Identification of MRT-2359, a Potent, Selective and Orally Bioavailable GSPT1-directed Molecular Glue Degrader (MGD) for the Treatment of Cancers with MYC-induced Translational Addiction

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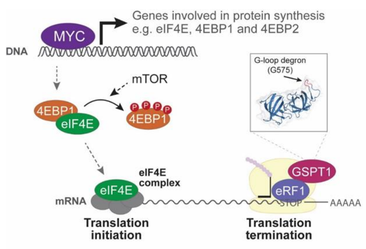
AACR 2022
Abstract #3929

GSPT1 is a Key Regulator and Therapeutic Vulnerability of MYC-induced Translational Addiction

Targeting MYC-driven Tumors and Their Addiction to Protein Translation



MYC-driven tumors are **addicted to protein translation** to sustain their growth

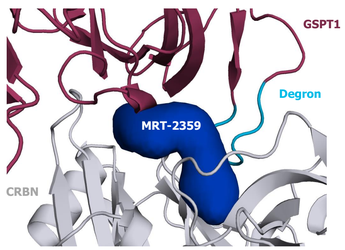
MYC hijacks the protein translation machinery by regulating the expression of key genes including the master regulator 4EBP1 and the initiation factor eIF4E

This addiction to protein translation creates a **dependency** on the translation termination factor **GSPT1**, a G-loop degron-containing protein

MRT-2359 is a GSPT1 MGD, which exploits this **vulnerability** by disrupting protein translation output and reducing MYC-oncogenic signaling leading to preferential anti-tumor activity in MYC-driven tumors

MRT-2359, a Rationally Designed GSPT1 MGD

CRBN/GSPT1 Induced Ternary Complex



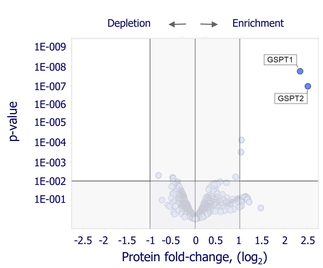
Molecular docking representation

In vitro, Cellular and ADMET Properties Overview

CRBN binding (HTRF; IC_{50})	113 nM
Ternary complex (HTRF; IC_{50})	7 nM
Ternary complex G575N GSPT1 mutant (HTRF; IC_{50})	>10000 nM
GSPT1 degradation in CAL51 (DC_{50}/D_{max})	5 nM /100%
GSPT1 degradation in CAL51 G575N mutant (DC_{50})	>10000 nM
72 hr viability in CAL51 (EC_{50})	150 nM
72 hr viability in CAL51 CRBN CRISPR KO (EC_{50})	>10000 nM
CYP DDIs (7 isoforms) / hERG (patch clamp)	>30000 nM
CEREP (panel with 44 proteins) tested at 10 µM	No off target

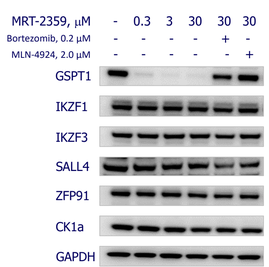
MRT-2359 is a Selective Inducer of Cereblon Proximity and GSPT1 MGD

Proximity Ligation Assay (Turbo ID)



CAL51 CRBN-Turbo ID 1 hr post treatment using 100 nM MRT-2359 or DMSO

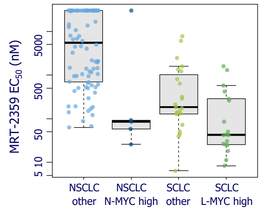
Selectivity Against Common CRBN Neosubstrates



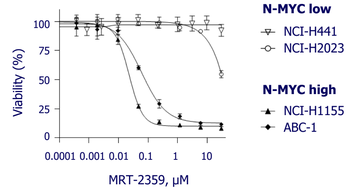
WB performed 6 hr post treatment in MM1S and Kelly (SALL4)

Preferential Anti-proliferative Activity of MRT-2359 in Lung Cancer Cell Lines with L-Myc and N-MYC High mRNA Expression

MRT-2359 Profiling in a Panel of Non-small (NSCLC) and Small Cell Lung Cancer (SCLC)



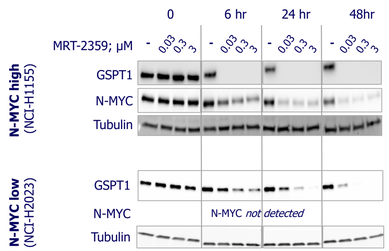
Representative Viability Curves in NSCLC Lines



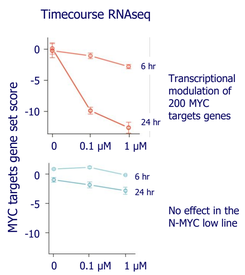
Cell viability assessed at 72 hr by CellTiter Glo (Promega). Not shown, equipotent GSPT1 degradation at 24 hr in NCI-H1155 (DC_{50} = 2.1 nM), ABC-1 (DC_{50} = 9.8 nM), NCI-H2023 (DC_{50} = 28.8 nM) and NCI-H441 (DC_{50} = 9.4 nM) with Dmax > 95% in all cases

MRT-2359 Induces the Degradation of GSPT1 Leading to the Downregulation of N-MYC and its Transcriptional Output

N-MYC Downregulation in N-MYC High Cells



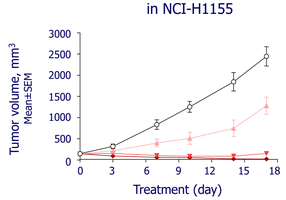
Repression of MYC Target Genes



RNAseq: Gene Set Enrichment Analysis (GSEA) displaying average Z-score normalized to DMS0

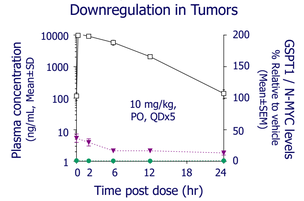
Dose-dependent Anti-tumor Activity of MRT-2359 in N-MYC High NSCLC Xenograft Model

Oral Dosing of MRT-2359 in NCI-H1155



PK, PD at day 5

GSPT1 Degradation and N-MYC Downregulation in Tumors



Vehicle PO, QD
MRT-2359 1 mg/kg PO, QD
MRT-2359 3 mg/kg PO, QD
MRT-2359 10 mg/kg PO, QD
MRT-2359 plasma concentration
GSPT1 level
N-MYC level

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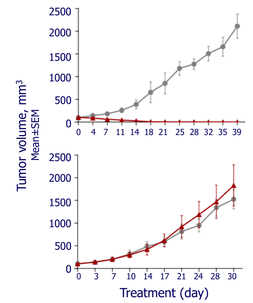
Oral Dosing of MRT-2359 Demonstrates Preferential Anti-tumor Activity in L-MYC and/or N-MYC High NSCLC Patient-derived Xenografts

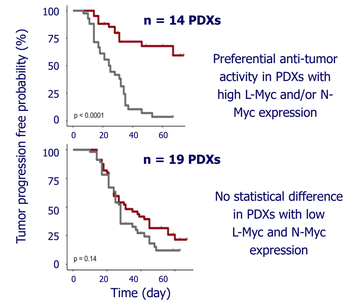
MRT-2359 Activity in **Representative NSCLC PDXs**



High L-MYC and/or N-MYC expression

Kaplan-Meier generated from 33 PDXs using tumor progression to ≥ 800 mm^3

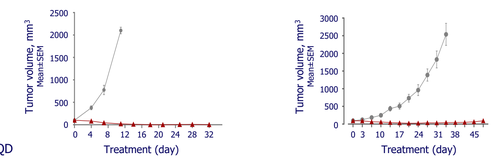
Low L-MYC and N-MYC expression



Preferential anti-tumor activity in PDXs with high L-Myc and/or N-Myc expression

No statistical difference in PDXs with low L-Myc and N-Myc expression

Additional Examples of MRT-2359 Anti-tumor activity in SCLC (left) and Neuroendocrine Lung Cancer (right) PDXs



Vehicle PO, QD
MRT-2359 10 mg/kg, PO, QD

Real-world Data Analysis of L-MYC and N-MYC mRNA Expression and Amplification in Lung Cancer

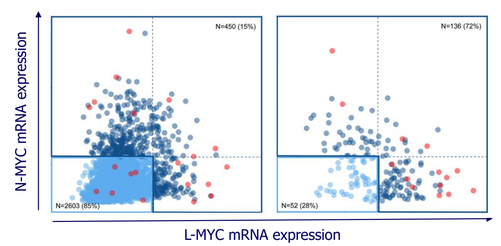
L-Myc and/or N-Myc are Highly Expressed in 15% of NSCLC (left) and 72% of SCLC (right) Tumor Samples

NSCLC

Total of 3053 samples

mRNA expression
High N-MYC or L-MYC | 15%
Low N-MYC and L-MYC | 85%

DNA amplification
N-MYC CNV ≥ 8
L-MYC CNV ≥ 8 | 1%



SCLC

Total of 188 samples

mRNA expression
High N-MYC or L-MYC | 72%
Low N-MYC and L-MYC | 28%

DNA amplification
N-MYC CNV ≥ 8
L-MYC CNV ≥ 8 | 7%

Real-world molecular and genomic data analyses performed on 3241 lung cancers (in collaboration with Tempus, Inc.)

Conclusion and Future Development

- MRT-2359 is a potent, selective and orally bioavailable GSPT1 MGD
- MRT-2359 induces the degradation of GSPT1, the associated downregulation of N-MYC and the modulation of its transcriptional output leading to preferential anti-proliferative activity in L-MYC and N-MYC driven cancer cells
- MRT-2359 administered orally demonstrates preferential anti-tumor activity in xenograft and PDX NSCLC models with high L-MYC and/or N-MYC mRNA expression levels
- Patient sample analyses indicate that 15% of NSCLC and 72% of SCLC have high L-MYC and/or N-MYC expression
- Taken together these data warrant the clinical development of MRT-2359 in MYC-driven solid tumors addicted to protein translation with a focus on NSCLC, SCLC and neuroendocrine lung cancer

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