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“Inhibiting Liver Cancer Stem Cells to Improve Response to Thermal Ablation”

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SCIENTIFIC ABSTRACT

Hepatocellular carcinoma (HCC) is the only cancer for which the incidence and mortality continue to rise. Most patients are not surgical candidates, so percutaneous thermal ablation (PTA) is the best chance for a local cure. PTA is a minimally invasive, image-guided procedure whereby a probe inserted percutaneously is used to destroy the tumor with heat. Incomplete PTA (iPTA) leads to recurrence. Heat stress stimulates cancer stem cells (CSCs), a rare population of self-renewing cells capable of recapitulating the tumor. Surviving HCC CSCs (hCSCs) are a source of disease recurrence after iPTA, yet no available HCC treatment targets CSCs. Combining PTA with hCSC inhibitors could improve disease response and decrease recurrence.

This proposal tests the hypothesis that iPTA-induced hCSC stimulation can be suppressed with the known CSC inhibitor niclosamide ethanolamine (NEN), an FDA-approved anti-helminthic drug. A clinically-relevant murine model of HCC that occurs spontaneously in the setting of cirrhosis and non-alcoholic steatohepatitis (NASH) will undergo ultrasound-guided iPTA with or without adjuvant NEN, and the hCSC population will be examined.

This study will be the first to assess the effect of combining NEN with PTA on hCSCs. Given the demonstrated efficacy and outstanding safety profile of NEN and the minimally invasive nature of PTA, this combined treatment could prove to be powerful and readily translatable to patients.

LAY ABSTRACT

Liver cancer, or hepatocellular carcinoma (HCC), is the 5th most common cancer and the world's 2nd leading cause of cancer-related death in adult men. According to the CDC, it is the only cancer for which the incidence and mortality are rising. An increasingly significant cause of HCC is fatty liver disease, for which obesity is a risk factor. Since 71% of Americans are overweight or obese, the number of HCCs is expected to rise. Surgery offers the best hope for a cure, yet most HCC patients are not surgical candidates. The best alternative is percutaneous thermal ablation, a minimally invasive way to destroy the tumor without surgery. Yet when cancer cells are left behind, HCC can recur. The likely source of recurrence is from treatment-resistant cells called “cancer stem cells” which become stimulated under the stress conditions induced by percutaneous thermal ablation. No current therapies target these cells. Our study proposes to combine niclosamide ethanolamine, an FDA-approved antiparasitic drug that inhibits cancer stem cells, with percutaneous thermal ablation in mice with fatty liver disease that

develop HCC. In the short term, this study will improve our understanding of the effect of percutaneous thermal ablation on HCC cancer stem cells in a singularly clinically-relevant model. In the long term, this study has the potential for rapid translation to clinical trials. If successful in improving outcomes after percutaneous thermal ablation, this combined approach with niclosamide ethanolamine could ultimately curb the mortality from HCC and help countless patients.a

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