Strong durable tumor regressions with the KRAS^{G12D} ON/OFF inhibitor VS-7375 in combination with PRMT5 inhibition in MTAP-deleted/KRAS^{G12D}-mutant pancreatic cancer

#LB183

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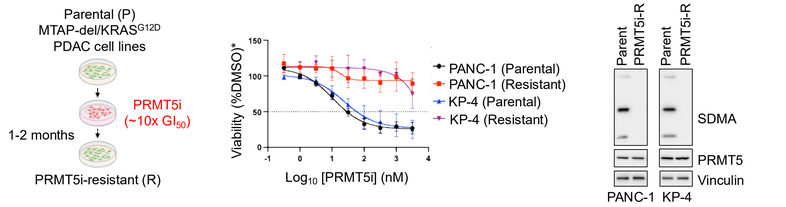
Abstract

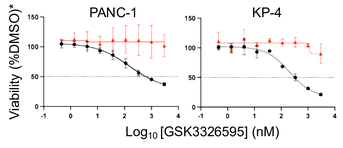
Clinical evaluation of RAS inhibitors has shown promising efficacy in KRAS-mutant pancreatic ductal adenocarcinoma (PDAC). However, intrinsic and acquired resistance limit the depth and durability of response, underscoring the need for rational combination strategies. We recently determined that treatment with the MTA-cooperative PRMT5 inhibitor BMS-986504 (PRMT5i) selectively inhibited the growth of MTAP-deleted/KRAS-mutant PDAC (Drizyte-Miller et al, Cancer Research, 2025). We further showed that concurrent PRMT5i treatment enhanced the efficacy of mutant-selective and pan-RAS inhibitors. Our findings support PRMT5i as an orthogonal combination strategy to overcome resistance to RAS inhibitors. To extend these findings, we first established PDAC cell models of resistance to PRMT5i, the KRAS^{G12D}-selective on-/off-state inhibitor VS-7375/GFH375 (G12Di), or the pan-RAS inhibitor RMC-6236 (pan-RASi). We cultured drug-sensitive KRAS^{G12D}-mutant pancreatic cancer cell lines continuously in the presence of PRMT5i, G12Di, or pan-RASi until resistant subpopulations emerged. PRMT5i-resistant cells retained sensitivity to G12Di and three of four RASi-resistant cell lines remained sensitive to PRMT5i. Thus, consistent with our determination that PRMT5 and KRAS regulate distinct molecular and cellular processes, resistance to each agent likely also involves distinct mechanisms. These data support PRMT5i as a therapeutic approach for patients who relapse on RAS-targeted therapy alone or in combination with RAS inhibitor therapies. Unexpectedly, PRMT5i-resistant cells exhibited a near-complete loss of symmetric dimethylation of arginine (SDMA), the catalytic product of PRMT5, despite retaining PRMT5 expression. PRMT5i-resistant cells also lost sensitivity to SAM-selective PRMT5 inhibitors, indicating that resistant cells have lost dependence on PRMT5 function. One potential mechanism of resistance may involve the type I methyltransferase PRMT1 that catalyzes asymmetric dimethylation of arginine (ADMA) residues. We examined ADMA levels and found no significant increase, consistent with PRMT1-independent mechanisms of resistance. Signaling analyses identified MYC as one possible basis of PRMT5i resistance. While RAS inhibition reduced viability of PRMT5i-resistant cells, it no longer suppressed MYC expression. Ongoing studies to further elucidate mechanisms of resistance to PRMT5i include global profiling of the transcriptomes and methylomes of sensitive versus resistant cells. Our findings define distinct resistance trajectories to RAS and PRMT5 inhibition that support the therapeutic potential of combination PRMT5 and RAS inhibition for the 25% of KRAS-mutant PDAC that harbor additional deletion of MTAP.

MTAP-deleted PDAC cell lines with acquired resistance to PRMT5i have lost dependency on PRMT5

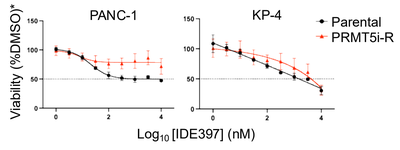
Isolation and characterization of BMS-986504 (PRMT5i)-resistant MTAP-deleted/KRAS^{G12D}-mutant PDAC cell lines



Cross-resistance to SAM-competitive PRMT5 inhibitor GSK3326595

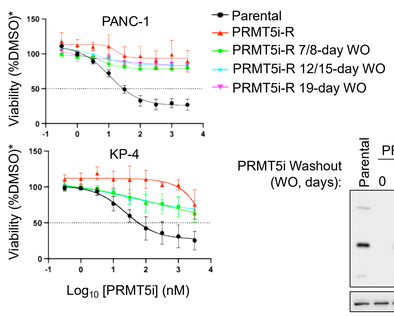


Cross-resistance to MAT2A inhibitor IDE397

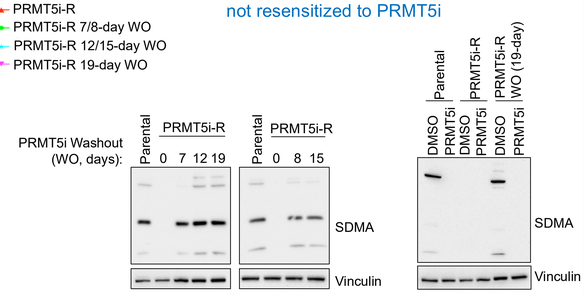


*5-day growth assay

Loss of PRMT5 dependency in PRMT5i-resistant cells is not due to loss of catalytically active PRMT5



SDMA expression is restored upon drug washout, but cells are not resensitized to PRMT5i

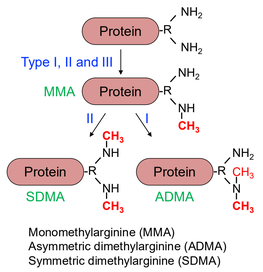


*5-day growth assay

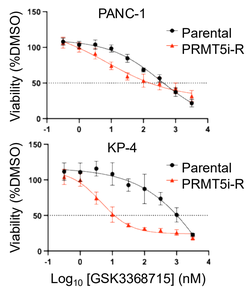
Inhibition of type I PRMT activity overcomes resistance to PRMT5i

GSK3368715 is a type I PRMT inhibitor

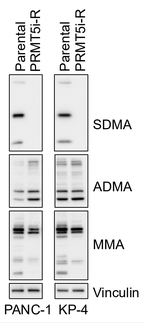
GSK3368715 activity in vitro		
Type	PRMT	IC_{50} (nM)
I	1	3.1
I	3	48
I	4	1148
I	6	5.7
I	8	1.7
II	5	>20,408
Fedoriw (2019) Cancer Cell		



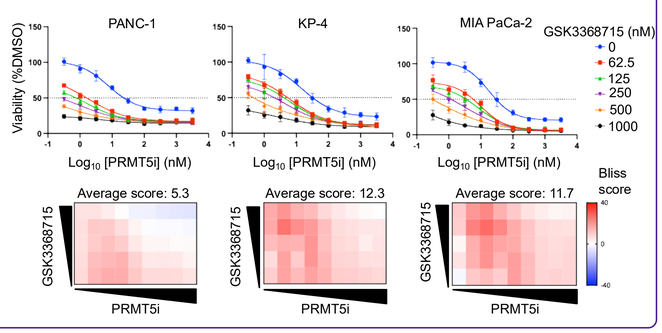
PRMT5i-resistant cell lines have increased sensitivity to type I PRMT inhibitor GSK3368715



ADMA is not elevated in PRMT5i-resistant cells

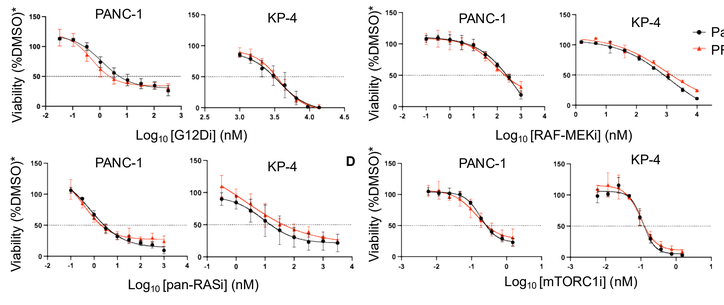


Type I PRMT inhibition overcomes resistance to PRMT5i and causes synergistic growth suppression

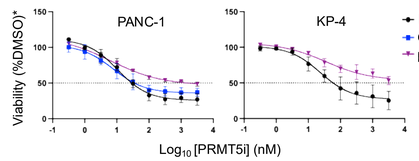


Inhibitors of RAS and PRMT5 induce distinct mechanisms of acquired resistance

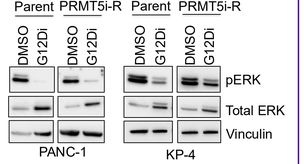
PRMT5i-resistant cell lines remain sensitive to RAS pathway inhibitors



RAS inhibitor-resistant cell lines remain sensitive to PRMT5i



PRMT5i-resistant cells retain sensitivity to G12Di suppression of ERK

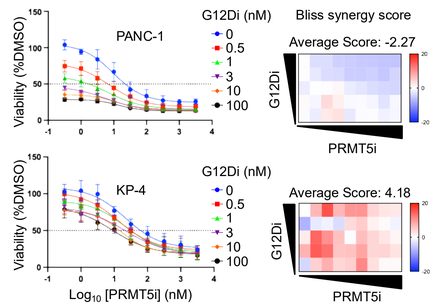


G12Di = VS-7375, RAF-MEKi = avutometinib, pan-RASi = RMC-6236/daraxonrasib, mTORC1i = RMC-5552

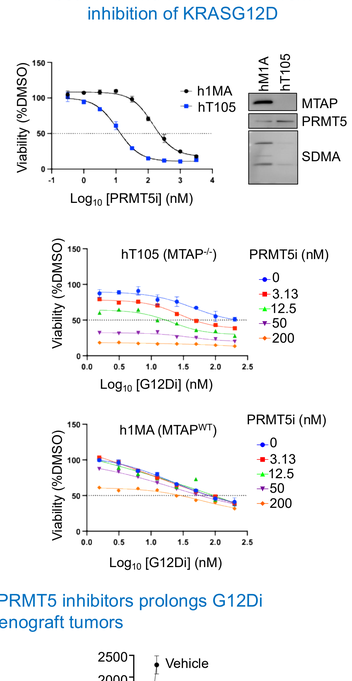
*5-day growth assay

Combination of the MTA-cooperative PRMT5 inhibitor BMS-986504 and the KRAS^{G12D} ON/OFF inhibitor VS-7375 induces strong and durable tumor regressions

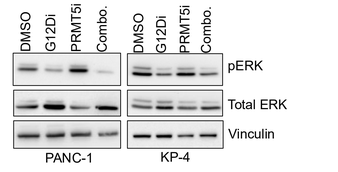
Concurrent PRMT5 and KRAS^{G12D} inhibition causes enhanced growth suppression



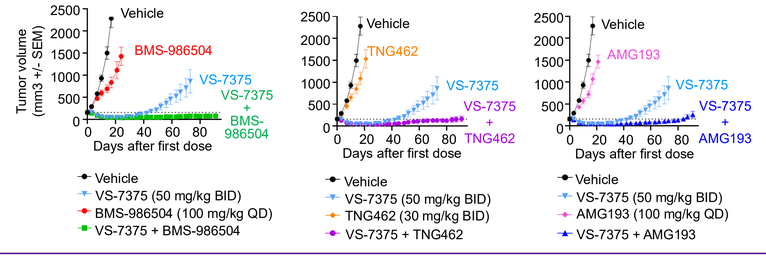
MTAP-deleted PDAC organoids are more sensitive to inhibition of PRMT5 both with and without concurrent inhibition of KRASG12D



G12Di + PRMT5i prevents compensatory reactivation of ERK



Combination treatment with MTA-cooperative PRMT5 inhibitors prolongs G12Di tumor suppression in KP-4 xenograft tumors



Summary

- PRMT5i-resistant cell lines have lost PRMT5 dependency and are cross-resistant to SAM-competitive PRMT5 and MAT2A inhibitors
- Type I PRMT inhibition overcomes acquired resistance to PRMT5i
- G12Di-resistant cell lines are sensitive to PRMT5i, and PRMT5i-resistant cell lines retain sensitivity to G12Di
- The dual ON/OFF KRAS^{G12D} inhibitor VS-7375 in combination with the MTA-cooperative PRMT5 inhibitor BMS-986504 effectively suppresses growth in MTAP-deleted/KRAS^{G12D}-mutant PDAC cell line, organoid and tumor models
- These data support clinical evaluation of VS-7375 with an MTA-cooperative PRMT5 inhibitor for patients with MTAP deleted/KRAS G12D PDAC

Support

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