Targeting STAT3 with Selective Protein Degraders for the Treatment of PTCL

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INTRODUCTION

The activity of Signal Transducer and Activator of Transcription 3 (STAT3) is dysregulated in many cancers, including aggressive hematologic malignancies with high unmet medical need. Ablation of STAT3 can promote the establishment and progression of malignant cells through regulation of cell survival and proliferation pathways and suppression of anti-tumour immunity. Inhibitors of STAT3 and other tumor intrinsic and tumor extrinsic mechanisms, respectively

Selective targeting of STAT3 has been challenging but targeted protein degradation mediated by heterobifunctional small molecule degraders is a novel therapeutic modality to target difficult-to-drug oncogenic proteins. These molecules bind to both the target protein and an E3 ligase, enabling the formation of a ternary complex which leads to ubiquitination and proteasomal degradation of the target protein.

AIM

We have discovered a series of heterobifunctional STAT3 degraders that potently and selectively degrade STAT3. We evaluated the in vitro and in vivo activity and molecular mechanisms of degrading STAT3 in models representing different subtypes of mature T and NK cell lymphomas.

RESULTS

Figure 1: STAT3 Degraders are Highly Active against NK and T Cell Lymphoma Cell Lines Including Cells Expressing STAT3 Mutants

- STAT3 regulates cell cycle and response to cytokines and is a key target for therapeutic intervention.
- STAT3 dysregulation is frequent in mature T and NK cell lymphomas.
- STAT3-regulated proteins have been linked to immune evasion and drug resistance.

Figure 2: Activity Against STAT3-mutant ALC-positive ALC Patient Derived Cells

- STAT3 proteins promote transcriptional and epigenetic alterations in tumors.
- STAT3-targeting degraders were shown to have potent antiproliferative and pro-apoptotic effects in multiple allo- and syngeneic NK cell and T cell lymphoma models.

Figure 3: Anti-tumor Activity of STAT3 Degrader in SU-DHL-1 Model Can Be Achieved with intermittent DFO Dosing

- STAT3 is a potential therapeutic target in T cell lymphomas.
- STAT3 is conserved in mature T and NK cell lymphomas.
- STAT3 dysregulation is frequent in mature T and NK cell lymphomas.
- STAT3-regulated proteins have been linked to immune evasion and drug resistance.

Figure 4: Rapid and Profound Down-regulation of STAT3 and STAT3-Regulated Targets with Tight Correlation between mRNA and Protein Changes

- STAT3 is a key transcription factor in mature T and NK cell lymphomas.
- STAT3 is conserved in mature T and NK cell lymphomas.
- STAT3 dysregulation is frequent in mature T and NK cell lymphomas.
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Figure 5: Time-Dependent Changes in Protein Levels Upon STAT3 Degradation

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Figure 6: Temporal Changes in Proteins Upon STAT3 Degradation

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METHODS

In vivo Experiments: Selective engrafted tumors were established in severe combined immunodeficient (SCID) mice for STAT3 knockdown studies. For NK and EMT cell lines, survival and expansion were assessed by measuring tumor size. Analysis of STAT3 gene expression before and after treatment with degrader. Analysis of protein expression using Western blotting. Analysis of tumor pathology using hematoxylin and eosin staining.

Conclusions

- Kymera has discovered a series of potent and selective STAT3 degraders.
- STAT3 degraders show activity against both wild-type and clinically-relevant mutant forms of STAT3 resulting in growth arrest and increased cell death of ALC1-ALCL as well as STAT3-mutant NK lymphomas and ALC1-ALCL cell lines in vitro and in vivo.
- Transcriptomic and proteomic analyses of STAT3 degrader-treated cells revealed tightly correlated changes in proximal STAT3-dependent genes and proteins in ALC1-ALCL cell lines.
- Subset of transcriptional responses to STAT3 degrader is conserved between ALC1-ALCL and STAT3-mutant NK and T cell lymphoma cell lines.
- Pathway analyses confirm down-regulation of STAT3-regulated processes including cytokine responses at 16, 24, and 72 hours and consistent transcriptional and up-regulation of immune pathways at 48 hours suggesting modulation of tumor cell intrinsic and extrinsic interactions in the tumor microenvironment.
- Additional in vivo models of PTCL and related hemat malignancies are being investigated, but these data illustrate the therapeutic potential of STAT3 degraders for the treatment of cancer with aberrant STAT3 activation.

REFERENCES


