# Targeting fructose metabolism as therapeutics for cancer cells in the liver

Duke LICENSING & VENTURES

## Value Proposition

Colorectal cancer (CRC) is a common and lethal disease. CRC commonly metastasizes to the liver, at which point the disease becomes challenging to treat. Current chemotherapy does not specifically target liver metastasis, due to the lack of specific genetic mutations common to CRC metastasis. New evidence suggests that tumor-specific non-genetic alterations (like metabolic reprogramming) caused by the microenvironment may potentially be targetable treatment options. Tumor cells in the liver have been shown to undergo metabolic reprograming to upregulate enzymes, such as ALDOB and KHK, involved in fructose metabolism. The liver microenvironment causes cancer cells to upregulate ALDOB, given that 70% of fructose is metabolized in the liver. ALDOB promotes fructose metabolism to fuel glycolysis and gluconeogenesis, which promotes the growth of cancer cells in the liver. A means to target fructose metabolism to suppress the growth of cancer cells in the liver would be beneficial to the treatment of patients.

## Technology

Using transcriptomic profiling of matched normal colon, primary CRC, and liver metastasis samples from 30 Stage IV CRC patients, the inventors found that liver metastasis resulted in highly altered activity of certain metabolic pathways. These results were further delineated in a murine model of CRC, which revealed that glycolysis, gluconeogenesis, fructose metabolism, and pentose phosphate pathways are upregulated in CRC cells isolated from the liver compared to CRC cells isolated from the primary lesion in the colon. Specifically, the enzyme ALDOB was upregulated in liver metastasis, and was found to be upregulated due to the liver microenvironment. ALDOB knockdown in CRC cells suppressed CRC liver metastasis.

## Other Applications

Modulating the fructose metabolism pathway by targeting the enzymes KHK or ALDOB may be applicable to other diseases in which abnormal fructose metabolism results in pathology, including other cancers and metabolic diseases

## Advantages

- KHK inhibitors are already in phase 2 clinical trials
- Small molecule inhibitors are easy to store and administer

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- Decreasing the likelihood of liver metastasis in CRC patients would dramatically improve patient outcomes.