New discovery for treatment of primary liver cancer shows promise in mice

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Credit: Monash University

A preclinical study led by Monash University has discovered a drug combination with the potential to treat one of the most fatal and globally widespread cancers, a type of primary liver cancer called hepatocellular

carcinoma (HCC).

The team of researchers from the Monash Institute of Pharmaceutical Sciences (MIPS) found the drug combination reverses the symptoms of nonalcoholic steatohepatitis (NASH) and, subsequently, markedly reduces the onset of NASH-driven HCC, without affecting the liver in mice.

The study, published in *Science Advances*, used a mouse model that mimics human NASH-driven HCC to implement a combination treatment of an endoplasmic reticulum (ER) stress inhibitor called "BGP-15" with the inflammation blocker, "Olamkicept."

Both of these drugs are already proven to be safe in humans and have progressed to Phase 2 and 3 human clinical trials for other metabolic and/or inflammatory diseases.

The study's lead author, Professor Mark Febbraio from MIPS, said this is an exciting discovery for a particularly widespread and devastating disease with a low survival rate.

"HCC is increasing at an alarming rate largely due to increased obesity and type 2 diabetes which may lead to NASH, a well known HCC risk factor," said Professor Febbraio.

The rise in HCC coincides with patients presenting with obesity and symptoms associated with the metabolic syndrome, especially metabolic dysfunction-associated fatty liver disease (MAFLD). Globally, a staggering 25 percent of the population are estimated to be living with MAFLD, with around 15% of those exhibiting signs of NASH.

"Despite the high prevalence of NASH and the alarming rise in NASH-driven HCC, there are currently no FDA approved treatments that halt

disease progression.

"Given that ER stress and inflammation are hallmarks of NASH-driven HCC, and that BGP-15 and Olamkicept have both already proven to be safe, we tested whether these drugs—as monotherapy, or in combination—would prevent NASH and/or NASH driven HCC in mice.

"Consistent with our hypothesis, the study shows that while monotherapy with either of the two drugs modestly slowed progression, when combined they have shown to be a realistic therapeutic strategy for treating human NASH and progression to HCC, diseases that are rapidly growing with a clinical unmet need."

Professor Febbraio said that given the significance of the discovery, combined with the urgent need for new safe and effective treatments for NASH and NASH-driven HCC, the team ultimately hope their findings will progress toward clinical trials.

"We have to stress that this study was performed in mice, not humans. However, as both drugs have been shown to be safe in several human clinical trials, the logical next step is testing the BGP-15/Olamkicept combination in clinical trials for patients with NASH and or HCC."

More information: Ebru Boslem et al, Therapeutic blockade of ER stress and inflammation prevents NASH and progression to HCC, *Science Advances* (2023). DOI: 10.1126/sciadv.adh0831

Provided by Monash University

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