Discovery of KYM-003, a potent and selective STAT3 degrader with anti-tumor activity in heme malignancies

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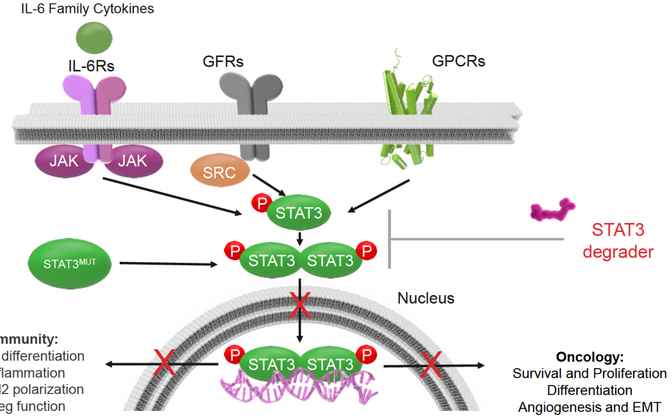
Introduction

- 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.
- Targeted protein degradation is a new therapeutic opportunity with the promise to target difficult-to-drug oncogenic proteins.
- 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.

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



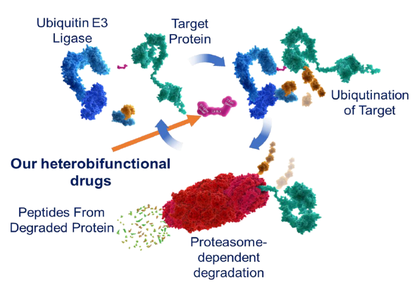
Overview of targeted protein degradation

BROAD OPPORTUNITY
ONLY BINDING SITE REQUIRED

EFFICIENT
CATALYTIC

PROLONGED IMPACT
TARGET PROTEIN DEGRADATION

HITCHING A RIDE
UPS INTACT & FUNCTIONAL

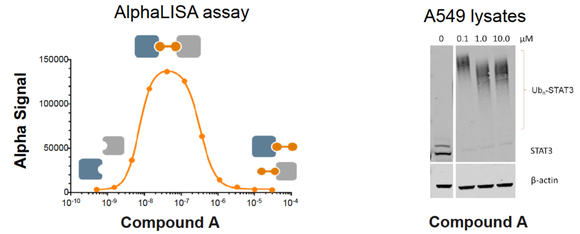


STAT3 degrader promotes the formation of the STAT3-Degrader-E3 ligase ternary complex and STAT3 ubiquitination

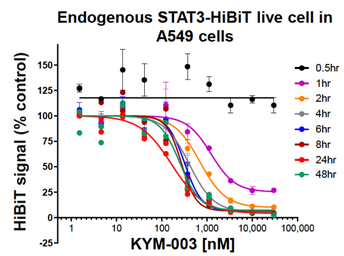
Compound A binds both STAT3 and E3 ligase

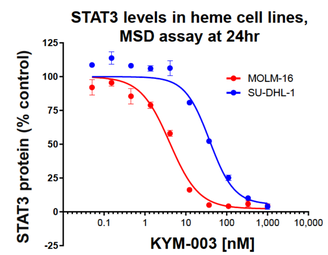
Binding assay		Compound A
E3 binding IC_{50} (μM)	-STAT3	0.37
STAT3 binding IC_{50} (μM)	-E3	0.39
	+E3	0.061

Efficient ternary complex formation and STAT3 ubiquitination

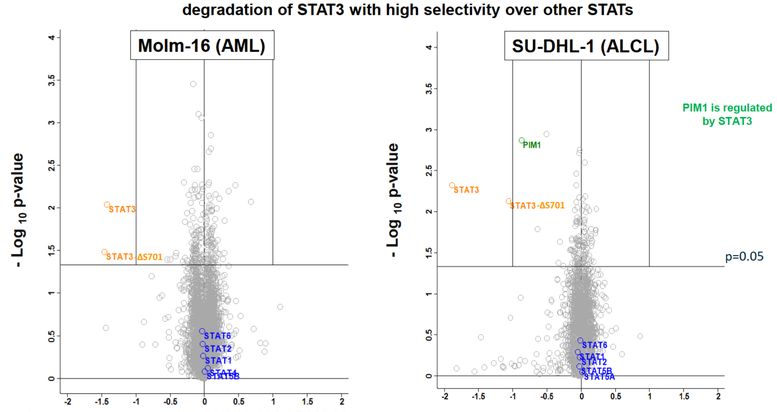


KYM-003 causes rapid, potent, and highly selective degradation of STAT3 in multiple cellular systems

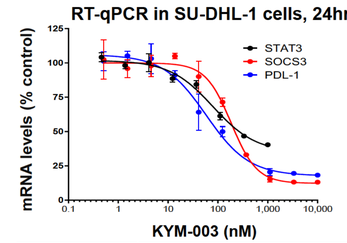




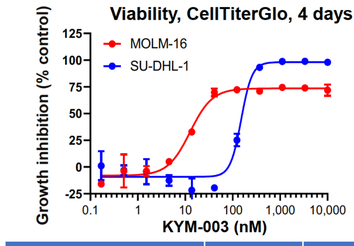
Deep Tandem Mass Tag proteomics at 8 h (>10,000 proteins monitored) demonstrates specific degradation of STAT3 with high selectivity over other STATs



KYM-003 downregulates STAT3-dependent gene expression and inhibits cell proliferation



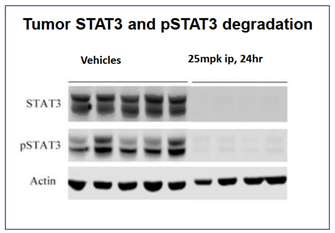
Gene	mRNA IC_{50} (nM)/Max inh% 24hr
STAT3	141 / 62
SOCS3	185 / 87
PDL-1	58 / 82

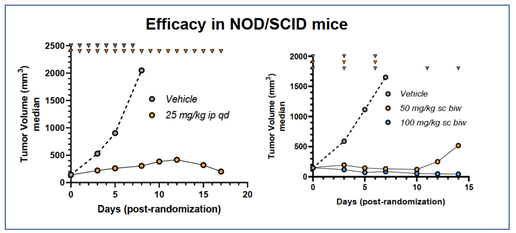


Assay	MOLM-16	SU-DHL-1
CTG IC_{50} (nM) at Day 4	16	167
STAT3 MSD DC_{50} (nM) at 24hr	4	28

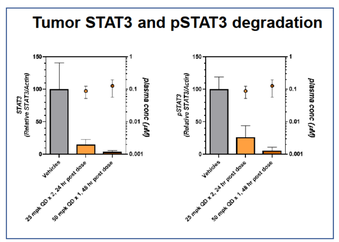
KYM-003 leads to significant regression in xenograft models of leukemia and lymphoma at well tolerated doses

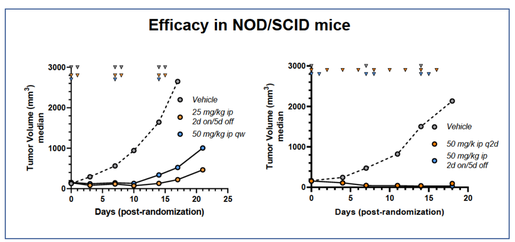
MOLM-16 tumor xenograft





SU-DHL-1 tumor xenograft





Conclusion

- Kymera Therapeutics has developed potent and highly selective STAT3 degraders with strong anti-tumor activity in heme cancer models.
- Our data supports STAT3 degradation as a promising new therapeutic opportunity in cancers driven by aberrantly activated STAT3.

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