INTRODUCTION

STAT3 is an undrugged transcription factor activated through a variety of different cytokine and growth factor receptors via Janus kinases, as well as through oncoprotein fusion proteins and mutations in STAT3 itself. In certain malignant cells, STAT3 activation is amplified, leading to a dampened immune response, tumor progression, and metastasis. The role of STAT3 as a cancer driver and tumor microenvironment modulator has been validated in a multitude of studies, making it a strong candidate to target in the treatment of cancer. With designed KT-333, a potent, highly selective, first-in-class, heterobifunctional degrader for the treatment of multiple STAT3-dependent pathologies, including hematological malignancies and solid tumors. Based on the potential of KT-333 as a target for cancer therapeutics and limitations of prior approaches, we developed KT-333, a first-in-class, potent, highly selective, heterobifunctional STAT3 degrader currently in Phase I clinical trials. Here, based on STAT3 degradation by multiple E3s based degraders, structure of STAT3-KT333-VHL and a hetero site-removed target ubiquitination model, we provide evidence for VHL as the ideal partner E3 for targeting STAT3 in cancer.

RESULTS

Figure 1: STAT3-E3 Pairing and Discovery of KT-333

increased & consistent better potency for VHL-based degradation compared to CRL4-based control.

Figure 2: Cryo-EM Determined STAT3-KT333-VHL Ternary Complex Structure Looks Native-like, Possibly Driven by the ‘Bent’ Linker-mediated Novel Pocket Between STAT3 and VHL

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Figure 3: KT-333 Induces Selective, Rapid and Site-specific Ubiquitination of the Most Proximal Lys Residues

KT-333 induced rapid and sustainable addition of ubiquitine to STAT3 by the VHL-E3 complex.

Figure 4: Selectivity of KT-333 for STAT3 Degradation

A. KT-333 mediated in the interactions with VHL and the Y705 site are not essential to other STAT family members. B. Selecting the specificity of KT-333 in the context of STAT3, STAT3, and a 1,2-diphosphonate

Figure 5: Antitumor Activity of KT-333 in SU-DHL-1, an ALK+ ALCI Tumor Model

Tumor intrinsic: KT-333 resistant STAT3 degradation leads to a rapid reduction of canonical downstream targets causing cell cycle arrest and subsequent apoptosis as the main drivers of efficacy for KT-333.

DISCUSSIONS


A Sohn S, Lee SB, Park SC, et al. STAT3 interacts with the MAP kinases MEK1 and ERK1/2 in a STAT5-dependent manner. Oncogene. 2007;26:5715-5722.

REFERENCES


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