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Identification of GSPT1-mediated molecular glue degraders for the treatment of Myc-driven cancers

LBA004

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I have the following financial relationships to disclose:

Employee of: Monte Rosa Therapeutics

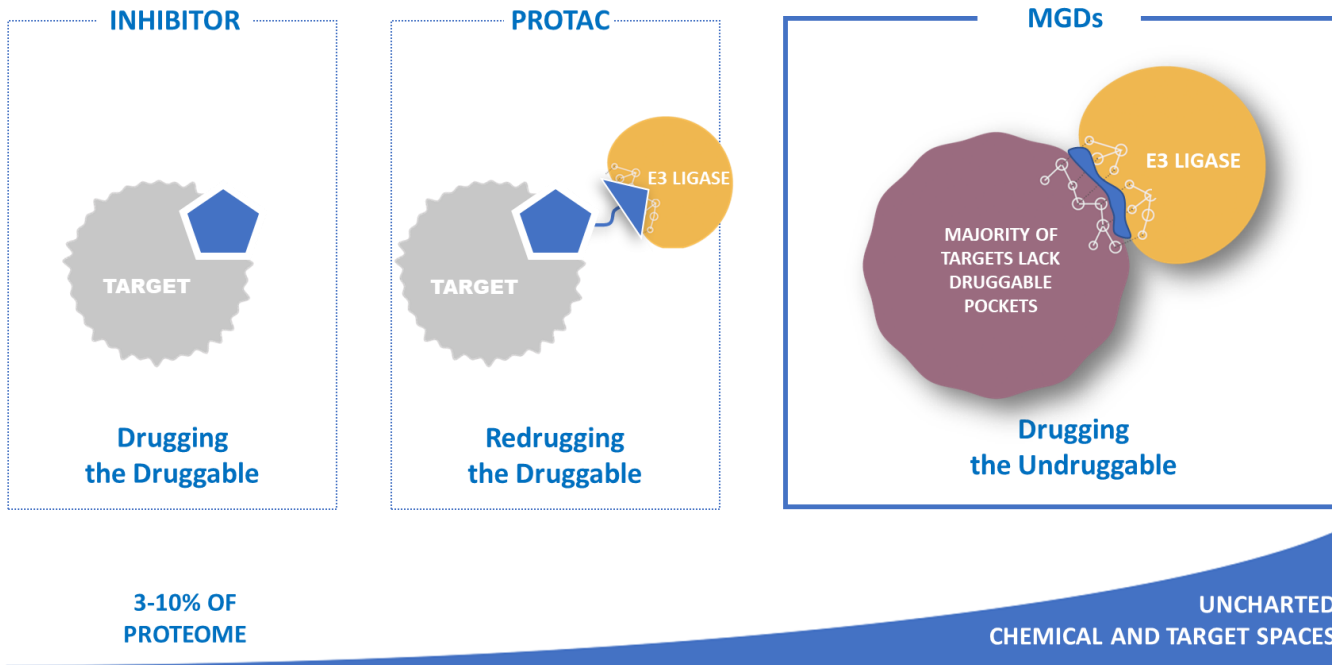
I will not discuss off label use and/or investigational use in my presentation.





Molecular Glue Degraders (MGDs)

Opportunities for expanding the target space and fostering a new generation of drugs

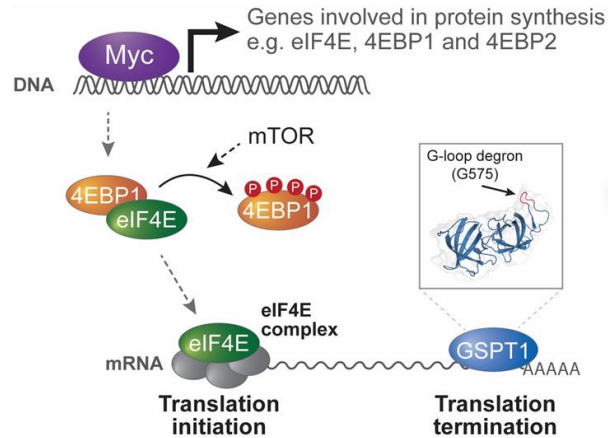




Targeting Myc-driven Tumors and Their Addiction to Protein Translation

GSPT1 is a key regulator and vulnerability of Myc-induced translational addiction

Myc hijacks the cellular protein translation machinery creating a vulnerability to GSPT1



Target profile

To sustain growth, Myc-driven tumors are **addicted to protein translation**

- Myc regulates the expression of key genes related to protein translation, including the master regulator 4EBP1 and eIF4E

This addiction to protein translation creates a possible **dependency** to the termination translation factor GSPT1 a degron-containing protein

GSPT1 MGDs exploit this **vulnerability** by:

- Disrupting protein translation output
- Reducing Myc-oncogenic signaling



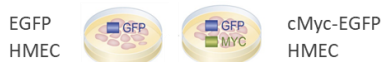


MRT-048 a Potent, Selective GSPT1 Degradator for Myc-driven Cancers

Replicating and targeting Myc biology in a breast model system

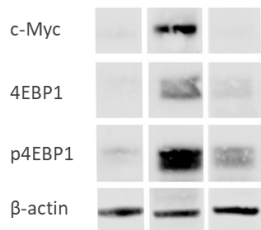
Myc-driven system
established for screening

Doxycycline-inducible cMyc HMEC model



Model recapitulates Myc-induced
enhanced protein translation

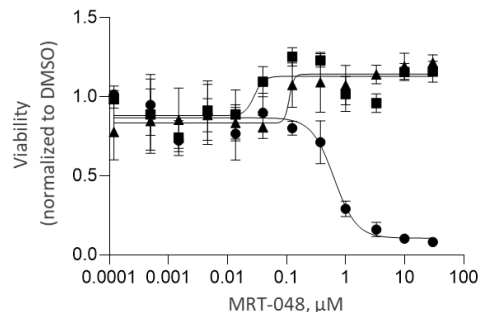
Dox	-	+	wash-off
	off	on	off
c-Myc			
4EBP1			
p4EBP1			
β-actin			



Human mammary epithelial cells (HMEC) – 3D model

Hits that specifically kill
Myc-driven cells identified

MRT-048 shown as
a representative hit

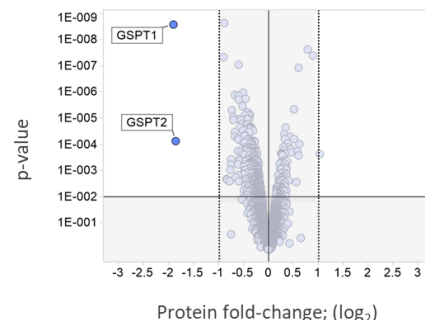


● Myc on $EC_{50} = 0.64 \mu M$
 ▲ Myc off (- Dox) $EC_{50} > 30 \mu M$
 ■ Myc off (wash-off) $EC_{50} > 30 \mu M$

HMEC, Cell-titer Glow (CTG): 72hr

MRT-048 is a highly
selective GSPT1 MGD

Quantitative proteomics
(>8500 other proteins identified)



Western blot validation
 $DC_{50} = 83 \text{ nM}$ / $D_{max} = 100\%$

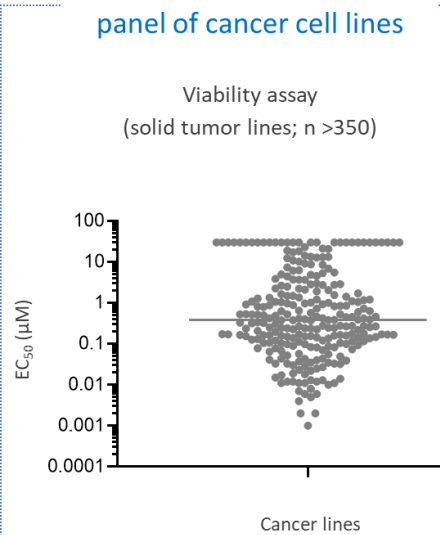
CAL51, 6 hr following treatment with MRT-048





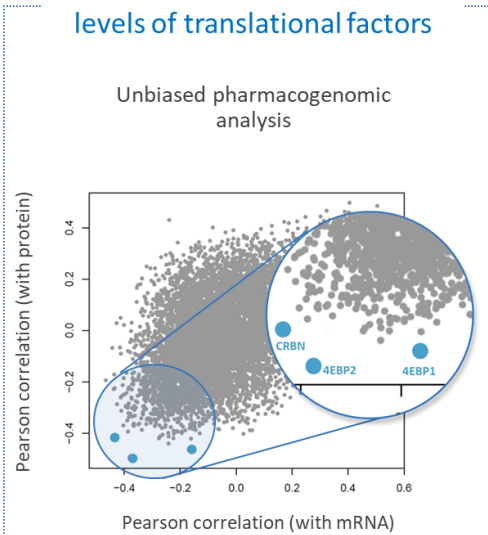
MRT-048 Sensitivity is Linked to Key Regulators of Protein Translation including p4EBP1 in Breast Cancer Cell Lines

Broad range of activity in a panel of cancer cell lines



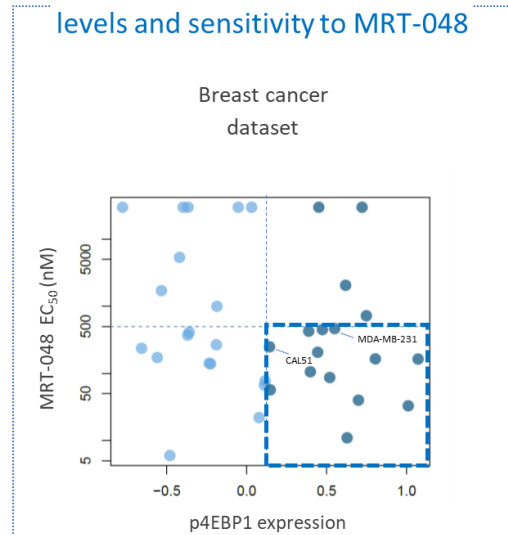
72 hr CTG assay across >10 cancer subtypes. — Median

Sensitivity associated with high levels of translational factors



Using CCLE dataset as reference

Association between p4EBP1 levels and sensitivity to MRT-048

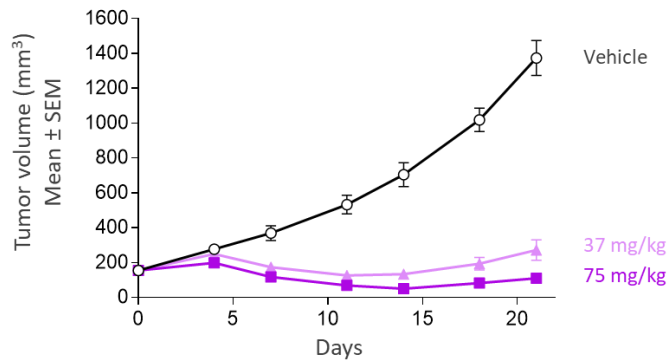
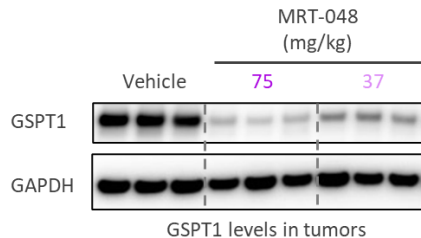




MRT-048 *in vivo* Efficacy Studies in High p4EBP1 Breast Cancer Models

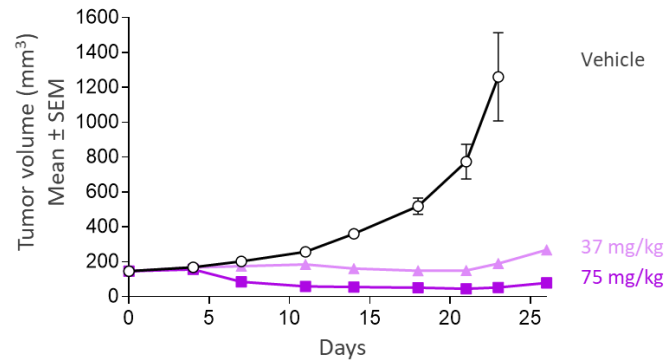
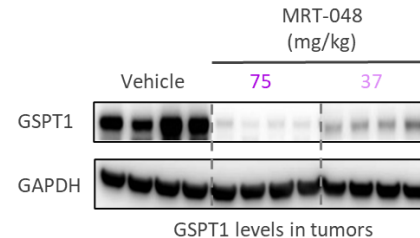
Potent anti-tumor activity and target engagement demonstrated

MDA-MB-231



MRT-048 dosed IP, QD*21. Tumors harvested 24 hr post 3rd dose

CAL51



MRT-048 dosed IP, QD*26. Tumors harvested 24 hr post 3rd dose

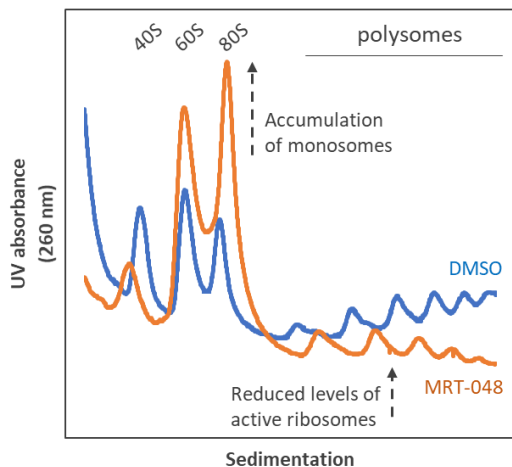




MRT-048 Impairs Protein Translation and Myc Oncogenic Signaling

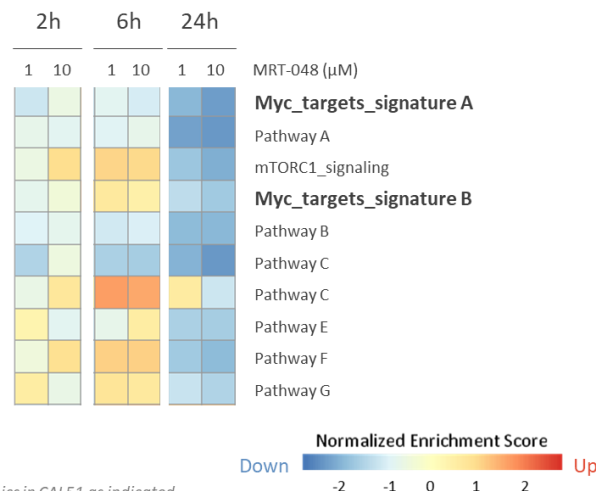
Myc gene signatures are strongly down-regulated following treatment with MRT-048

Reduced initiation
and translational activity



Polysome profiling in CAL51 24 hr post treatment with MRT-048 (1 μ M)

Myc signatures are top hits in gene
set enrichment analysis



Transcriptomics in CAL51 as indicated



Targeting Myc-addicted Tumors with GSPT1 MGDs

- Cellular system replicating Myc biology established in breast model and used for screening
- GSPT1 degraders that specifically kill Myc-driven cells identified
- MRT-048 is a potent and selective GSPT1 degrader
- MRT-048 impairs protein translation and Myc oncogenic signaling
- Patient stratification hypothesis developed and robust anti tumor activity demonstrated *in vivo*



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