Targeting deteriorating cells to improve function and prevent cancer in a mouse model of liver failure

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Senolytics—drugs that can selectively kill senescent cells (SnCs) in specific tissues—have the potential to be developed as therapeutics for many age-related diseases in which the accumulation of SnCs plays a causative role. Previously, SnCs have been demonstrated to cause progression and pathogenesis of metabolic dysfunction-associated steatotic liver disease (MASLD).

Here, the authors report the development of a tissue-selective compound, 753b, that acts as a potent and liver-tropic senolytic. The study found that 753b could effectively kill SnCs derived from several different tissue origins in vitro. Treatment with 753b of both aged mice and a mouse model (STAM) for metabolic dysfunction-associated steatohepatitis (MASH), metabolic dysfunction-associated steatotic liver disease (MASLD), liver fibrosis, and hepatocellular carcinoma showed that 753b selectively reduced SnCs in the liver. Furthermore, treatment could effectively slow the progression of MASLD and prevent the development of hepatocellular carcinoma (HCC) in STAM mice. The **Figure** to the right shows how quantitative MRI was used to measure the effect of 753b treatment on tumor burden in the mice even after they developed substantial metabolic dysfunction-associated steatohepatitis (MASH) and hepatic fibrosis (panels **a** and **c**). This was confirmed by conventional pathology after the mouse livers were retrieved at the end of the study (panels **b, d, e**).

Further research will investigate if additional modifications and optimization of 753b's chemical structure can improve its safety and senolytic activity. This could eventually result in novel treatments for MASLD and associated pathologies.

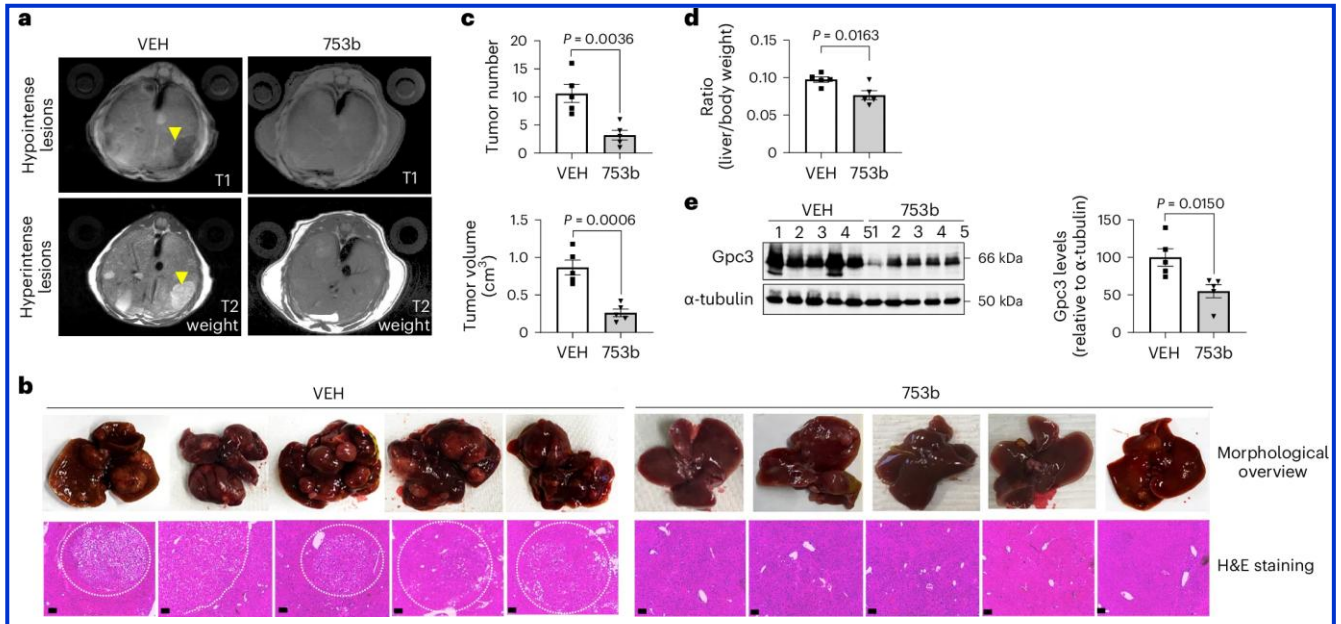

Figure: Representative MRI T_1 pre-contrast and T_2-weighted images of control and 753b-treated STAM mice; tumors indicated by yellow arrows Tumor lesions (indicated by yellow arrows) were determined based on hypointense signals in T_1 and hyperintense signals in T_2-weighted images **(a)**. Representative morphological overviews of the whole livers and images of pathology staining of the liver tissues (tumors circled with white dotted lines) **(b)**. Number and volume of liver tumors based on the MRI images **(c)**. The ratios between liver and body weight of control and 753b-treated STAM mice **(d)**. Western blotting to measure the Liver cancer marker glypican 3 (Gpc3) in the liver tissues from control and 753b-treated STAM mice **(e)**.

Facilities and instrumentation used: AMRIS Facility (University of Florida): 4.7 T/33cm horizontal bore MRI system and mouse abdomen MRI coil

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