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MOLECULAR TARGETS AND CANCER THERAPEUTICS

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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:

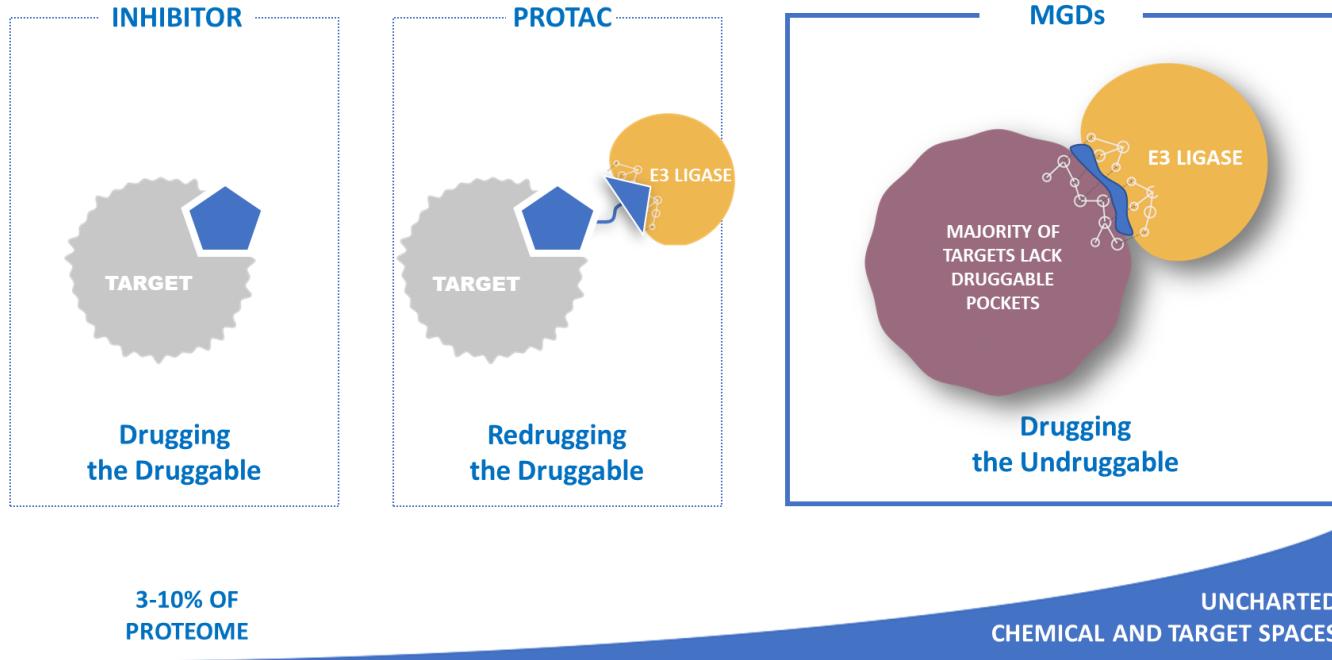
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I will not discuss off label use and/or investigational use in my presentation.



Molecular Glue Degraders (MGDs)

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

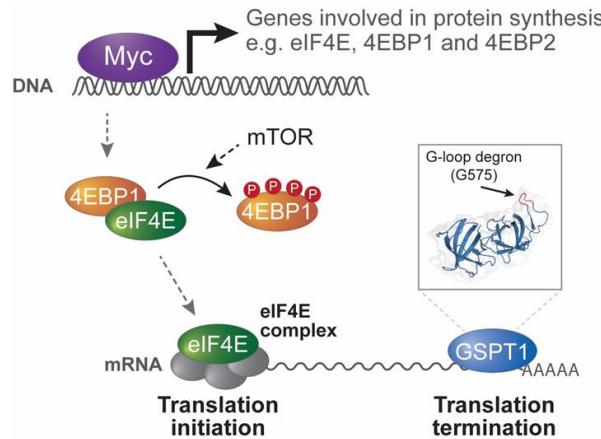


Targeting Myc-driven Tumors and Their Addiction to Protein Translation

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 elF4E

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

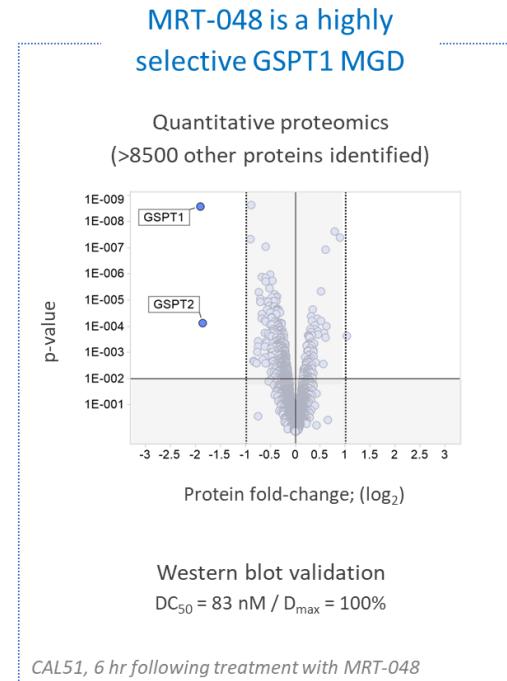
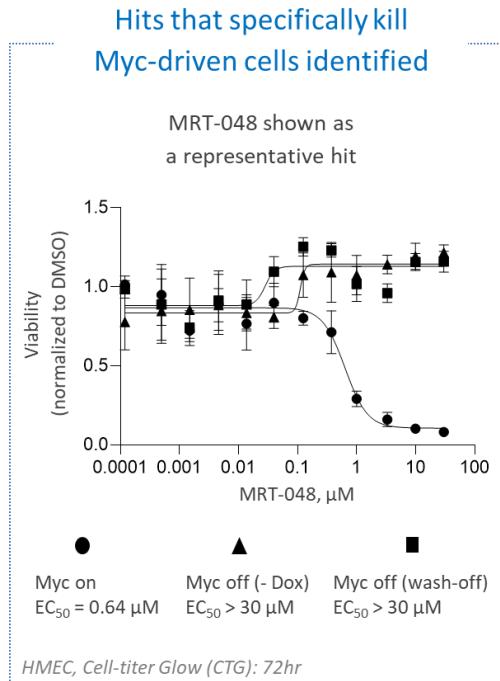
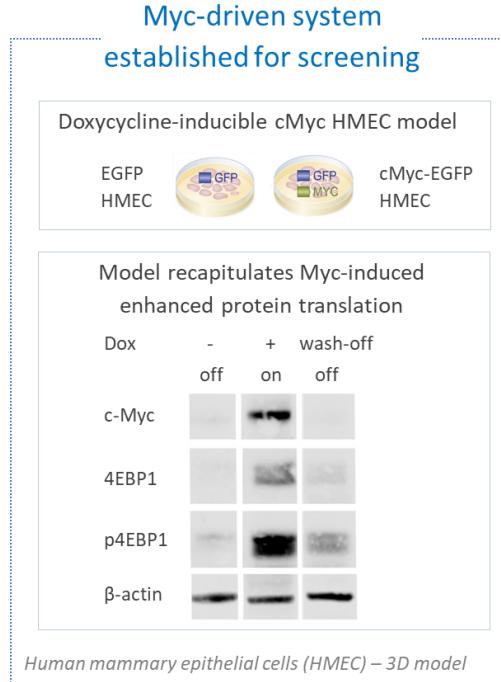
GSPT1 MGDs exploit this **vulnerability** by:

- Disrupting protein translation output
- Reducing Myc-oncogenic signaling



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

Replicating and targeting Myc biology in a breast model system

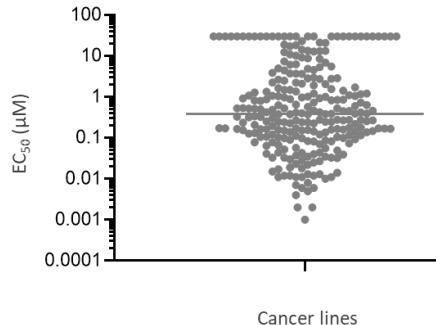


MRT-048 Sensitivity is Linked to Key Regulators of Protein Translation including p4EBP1 in Breast Cancer Cell Lines



Broad range of activity in a panel of cancer cell lines

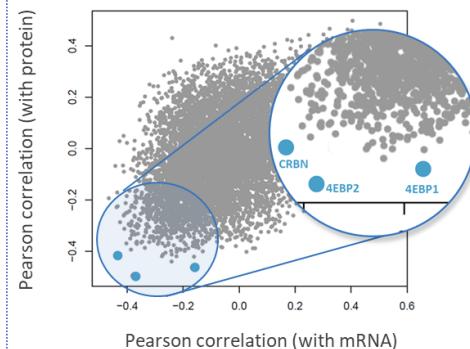
Viability assay
(solid tumor lines; n >350)



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

Sensitivity associated with high levels of translational factors

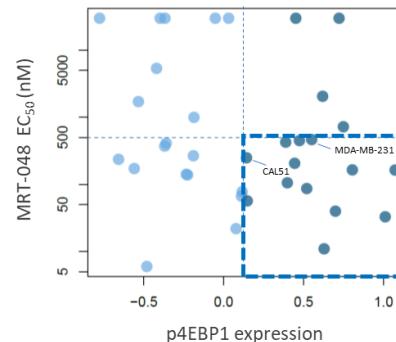
Unbiased pharmacogenomic analysis



Using CCLE dataset as reference

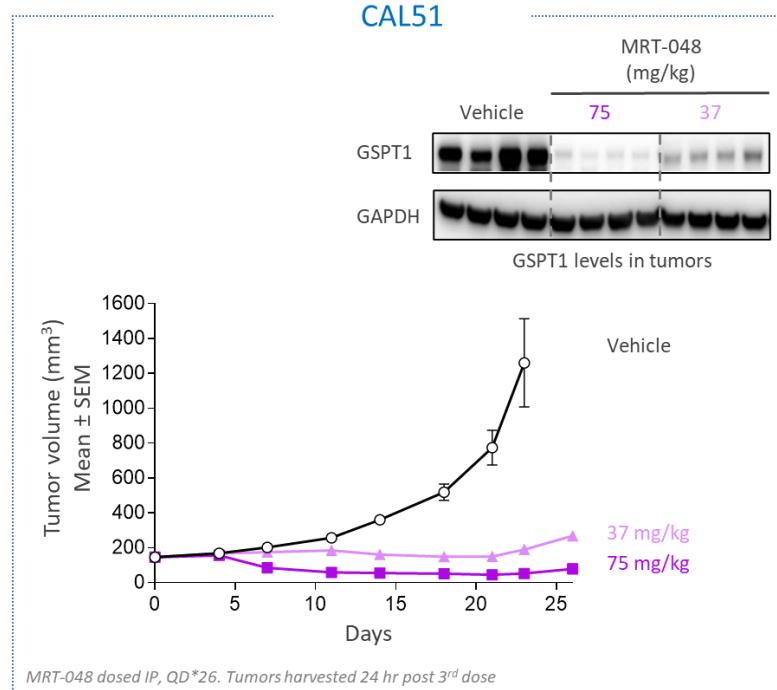
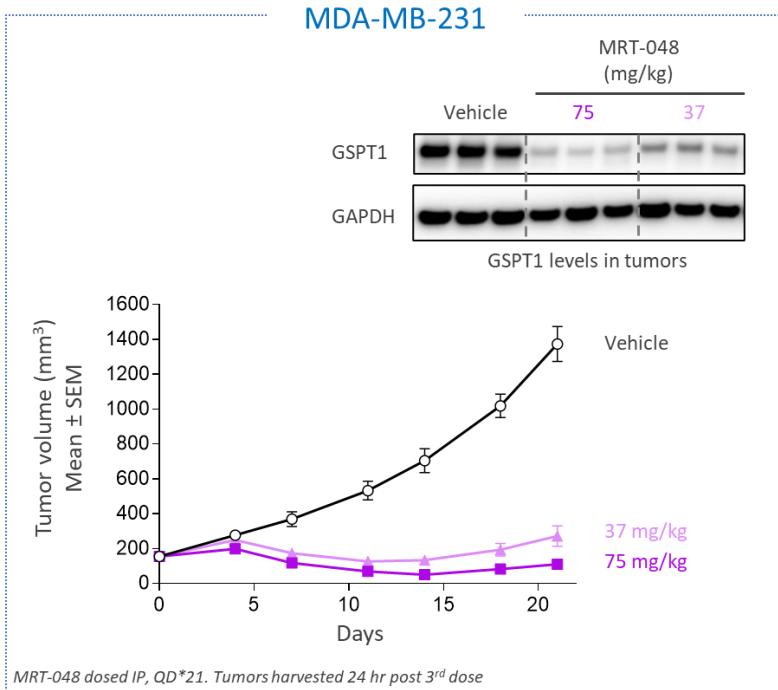
Association between p4EBP1 levels and sensitivity to MRT-048

Breast cancer dataset



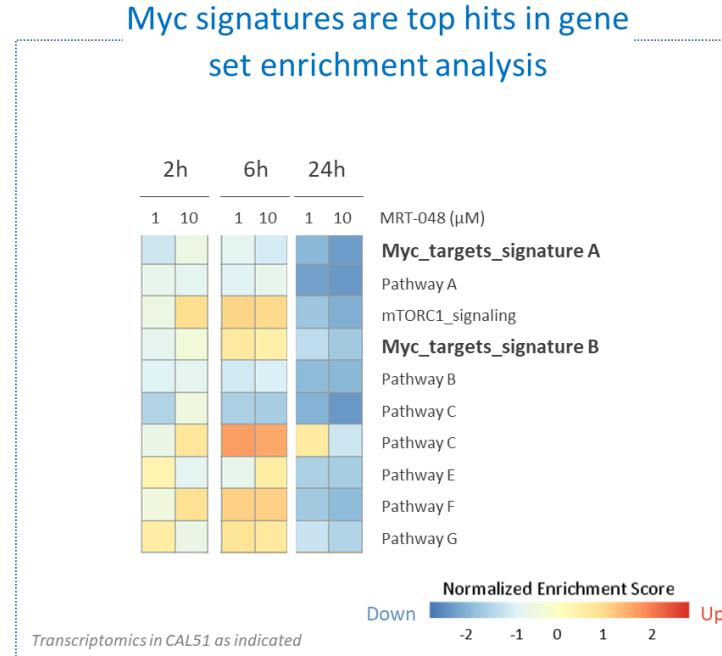
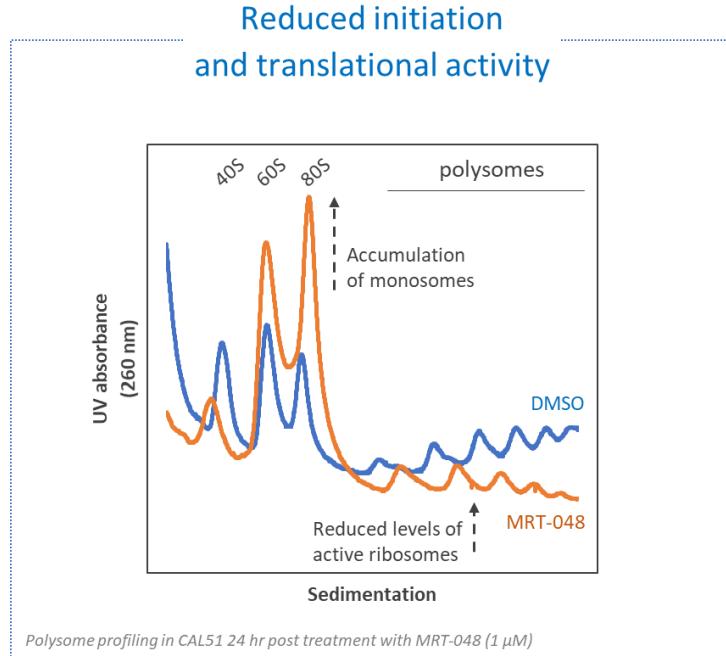
MRT-048 *in vivo* Efficacy Studies in High p4EBP1 Breast Cancer Models

Potent anti-tumor activity and target engagement demonstrated



MRT-048 Impairs Protein Translation and Myc Oncogenic Signaling

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



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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