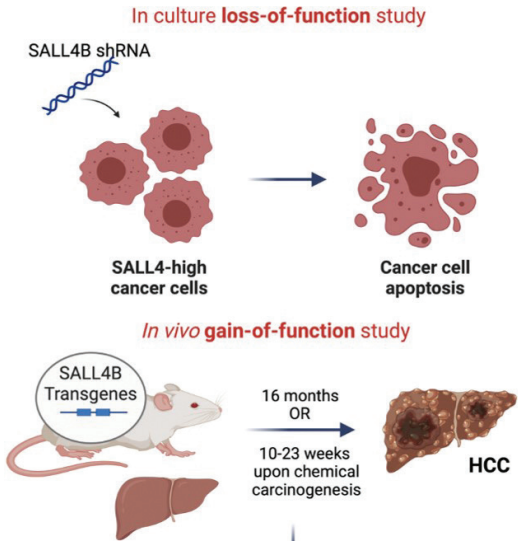

Fig. 1: SALL4B is the dominant oncogenic isoform.

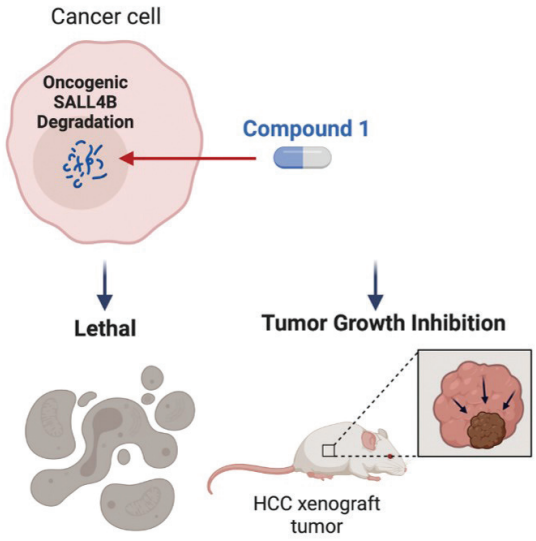

Fig. 2: Discovery of a non-IMiD SALL4 degrader.

Novel mechanism and compound targeting oncogenic transcription factor SALL4 in cancer

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Research in the Chai lab focuses on transcription factors (TFs), gene regulation, and their therapeutic applications. Oncogenic TFs, critical for cancer development and survival, historically have been viewed as “undruggable”. However, recent breakthroughs and successes have highlighted TF degradation as one of the most exciting new frontiers in the development of novel cancer drugs. Dr. Chai has led a team studying an oncogenic TF protein, SALL4, for the last 20 years.

The zinc finger TF protein SALL4 is mainly expressed in fetal tissues and silenced in most adult tissues. However, it is aberrantly re-expressed in approximately one-third of cancer patients across almost every human cancer type. We have uncovered direct evidence of the causative role of SALL4 in cancer using SALL4 transgenic mice that develop leukemia and/or liver tumors. Loss-of-function studies by knocking down SALL4 using shRNA showed cell growth inhibition and cell death in leukemias and SALL4-expressing solid tumors in both cell culture and in vivo xenotransplants. These findings demonstrate the significant potential of SALL4 as a cancer target. Further, we expect that SALL4 can be targeted with limited toxicity due to its limited expression in normal tissues.

Immune-modulatory imide drugs (IMiDs) are molecular glues that drive protein degradation; several IMiDs are approved for hematological malignancies. The mechanism of action of IMiDs involves degradation of several TFs, including SALL4. However, IMiDs do not inhibit proliferation of SALL4-expressing cancer cells. We recently discovered that IMiDs only degrade the SALL4A isoform and not SALL4B, which is likely essential for SALL4-mediated cancer cell survival. We have shown that SALL4B knockdown increases apoptosis and inhibits cancer cell growth. Further, SALL4B gain-of-function leads to liver tumor formation in mice (Fig. 1). Through a novel screening approach, we identified a new non-IMiD SALL4 degrader that can also target SALL4B via proteasomal degradation. This compound exhibits potent anticancer activity in cell culture and inhibits in vivo tumor growth by 62% (Fig. 2). This TF-targeting approach represents a promising novel IMiD-independent mechanism for cancer therapy.