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

3803

Fred Csibi, Bin Yang, Karen Yuan, Michele Mayo, Haojing Rong, Scott Rusin, Kirti Sharma, Henry Li, Sharon Townson, Hari Kamadurai, Mike Sintchak, Yogesh Chutake, Jesse Chen, Christine Loh, Jared Gollob, Duncan Walker, Nan Ji and Nello Mainolfi, Kymera Therapeutics, Inc. 300 Technology Square, Cambridge, MA 02139. Contact: fcsibi@kymeratx.com

PosterCast

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 including the IL-6/JAK pathway.
- Activating mutations and aberrant activation of STAT3 drive a subset of tumors via induction of autocrine factors that promote tumor proliferation and survival, as well as 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, represented here with KYM-003 and its analog compound A. These compounds potently and selectively degrade STAT3 protein and display strong anti-tumor activity in models of heme malignancies.

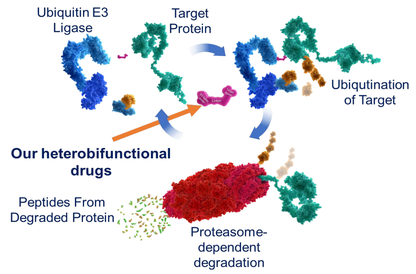
Overview of targeted protein degradation

BROAD OPPORTUNITY
ONLY BINDING SITE REQUIRED

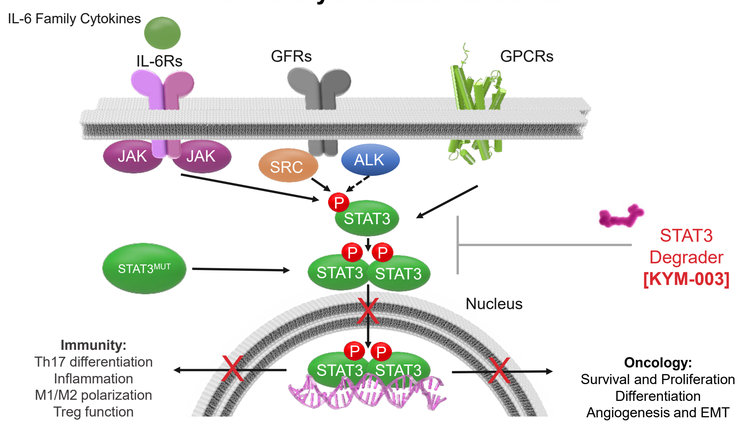
EFFICIENT
CATALYTIC

PROLONGED IMPACT
TARGET PROTEIN DEGRADATION

HITCHING A RIDE
UPS INTACT & FUNCTIONAL

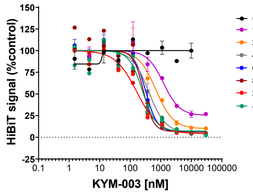


STAT3 integrates multiple upstream signaling events to regulate a wide variety of cellular functions



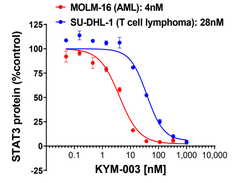
KYM-003 causes rapid, potent, and highly selective degradation of STAT3 in multiple cellular systems

Endogenous STAT3-HiBiT live cell assay (A549 cells)

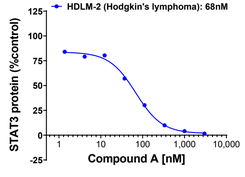


KYM-003 degrades both wild-type and mutant STAT3 in heme cell lines

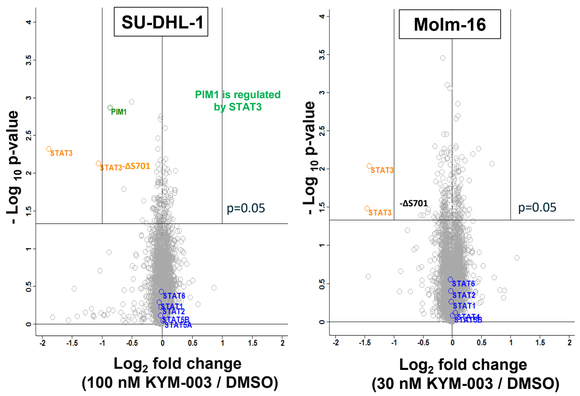
STAT3^{WT} (DC_{50}, MSD, 24 hr)



STAT3^{D661Y} (DC_{50}, WB, 24 hr)

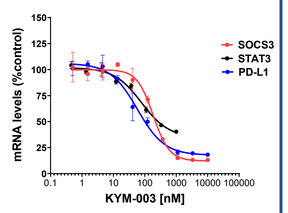


Deep Tandem Mass Tag proteomics at 8h (>10,000 proteins detected) demonstrates selective STAT3 degradation



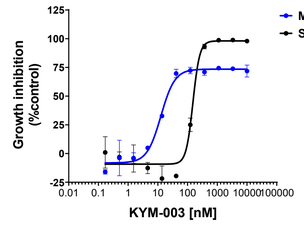
KYM-003 decreases STAT3-dependent gene expression

RT-qPCR in SU-DHL-1 cells, 24 hr



Gene	IC_{50} (μM) / % Max inhibition, 24 hr
SOCS3	0.185 / 87
STAT3	0.141 / 62
PD-L1	0.058 / 82

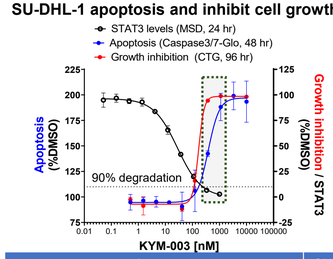
KYM-003 represses the growth of multiple heme cell lines



Cell line	Tumor type	CTG, GI_{50} μM (%Max inh), Day 4
SU-DHL-1 (shown)	ALCL (ALK+)	0.167 (>95)
MOLM-16 (shown)	AML	0.016 (80)
A3/KAW	DLBCL	1.9 (50-55)
SUP-M2	ALCL (ALK+)	0.61 (>95)
DEL	ALCL (ALK+)	0.11 (>95)
KARPAS-299	ALCL (ALK+)	0.14 (50-55)
SR-786	ALCL (ALK+)	3.8 (75)

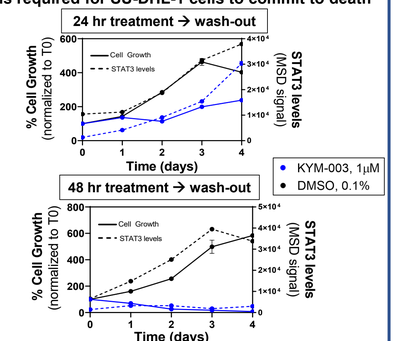
A sustained and robust degradation of STAT3 with KYM-003 leads to profound anti-tumor activity *in vitro* and *in vivo*

A decrease of STAT3 by 90% is necessary to induce SU-DHL-1 apoptosis and inhibit cell growth



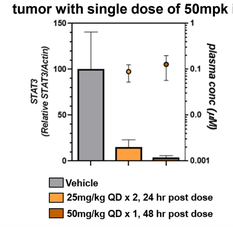
Assay	SU-DHL-1
STAT3 levels, MSD DC_{90} (μM) at 24 hr	0.15
Apoptosis, Caspase3/7-Glo IC_{50} (μM) at 48 hr	0.38
Growth inhibition, CTG IC_{50} (μM) at 96 hr	0.167

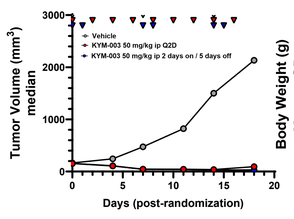
Wash-out study demonstrates sustained degradation is required for SU-DHL-1 cells to commit to death

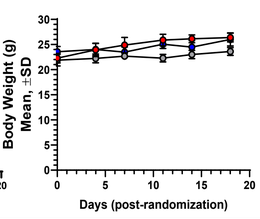


KYM-003 leads to significant regression in SU-DHL-1 tumor xenograft model at well tolerated doses

Robust degradation of STAT3 for 48hr in tumor with single dose of 50mpk ip

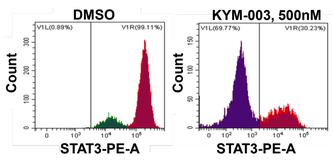




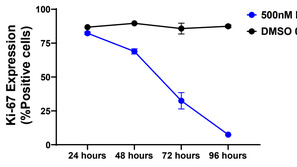


KYM-003 treatment leads to apoptosis induction and cell cycle defects in SU-DHL-1 lymphoma line

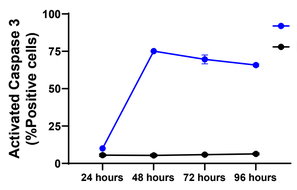
Decrease of STAT3 at 24 hours



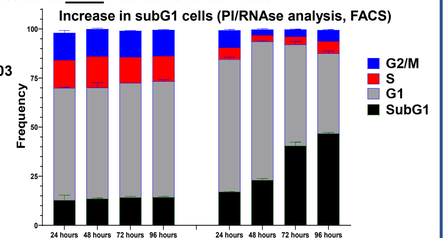
Time-dependent inhibition of proliferation with KYM-003



KYM-003 treatment induces apoptosis at 48 hr that leads to cell death



Increase in subG1 cells (PI/RNAse analysis, FACS)



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.

Disclosures: Csibi, Yang, Mayo, Yuan, Rong, Rusin, Sharma, Li, Townson, Kamadurai, Sintchak, Chutake, Gollob, Walker, Ji and Mainolfi: *Kymera Therapeutics:* Employment, Equity Ownership.