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802.CHEMICAL BIOLOGY AND EXPERIMENTAL THERAPEUTICS

Targeting the Oncofetal Transcription Factor Protein SALL4 in Cancer By a Non-IMiD Degrader

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Sal-like protein 4 (SALL4) is a C2H2 zinc finger transcription factor (TF) with two naturally occurring isoforms; SALL4A and SALL4B. It is typically detected in fetal tissues and silenced in most normal adult tissues. It is therefore intriguing that SALL4 is aberrantly re-expressed in about one-third of almost all primary human malignancies, presumably by demethylation dependent mechanisms. Direct evidence of the causative role of SALL4 in cancer has been demonstrated in SALL4 transgenic mice, which developed myelodysplastic syndrome (MDS), acute myeloid leukemia (AML) and/or liver tumors. Loss-of-function studies by SALL4 knock-down using shRNA showed cell growth inhibition and death in leukemias and solid tumors in culture and in *in vivo* xenotransplants.

TF's, such as SALL4, which are critical for cancer development and survival, have historically been viewed as "undruggable". However, rather than blocking activity, an alternative approach to target TFs is to induce protein degradation. Immunomodulatory imide drugs (IMiDs), including thalidomide, lenalidomide and pomalidomide, are used in treating patients with multiple myeloma (MM), MDS with 5q deletion, mantle cell lymphoma (MCL), and other hematological malignancies. Recently, several groups have reported that IMiDs can degrade SALL4 in a proteasome-dependent manner. To that end, we sought to investigate whether IMiDS could be utilized to treat SALL4-positive/expressing cancers.

Initially, our studies observed that IMiDs had no effect on SALL4-positive cancer cells. Additional investigations thereafter demonstrated that IMiDs could only degrade SALL4A. These findings suggested that SALL4B may not be affected by IMiDs, and may be essential for SALL4-mediated cancer cell survival. Further investigation revealed that SALL4B knockdown led to an increase in apoptosis and inhibition of cancer cell growth. Moreover, through high-throughput screening, we identified a new non-IMiD SALL4 degrader that targets SALL4B via proteasomal degradation and which exhibited potent anti-cancer activity, inhibiting cancer cell proliferation in culture and *in vivo*tumor growth by 70%.

Our observation therefore suggest that protein degraders could possess isoform specific effects. Additionally, our results exemplify the importance of delineating drug action and oncogenesis at the isoform level to develop more effective cancer therapeutics.

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