Targeting MAT2A in CDKN2A/MTAP-deleted Cancers

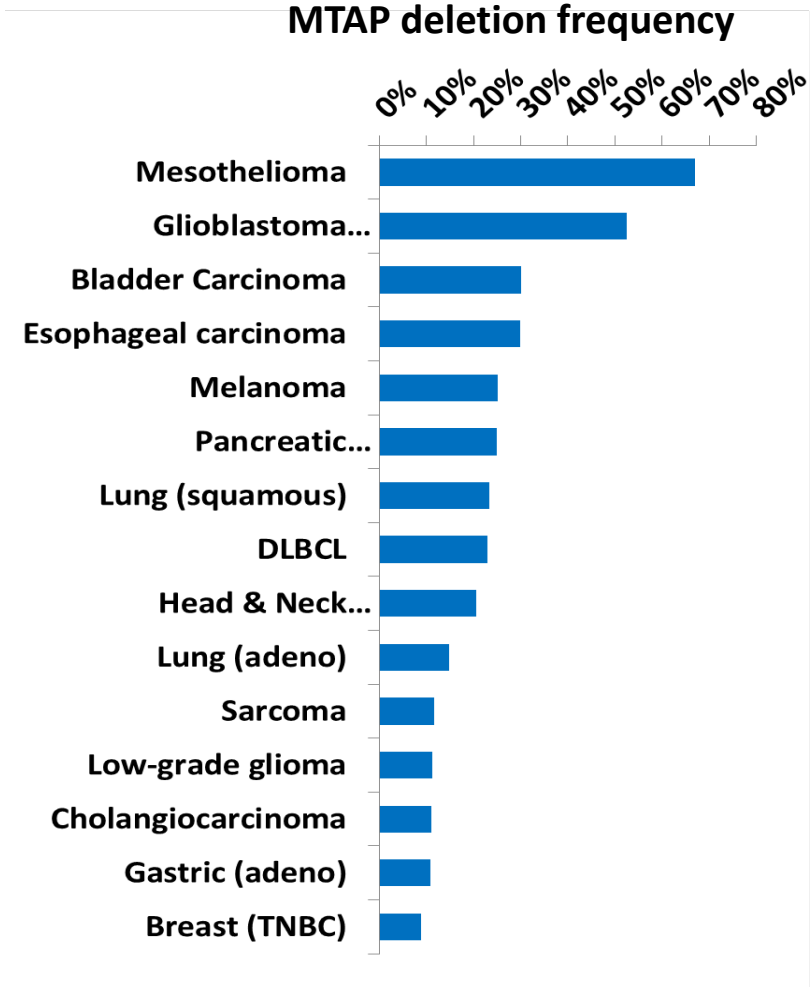
American Association for Cancer Research

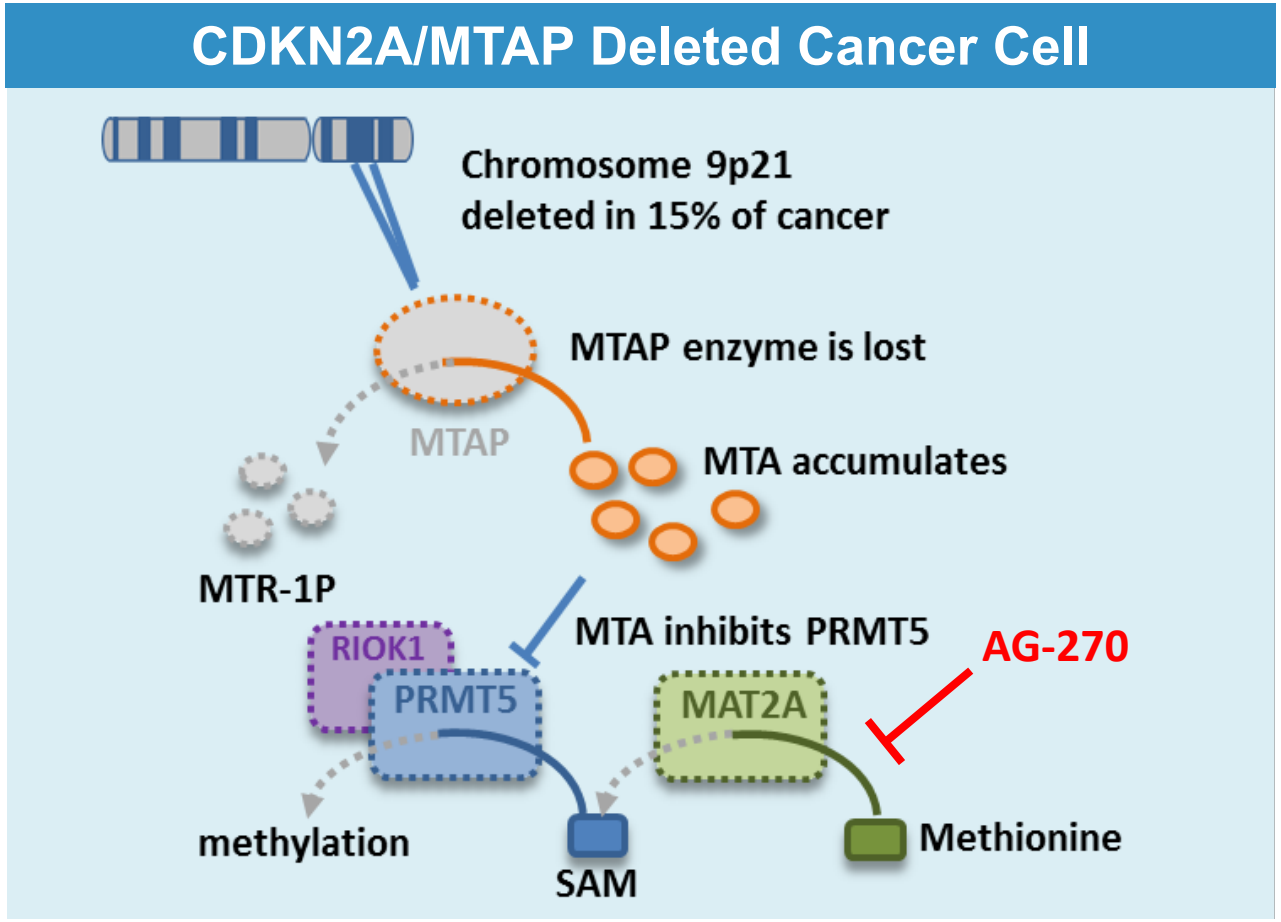
2019 Annual Conference

Symposium on Exploiting Metabolic Vulnerabilities of Cancer

April 1st 2019

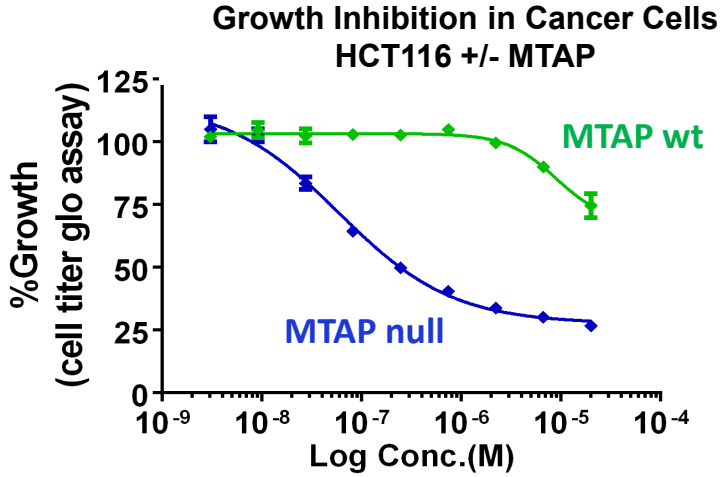
Targeting MAT2A in Cancers with Deletion of CDKN2A/MTAP

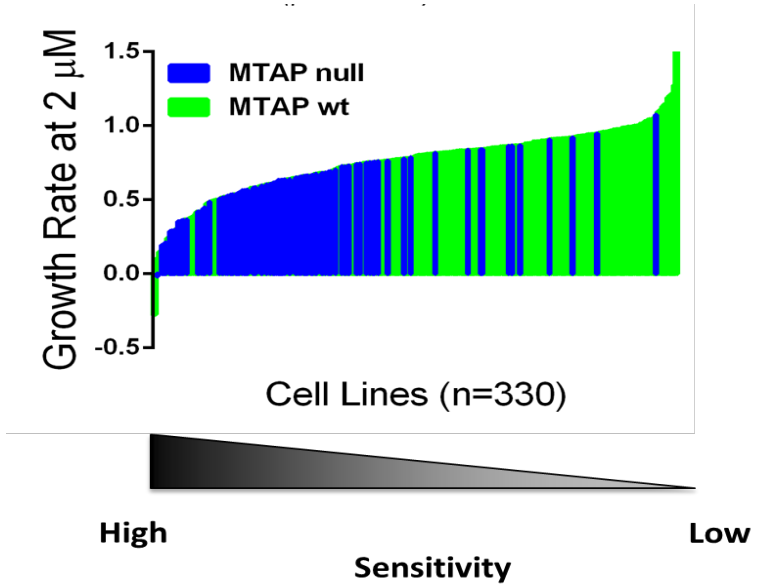


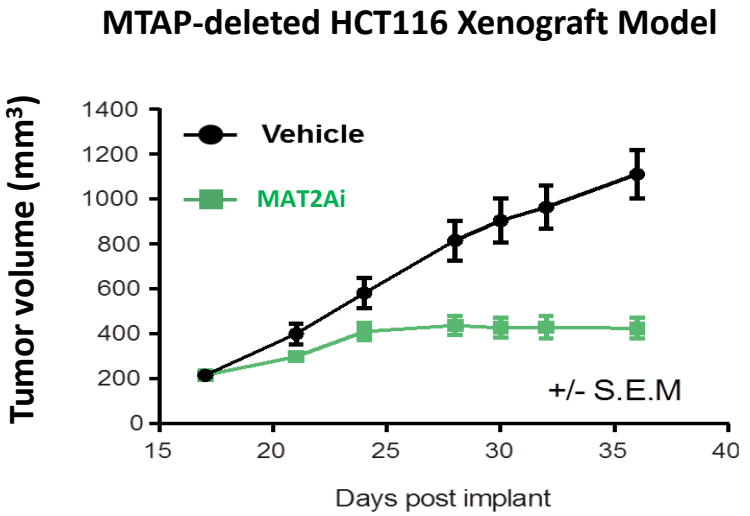


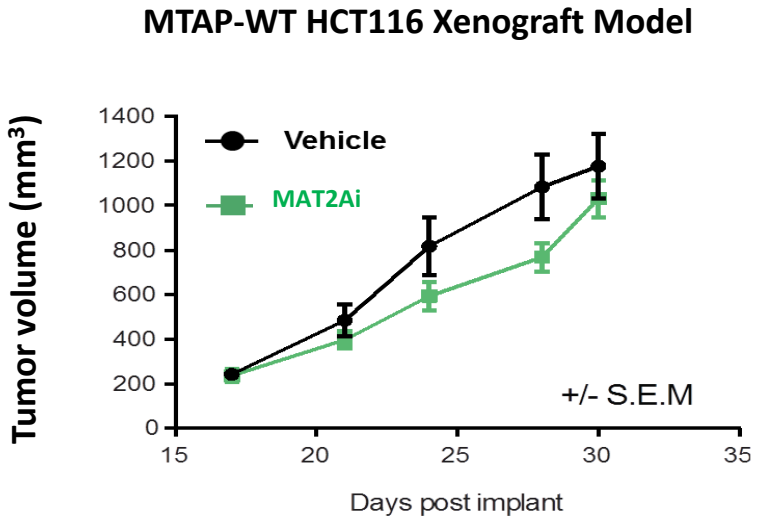
Marjon et al. Cell Reports 2016

Agios MAT2A Inhibitors Selectively Impact Proliferation of MTAP-null Cancers

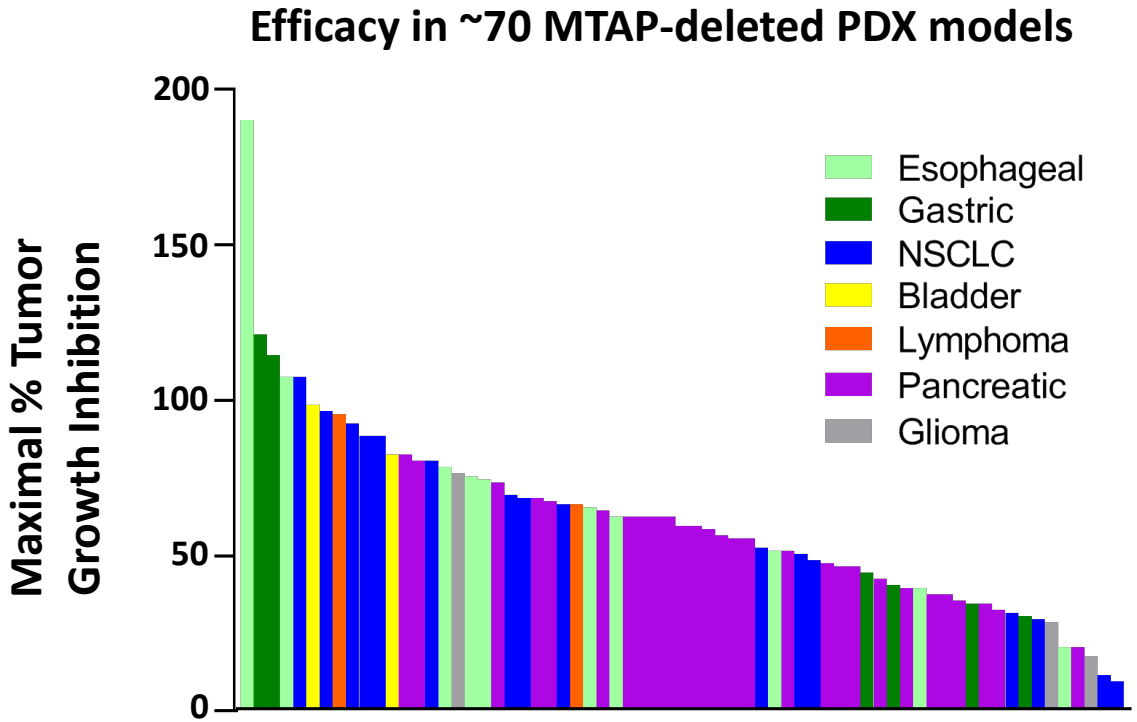


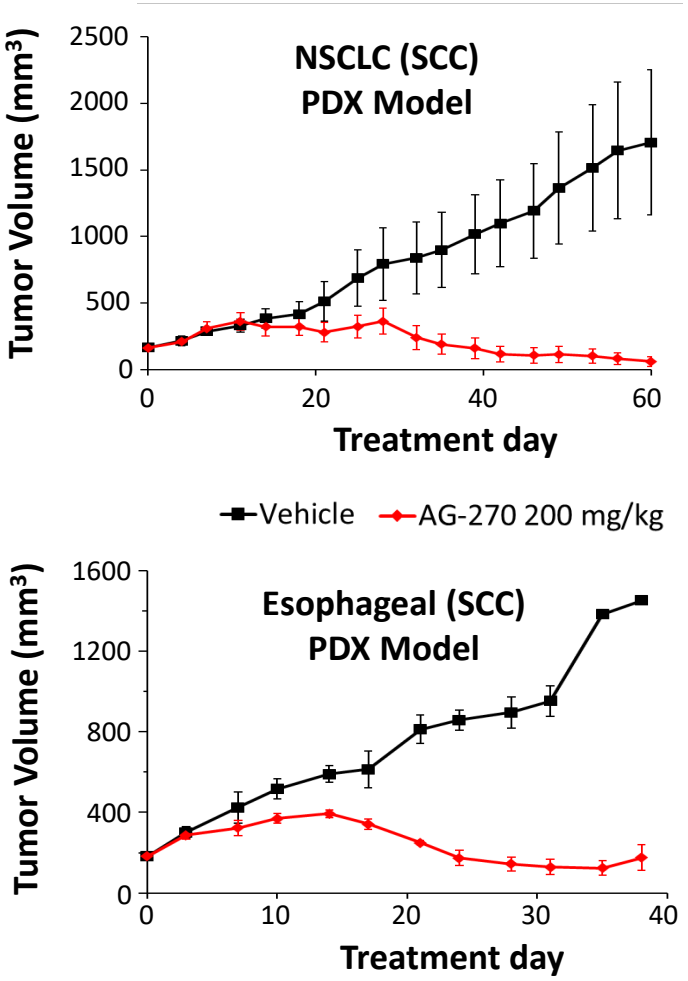






MAT2A Inhibitor AG-270 Possesses Broad Activity in 'Mouse Clinical Trial' Using Patient Derived Xenograft Models

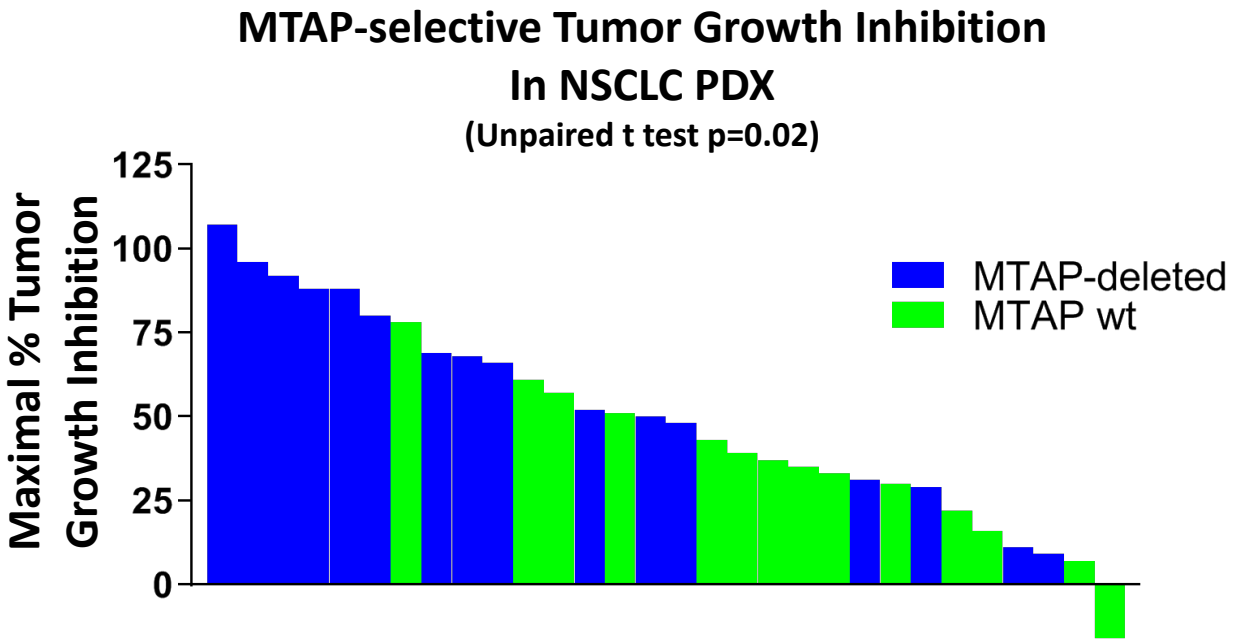


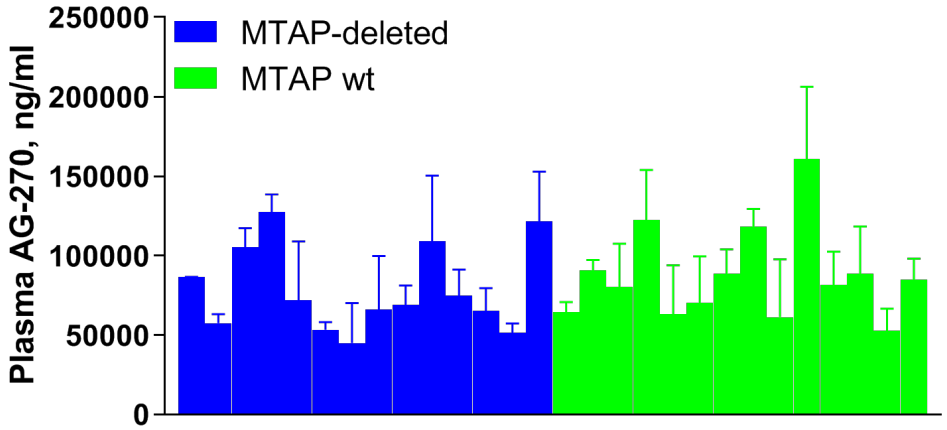


Anti-tumor activity observed in a variety of models, with examples of regressions / tumor stasis

N=3 per model; established tumors treated at 200 mpk AG-270 QD

MTAP-deletion Enriches for AG-270 Sensitivity in NSCLC PDX Models





- MTAP-deleted and MTAP wt tumors have similar drug exposure

NSCLC PDX models validate MTAP-deletion as a biomarker

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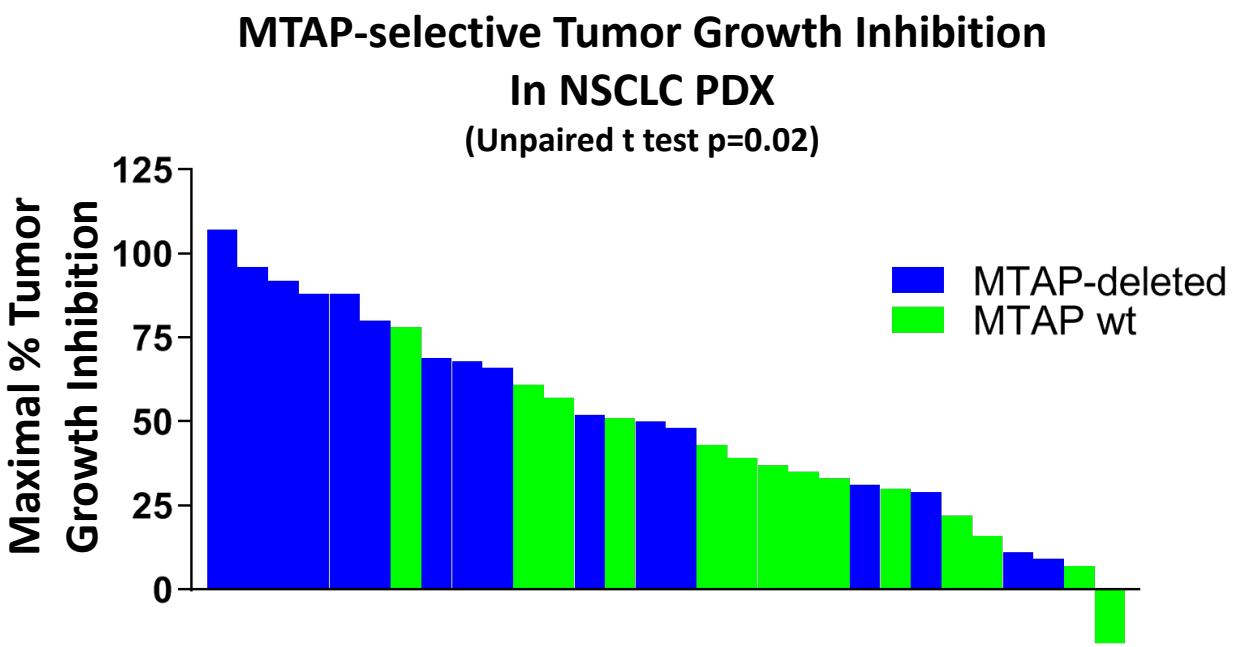

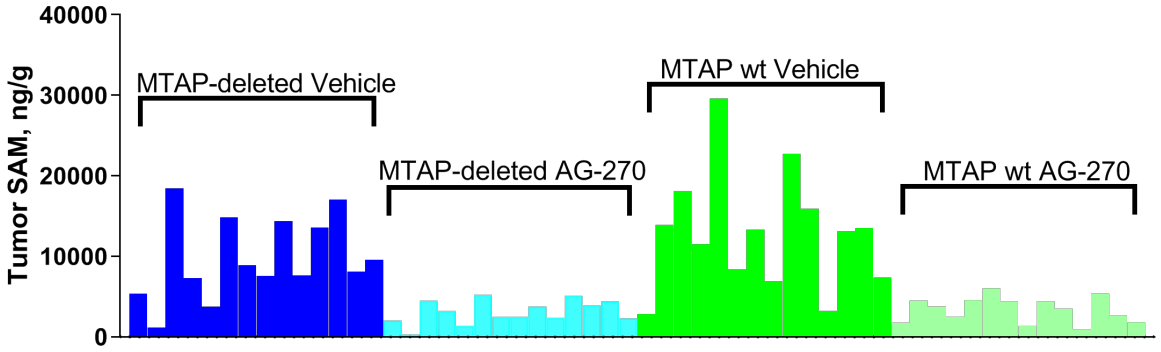

- MTAP-deleted and MTAP wt tumors have similar drug exposure **and similar reductions in Tumor SAM**

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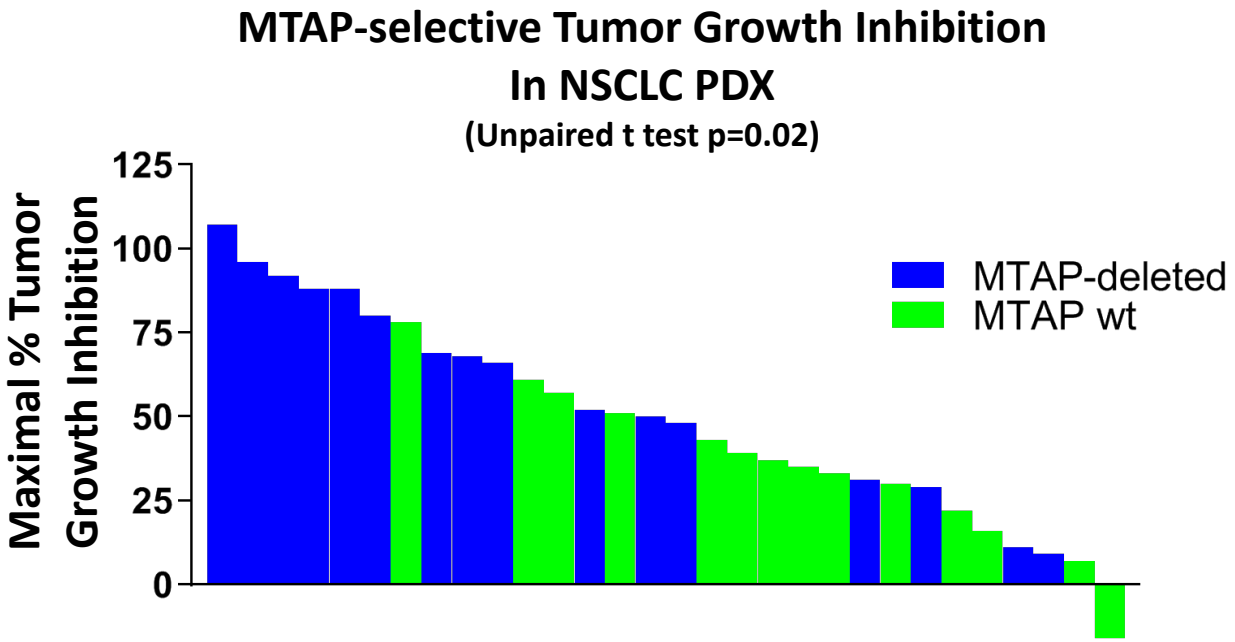
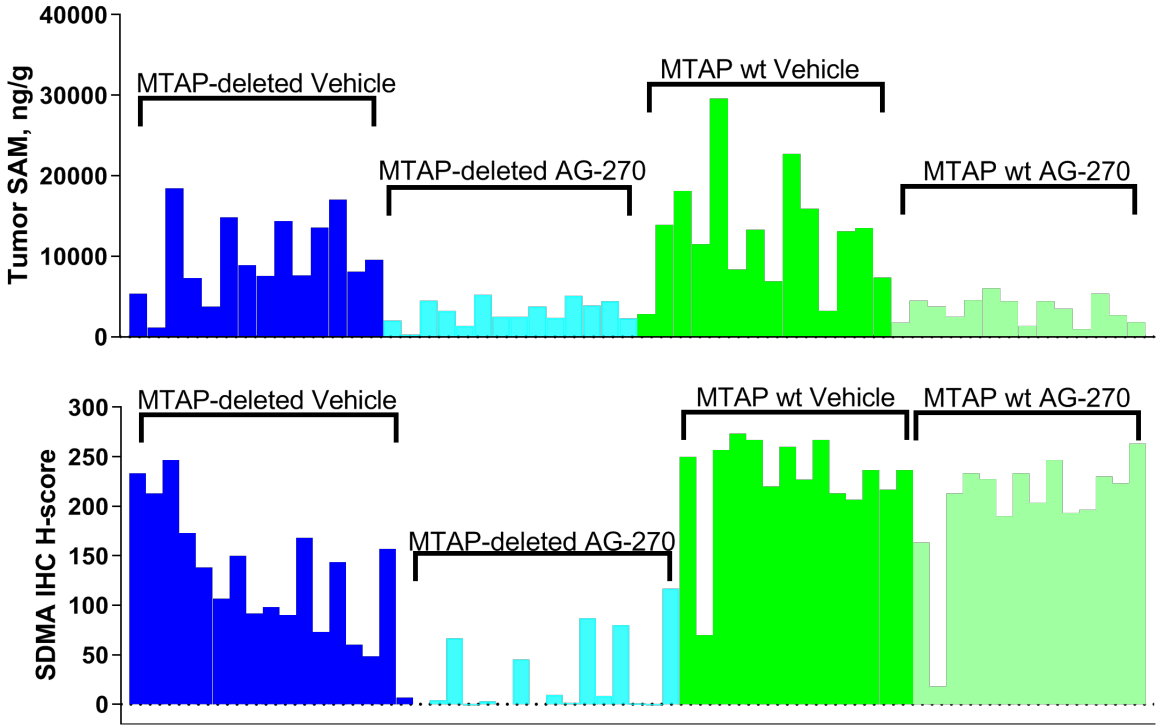




- MTAP-deleted and MTAP wt tumors have similar drug exposure and similar reductions in Tumor SAM **but PRMT5 methyl marks only decrease in MTAP-deleted tumors**

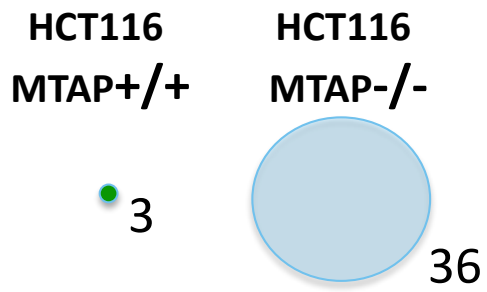
NSCLC PDX models validate MTAP-deletion as a biomarker
…and provide evidence supporting the MTAP→PRMT5/MAT2A mechanism

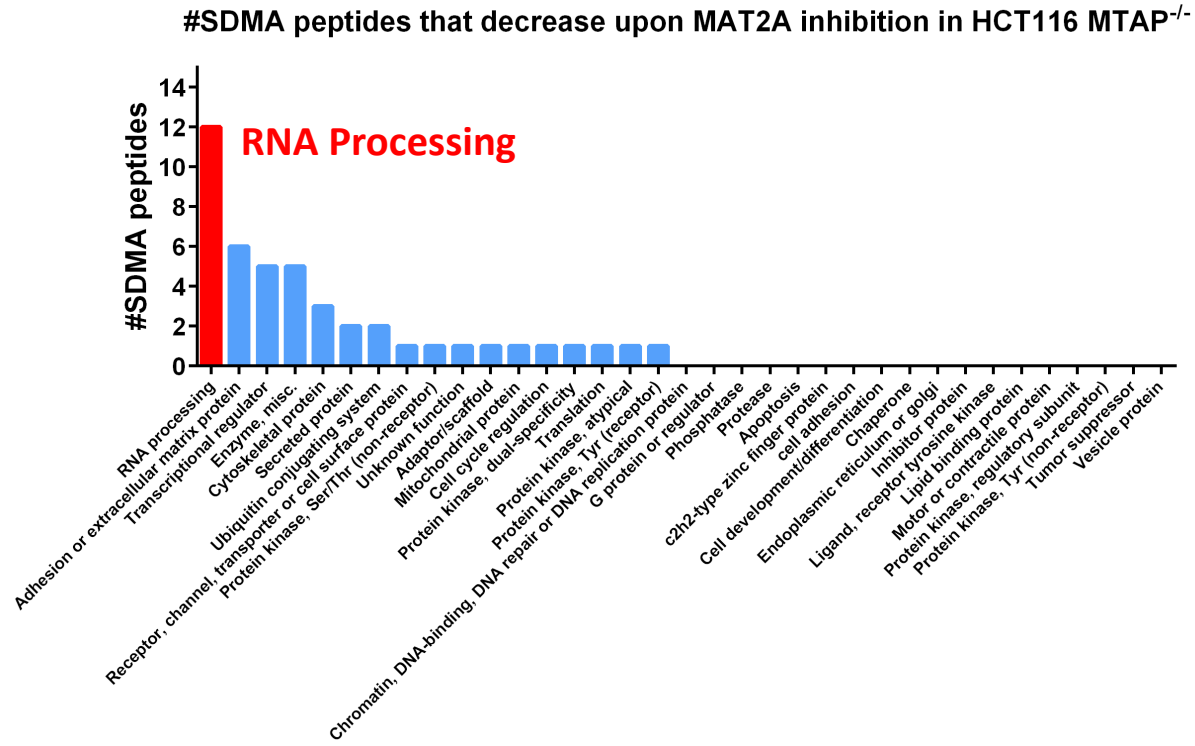
Methylation Proteomics Corroborates Role for PRMT5 as a Key Downstream Mediator of MAT2A Inhibition in MTAP-deleted Cells

HCT116 MTAP$^{-/-}$ and HCT116 MTAP wt cells → 3-day treatment with MAT2Ai or DMSO → IP with PTM-specific antibodies → LC-MS/MS

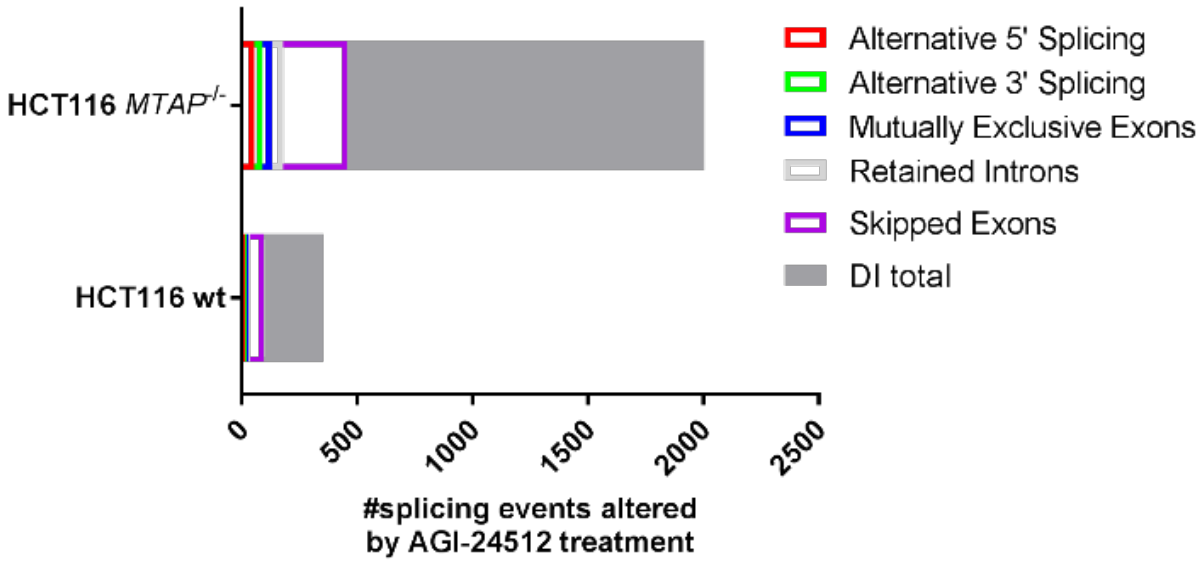
- Mono-Methyl-Arginine
- Asymmetrical di-methyl Arginine
- Symmetrical di-methyl Arginine
- Pan-methyl Lysine

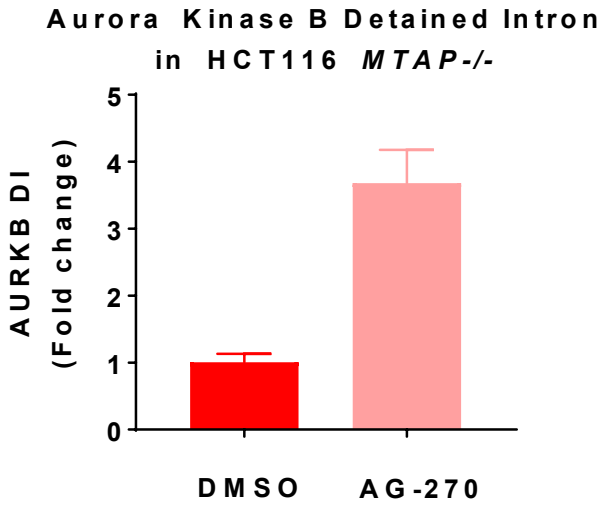
 # PRMT5 SDMA peptides reduced >4-fold upon MAT2Ai treatment:

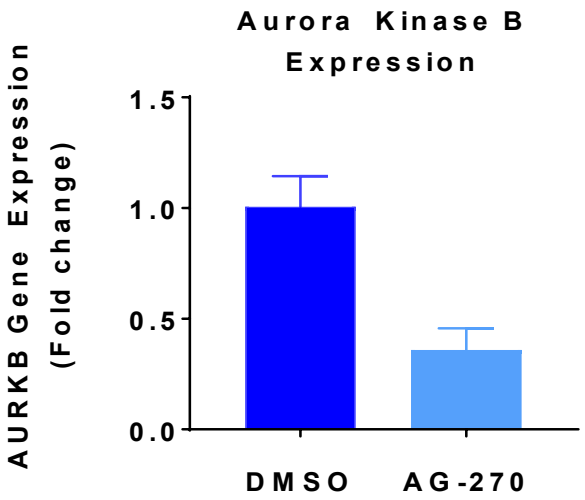




MAT2A Inhibition Selectively Disrupts Splicing in MTAP-deleted Cells

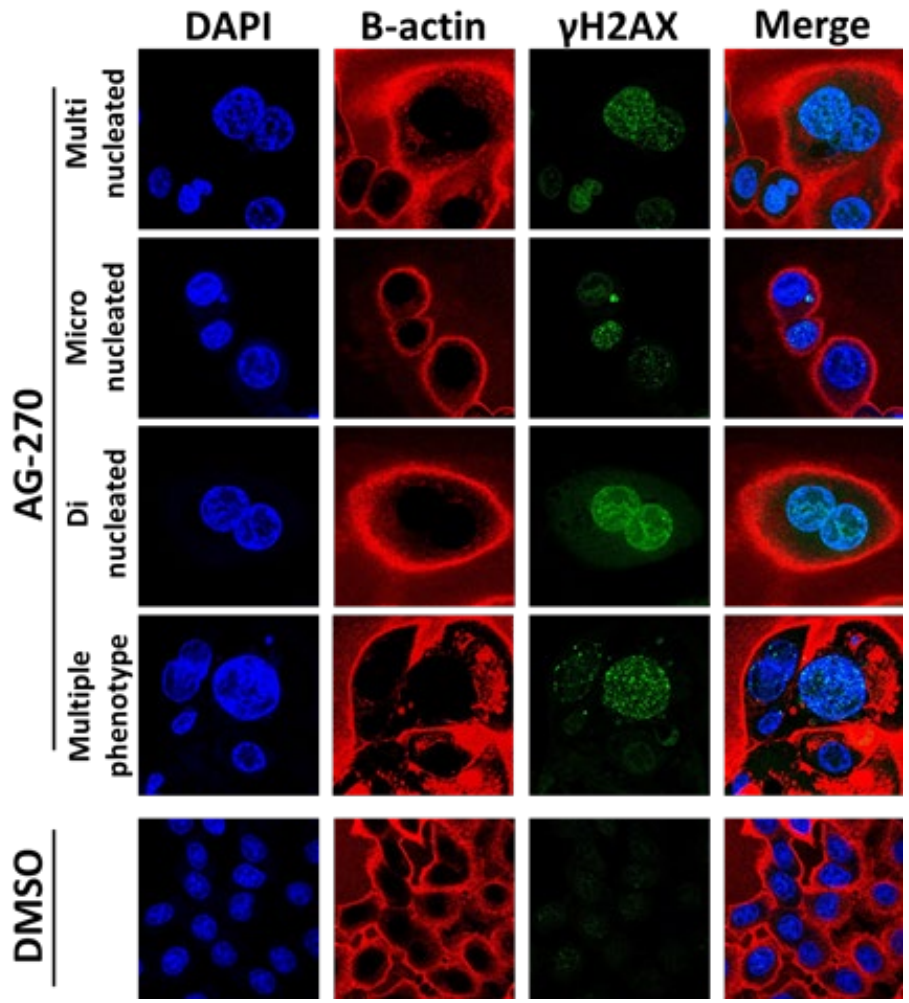


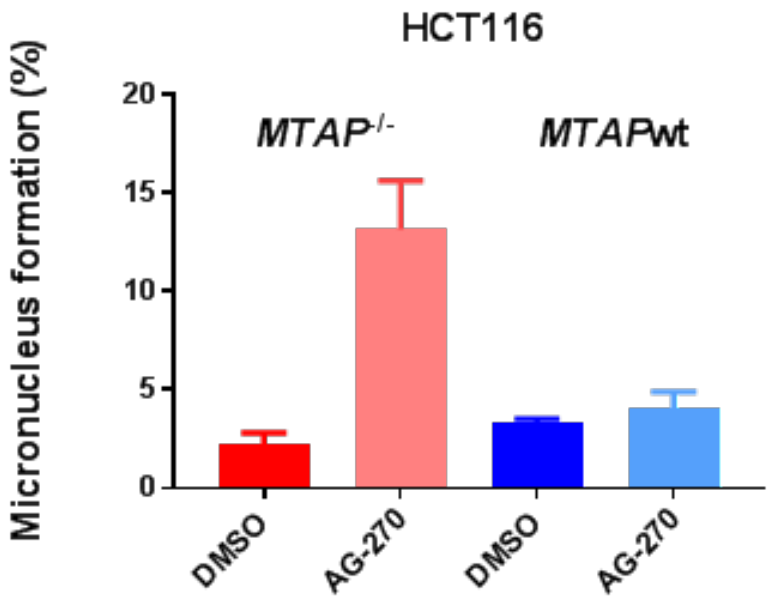




- MAT2A Inhibition leads to substantial dysregulation of splicing, including large increase in transcripts containing Detained Introns (DIs)
- DI-containing transcripts fail to export into the cytosol and thus are not translated (Boutz et al G&D 2015)
- MAT2A Inhibitor treatment DIs include critical genes in DNA damage repair and cell cycle

AG-270 Treatment Induces Substantial Mitotic Defects in HCT116 MTAP$^{-/-}$ cells





- Single Agent AG-270 treatment leads to DNA damage (γH2AX) and micronuclei formation
- Effects are selectively observed in *MTAP*-/- cells and not in *MTAP*-wt cells

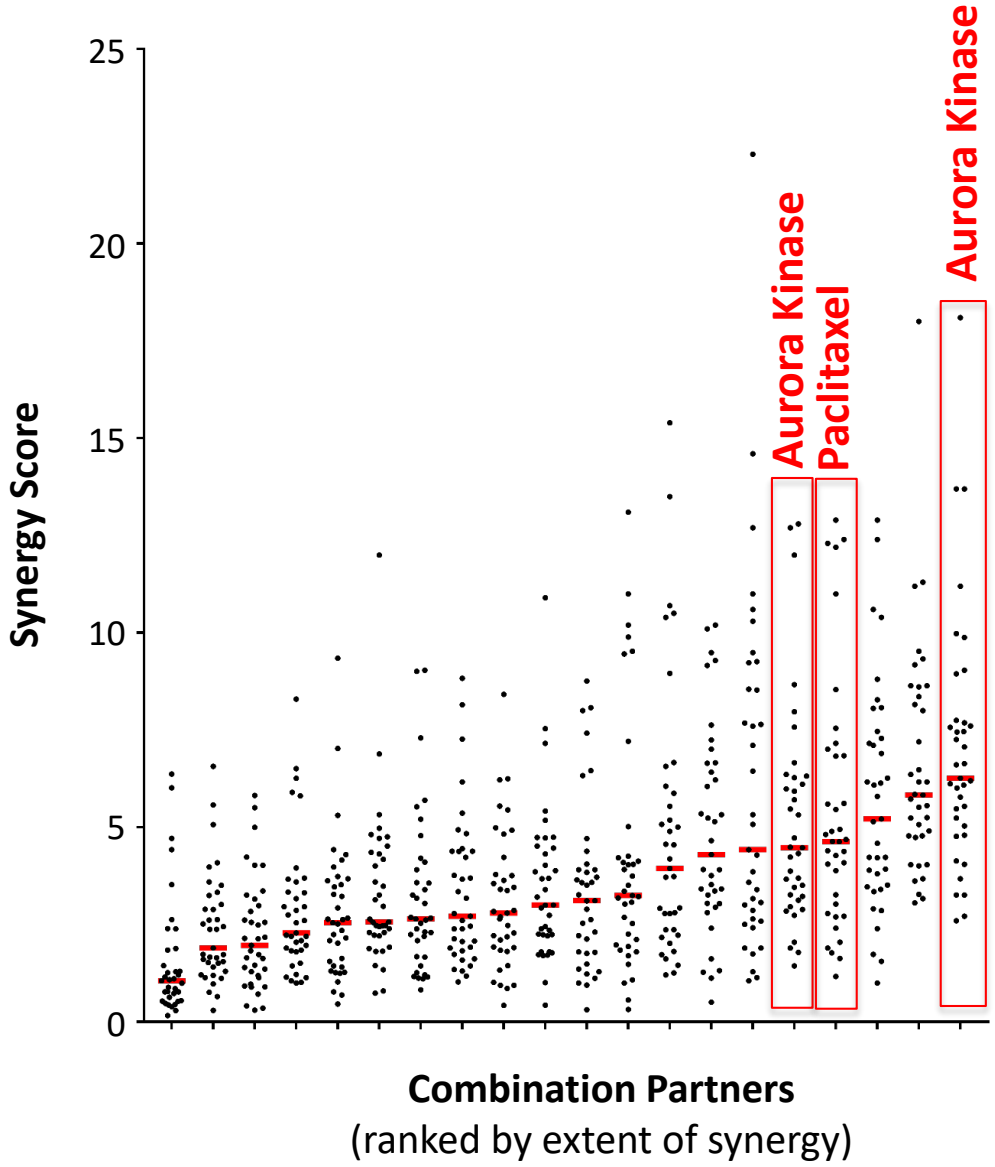
In Parallel, a Large-scale Synergy Screen in >30 Cell Lines Revealed Synergy between AG-270 and Antimitotics

Large Scale Synergy Screen:

20 candidate combo partners
X
36 MTAP-null cell lines

- Full dose curve matrices
- Cell lines included (n):

Lung (17), Esophageal & Gastric (8), Pancreatic (7), Colorectal (3), Kidney (1)



AG-270 Synergizes with AuroraB Kinase Inhibitors and Other Anti-mitotic Agents *in vitro*

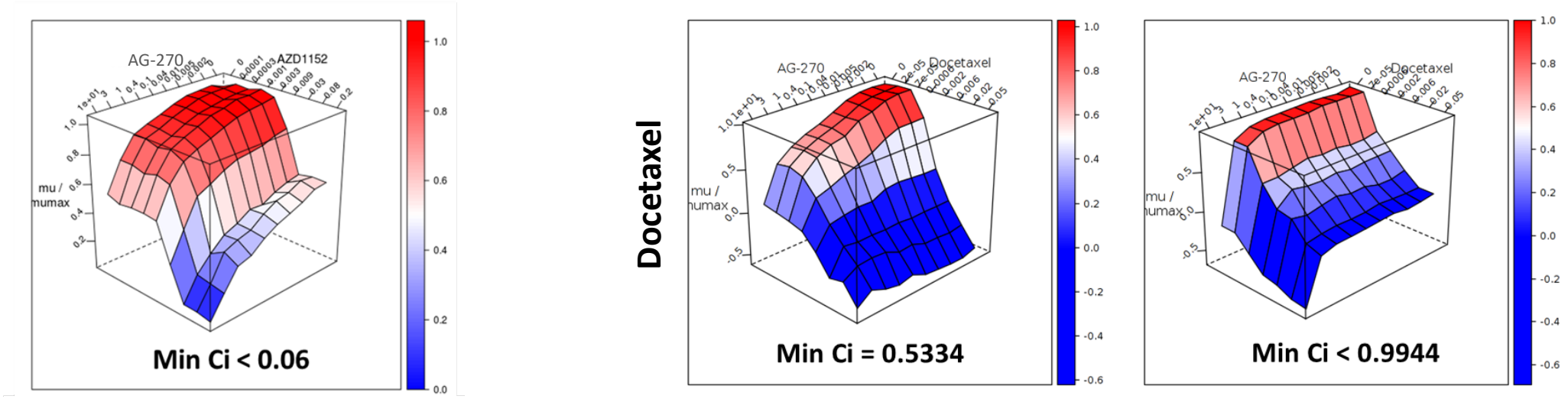
KP4 (MTAP-deleted)

HCT116 *MTAP-/-*

HCT116 *MTAP+/+*

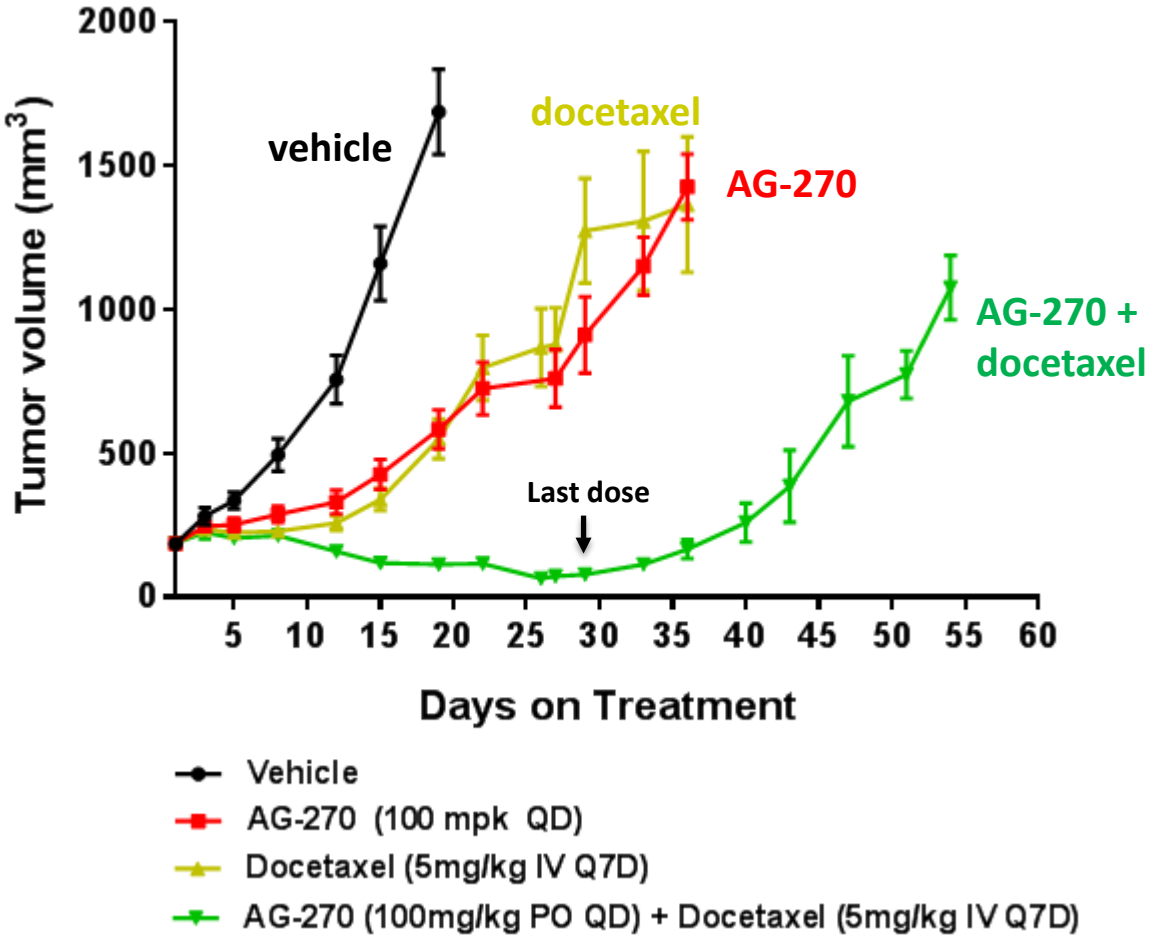
AuroraB Kinase Inhibitor (AZD1152)

Docetaxel



- AG-270 synergizes with AuroraB Kinase Inhibitors and taxanes *in vitro*
- Synergy is selectively observed in MTAP-/- cells and not in MTAP-wt cells

AG-270 Synergizes with Docetaxel in MTAP-null KP4 Pancreatic Ductal Adenocarcinoma Xenograft Model



AG-270 + docetaxel combination in KP4

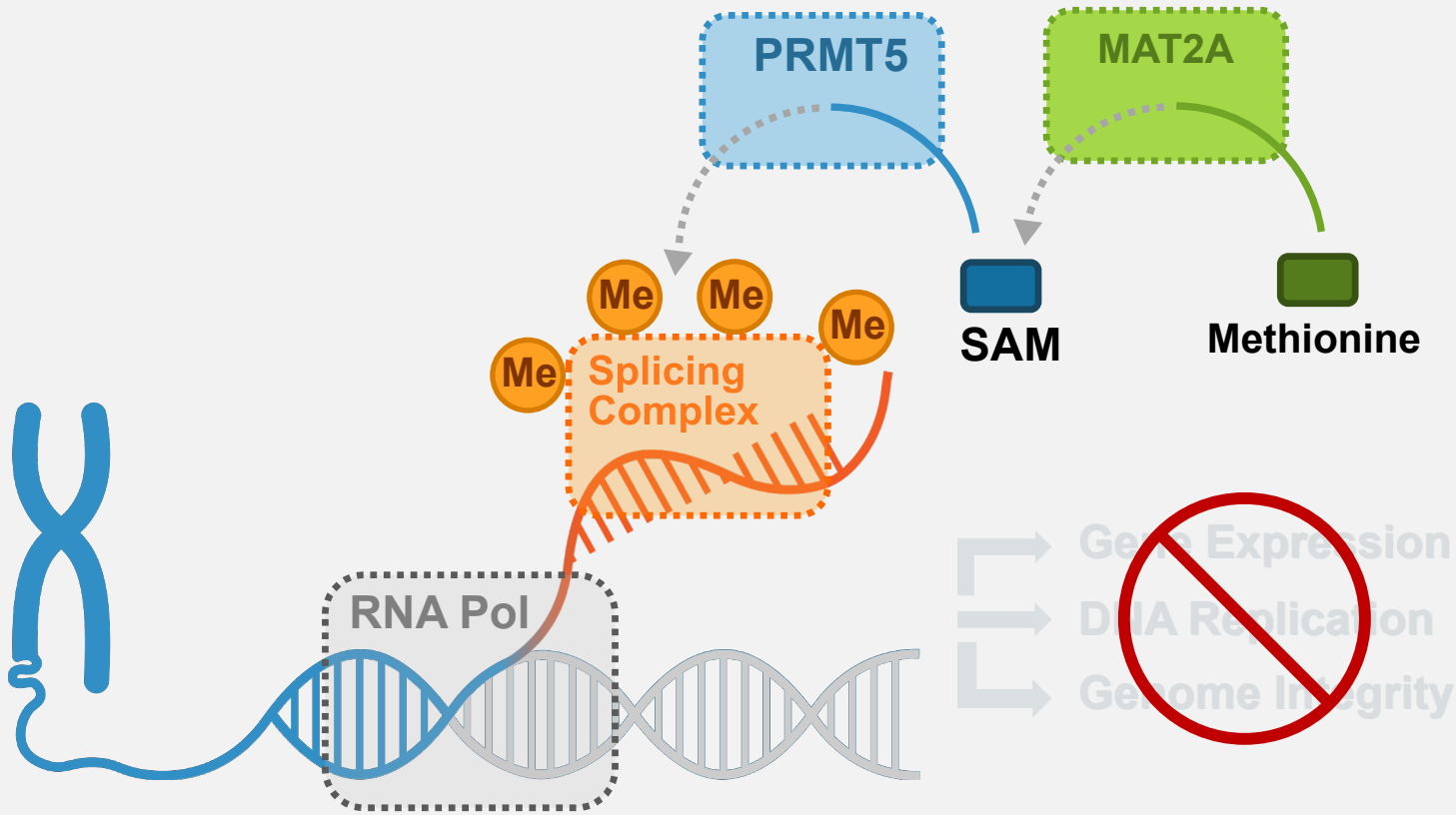
- Single agent and combination treatments were well-tolerated (<5% BWL)
- AG-270 + docetaxel combo is synergistic

Additional AG-270 + taxane combo studies

- AG-270 + taxane combinations tested in a variety of PDX models
- Combination benefit seen in tumors of multiple indications, including lung, pancreatic, esophageal
- Combination benefit seen with both paclitaxel and docetaxel
- PK studies rule out a drug-drug PK interaction

Mechanistic Understanding of the Pathway Downstream of MAT2A

1. RNA splicing concurrent with transcription
2. Splicing complex requires PRMT5
3. MAT2A inhibition blocks splicing
4. Defects in gene expression, DNA replication, genome integrity
5. DNA repair and cell cycle defects, leading to actionable combination partners including taxanes



Summary

- MAT2A inhibition selectively blocks the proliferation of MTAP-deficient cancers *in vitro* and *in vivo*
- Inhibition of MAT2A leads to MTAP-selective effects on PRMT5 methylation, leading to substantial increase in mis-spliced transcripts
- Mis-spliced transcripts include cell cycle regulators such as Aurora Kinase B; consistent with this, MAT2A inhibition leads to mitotic defects including micronuclei formation
- Mitotic defects downstream of MAT2A create a synergistic vulnerability to antimitotics including clinically-applicable taxanes which are used as standard of care in several malignancies with frequent deletion of MTAP

Acknowledgements