Liver cancer is the most rapidly rising cancer in the US showed. Intrahepatic cholangiocarcinoma (ICC) is second most common type of primary liver cancer. Often at the time of diagnosis, ICC is already in the advanced stages of the disease. Unresectable ICC with the current standard of care gemcitabine/ cisplatin has a median survival < 1 year. Scarcity of biopsy tissue and relevant model systems as a major hurdle in ICC translational research.

Isocitrate dehydrogenase mutations
- Most frequent genetic lesions in ICC (20-40% of cases)
- Mutations in isocitrate binding site IDH1 (R132C) result in production of (R) - 2-hydroxylutarate (2-HG), a proposed 'oncometabolite'
- 2-HG blocks hepatocyte differentiation, leading to the accumulation of undifferentiated cells susceptible to additional oncogenic hits leading to ICC (Saha et al. Nature 2014)

Model for IDH mutant ICC Pathogenesis
- 2HG inhibits hepatocyte differentiation, which involves the decrease in HNF4a.
- Additional oncogenic hits lead to oval cell expansion and progression to ICC.

Clinical Activity of IDHm Inhibitorivosedenib (AG120) - FDA approved in August 2021

Study Objectives
1. Characterize the effects of mIDH inhibition on chromatin marks in IDHm ICC models
2. Identify the downstream target(s) of mIDH within the aKG dependent dioxygenase family that promote ICC pathogenesis
3. Identify the mechanism of ivosidenib in inducing differentiation in ICC tumor

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Mutant IDH Promotes Biliary Cancer Through Altering Histone Methylation Critical for Liver Differentiation

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