

Next-generation PRMT5 activity modulation through directed degradation

Jose C. Clemente, Xuqing Zhang, Brian Vidal, Aaron Snoberger, Sudeep Banjade, Cory Rice, Nathan M. Kendsersky, Curran A Rhodes, Matthew Tudor, Qiaolin Deng, Bomie Han, Clemente Aguilar-Bonavides, Elham Behshad, Steven D. Knight, Corey Strickland, Larry J. Jolivet, Ryan G Kruger

SK Life Science Labs, King of Prussia, PA; contact: jclemente@skslabs.com

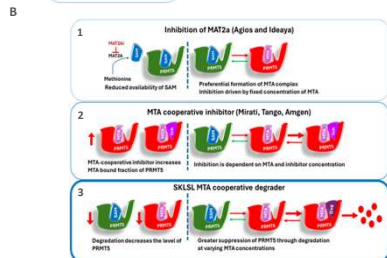
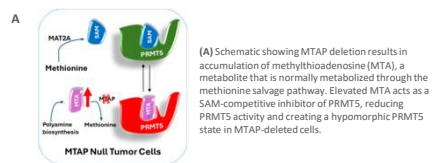
Background

- PRMT5 is a central regulator of transcription, RNA splicing, and broader tumor cell fitness, and has been under investigation as an attractive therapeutic target across multiple cancer types¹.
- To date, development of PRMT5 inhibitors has been limited by toxicity, as PRMT5 activity is also required for normal cellular homeostasis².
- PRMT5 has emerged as an exciting target in MTAP-deleted tumors where MTA accumulation creates a mechanistically defined selective vulnerability³.
- We postulate that MTA-cooperative PRMT5 degraders may deliver deeper pathway suppression and greater potency versus inhibition alone.

Key Findings

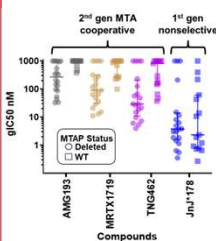
- The degrader drives rapid and robust loss of PRMT5 protein, consistent with efficient target engagement.
- PRMT5 can be selectively degraded with simultaneous loss of MEP50.
- PRMT5 degradation drives potent growth inhibition in MTAP-deleted cells.

Introduction



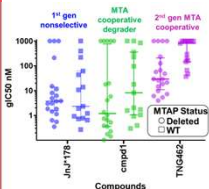
(B) This schematic highlights the two currently clinically pursued and SKSL proposed degrader mechanisms of action (MOA) targeting PRMT5 in MTAP-deleted cancers: (1) MAT2A inhibition reduces SAM concentration, enhancing endogenous MTA-mediated inhibition of PRMT5; (2) MTA-cooperative inhibitors selectively bind the MTA-bound PRMT5 state; (3) a cooperative degrader couples MTA-dependent binding mode with protein degradation to achieve combined inhibition and target removal.

Figure 1. PRMT5 MTA cooperative degraders can surpass 1st and 2nd Gen inhibitor potencies



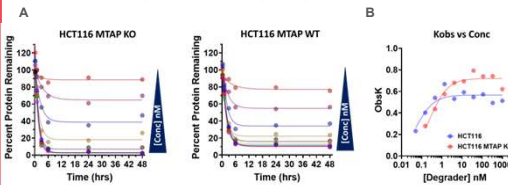
Across MTAP KO and WT NSCLC and B-cell lymphoma cell lines, 1st generation inhibitors show broader and deeper anti-proliferative effects than clinical MTA-cooperative inhibitors. These findings suggest that MTA-cooperative inhibitors selectivity comes at the price of potency. (JNJ-178: JNJ-64619178)

Figure 2. PRMT5 MTA cooperative degraders can surpass 1st and 2nd Gen inhibitor potencies



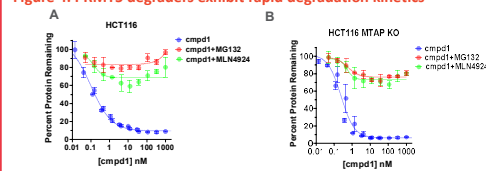
Across MTAP-deleted models, the MTA-cooperative PRMT5 degrader shows the strongest overall activity relative to both JNJ-178. 1st generation nonselective PRMT5 inhibitor and a 2nd generation MTA-cooperative inhibitor TNG462, supporting the idea that cooperative degradation can deliver deeper pathway suppression than inhibition alone.

Figure 3. PRMT5 degraders exhibit rapid degradation kinetics



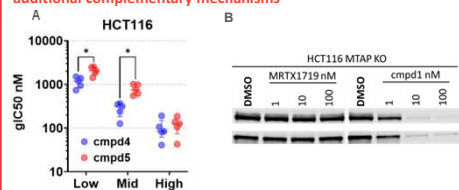
(A) Kinetic analysis shows that PRMT5 degradation is concentration-dependent in both MTAP KO and WT cells, but is faster in MTAP KO cells. (B) Plotting degradation rate versus degrader concentration reveals higher degradation rates in MTAP KO cells above 1 nM, consistent with enhanced target engagement in the MTAP-deleted state.

Figure 4. PRMT5 degraders exhibit rapid degradation kinetics



Dose-response analysis in isogenic WT (A) and MTAP-deleted (B) cells demonstrates robust, degrader-induced PRMT5 degradation. Suppression of degradation by co-treatment with the proteasome inhibitor MG132 or the NEDDylation inhibitor MLN4924 is consistent with a UPS-dependent mechanism.

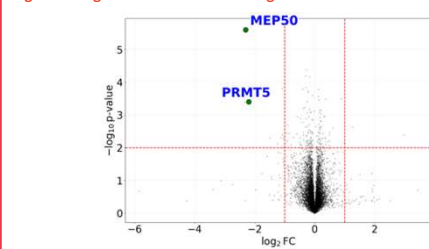
Figure 5. PRMT5 MTA-cooperative degraders may surpass inhibitors via additional complementary mechanisms



cmpd5: Degradation disabled heterobifunctional version of cmpd4

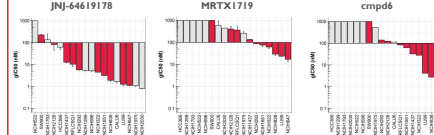
(A) Comparison of anti-proliferative activity of degrader (cmpd4) versus disabled non-E3 binding heterobifunctional (cmpd5). The active degrader (cmpd4) shows the greatest differentiation under limiting MTA conditions versus inhibition alone (cmpd5), suggesting that coupling degradation to MTA-cooperative binding may provide greater anti-proliferative activity than inhibition alone under non-saturating MTA levels. (B) Comparison of PRMT5 levels after treatment with MRTX1719 and degrader cmpd1. In contrast to MTA-cooperative inhibition, which leaves PRMT5 protein intact, PRMT5 degradation drives loss of both PRMT5 and MEP50. Consequently, recovery of PRMT5 activity after degrader treatment would require resynthesis of both complex components, potentially enabling more durable pathway suppression than inhibition alone.

Figure 6. Degraders show selective degradation of PRMT5 and MEP50



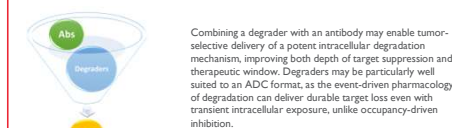
Global proteomics studies confirm selective degradation of PRMT5 and associated loss of MEP50.

Figure 7. Advanced degrader (cmpd6) exhibited greater potency and selectivity than MTA-cooperative inhibitor



gIC50 values from six-day proliferation assay across NSCLC cell lines grouped by MTAP status (null (red) vs wild-type (gray))

Figure 8. How do we maximize the therapeutic window?



Conclusions

- The PRMT5 degrader drives rapid, concentration-dependent target loss in MTAP-deleted cells.
- PRMT5 degradation is selective and mechanistic, requiring the UPS system.
- Global proteomics confirms selective PRMT5 degradation accompanied by loss of MEP50, revealing an additional mechanism that may contribute to enhanced pathway suppression and anti-proliferative activity.
- Across NSCLC models, the degrader delivers stronger MTA dependent anti-proliferative activity than MTA-cooperative PRMT5 inhibitors, supporting the potential for deeper and more durable pathway suppression than clinical MTA-cooperative inhibitors.

- Kim H, Rosati ZA. PRMT5 function and targeting in cancer. *Cell Stress*. 2020 Jul 13;4(8):199-215.
- Vietto M, Moreno V, Spreafico A, et al. Phase I Study of JNJ-64619178, a Proton Arginine Methyltransferase 5 Inhibitor, in Advanced Solid Tumors. *Clin Cancer Res*. 2023;29(8):3592-3602.
- Smith CR, Aranda R, Bobinski TP, et al. Fragment-Based Discovery of MRTX1719, a Synthetic Lethal Inhibitor of the PRMT5-MTA Complex for the Treatment of MTAP-Deleted Cancers. *J Med Chem*. 2022;65(3):1749-1766.