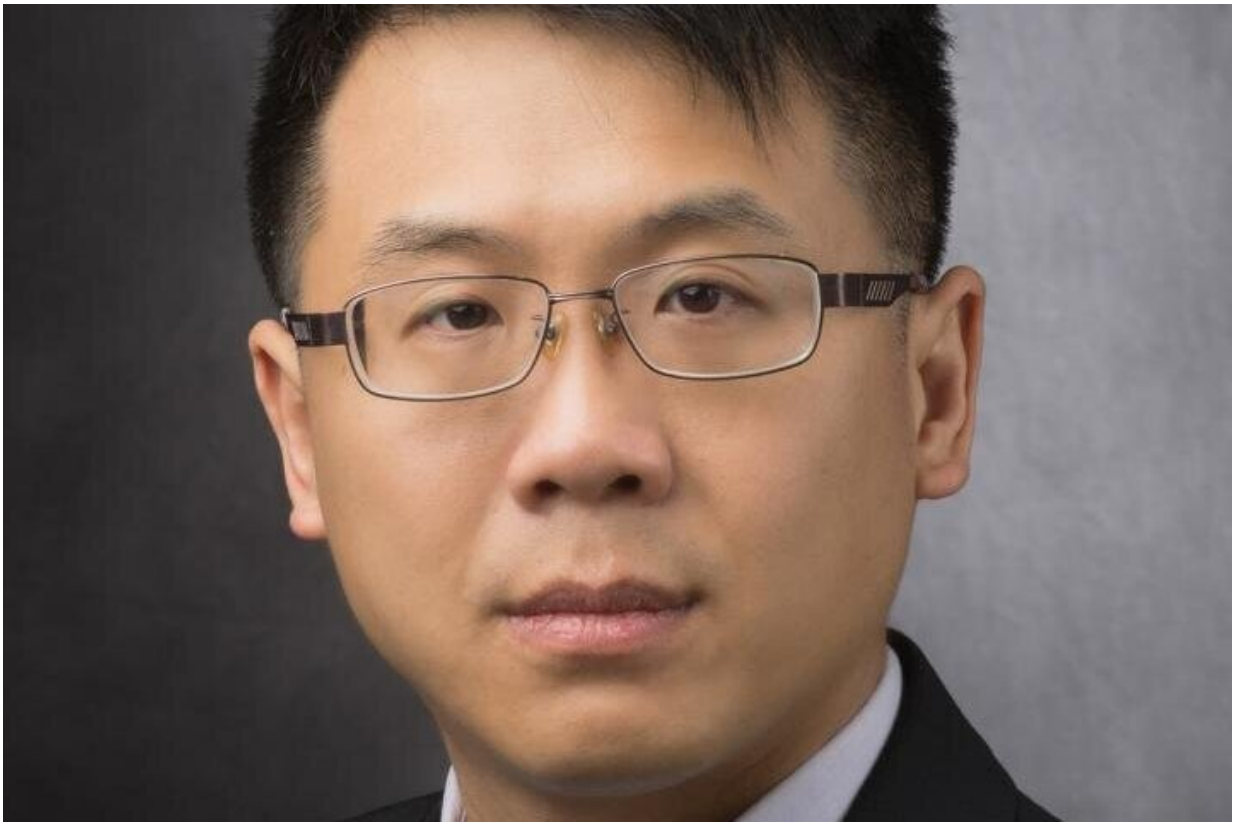

Li-Chuan Chan, Ph.D., Credit: MD Anderson Cancer Center

A study at The University of Texas MD Anderson Cancer Center discovered a cellular pathway tied to cancer that may be beneficial in reducing side effects and extending duration of immunotherapy in some

patients with hepatocellular carcinoma, the most common form of liver cancer.

Researchers looked at a cellular pathway formed when a protein known as interleukin-6 (IL-6) activates an enzyme called Janus kinase 1 (JAK1), and the potential for anti-IL-6 antibodies and anti-T-cell immunoglobulin mucin-3 (anti-Tim-3) in augmenting immunotherapy. Study results were published in the July 15 online issue of the *Journal of Clinical Investigation*.

The IL-6/JAK1 pathway is often observed in tumors and may play a role in cancer evasion by regulating a crucial cellular function in programmed death ligand 1 (PD-L1), a type of protein known to suppress the immune system.

"Our results demonstrated that anti-IL-6 antibodies, when combined with anti-Tim-3 antibodies, boosted T-cell killing effects in mouse models," said Li-Chuan Chan, Ph.D., a postdoctoral fellow in the Department of Molecular and Cellular Oncology "We identified a mechanism regulating PD-L1 glycosylation initiation, suggesting that a combination of anti-IL-6 and anti-Tim-3 as an effective marker-guided therapeutic strategy."

The researchers looked at the correlation between IL-6 and PD-L1 expression in tumor samples from 183 liver patients and found that patients with high IL-6 expression also had elevated PD-L1 expression. Previous MD Anderson studies reported that high IL-6 levels are associated with poorer prognosis in liver cancer patients. The team's new findings suggested that IL-6 is "physiologically significant and clinically relevant" to PD-L1 expression in liver cancer.

"We also found that the IL-6/JAK1 pathway contributed to PD-L1 phosphorylation, which appeared to be the dominant driver of cancer

immune evasion in a liver cancer mouse model," said Chan. "Together, these findings may provide a potential mechanism on how activated JAK1 translocates to other cellular compartments and warrant further investigation in the future."

The study also pointed to a potential benefit for lessening immunotherapy side effects, which sometimes can shorten the amount of time patients can stay on treatment. Immune checkpoint inhibitors have been shown to stimulate the production of IL-6 serum, which can cause arthritis, Crohn's disease and a psoriasiform dermatitis.

"Therefore, blocking the IL-6 pathway may resolve these side effects and extend the duration of immunotherapy," said Chan.

Provided by University of Texas M. D. Anderson Cancer Center