Small Molecule-Induced, Selective STAT3 Degradation Leads to Anti-Tumor Activity in STAT3-Dependent Heme Malignancies

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SCHEMATIC DRAWING

Overview of targeted protein degradation

STAT3 integrates multiple upstream signaling events to regulate a wide variety of cellular functions.

Introduction

- Targeted protein degradation is a new therapeutic modality that expands the ability to target difficult-to-drug oncogenic proteins.
- STAT3 is a transcription factor downstream of several signaling events involving the IL-6/JAK pathway.
- Activating mutations and aberrant activation of STAT3 drive a subset of tumors via induction of proteins that may contribute to a tumor permissive environment.
- STAT3 is therefore a highly attractive target for oncology. However, potent and selective agents specifically and directly targeting STAT3 have remained elusive.
- Degrading STAT3 will abrogate the JAK/STAT3 signaling axis to induce tumor cell death.
- Kymera Therapeutics is developing degraders of STAT3 with drug-like properties, and STAT3 degraders are active in models of heme malignancies including ALCL and AML, and STAT3 degraders are active in models of heme malignancies including ALCL and AML. KYM-003 leads to significant regression in SU-DHL-1 tumor xenograft model at well tolerated doses to induce tumor cell death.

KYM-003 represses the growth of multiple heme cell lines

A sustained and robust degradation of STAT3 with KYM-003 leads to profound anti-tumor activity in vitro and in vivo

KYM-003 treatment leads to apoptosis induction and cell cycle defects in SU-DHL-1 lymphoma line

Conclusions

- Kymera has developed potent and highly selective STAT3 degraders with activity against mutant and wild type STAT3.
- Sustained STAT3 degradation of 90% or greater leads to apoptosis induction and cancer cell death within 48 hours in vitro and in vivo.
- STAT3 degraders are active in models of heme malignancies including ALCL and AML, supporting these as potential initial indications for clinical development.
- Kymera plans to develop STAT3 degraders in a variety of oncology and immunology indications.

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