

Introduction

Pancreatic ductal adenocarcinoma (PDAC) remains a leading cause of cancer related mortality with a critical need for novel therapeutic strategies. Cyclin dependent kinase 9 (CDK9) is a transcriptional regulator of RNA polymerase II (Pol II) by phosphorylation of serine residues on the C terminal domain of the positive transcription elongation factor (pTEF). Tri-complex RAS(ON) inhibitors are emerging in clinical practice including daraxonrasib (RMC-6236) and zoldonrasib (RMC-9805), a KRASG12D selective inhibitor with favorable toxicity. Here, we examine a patient-derived cancer organoid (PCO) model that is MYC-amplified to assess the activity of combining CDK9 inhibition (SLS009) with tricomplex RAS (ON) inhibitors studying both RMC-6236 and RMC-9805.

Mechanism

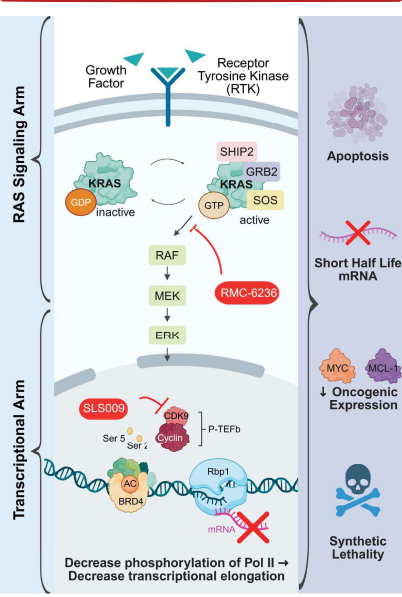


Figure 1. Proposed mechanism of combined RAS/MAPK and transcriptional pathway inhibition. RMC-6236, a multi-selective RAS(ON) inhibitor, suppresses active KRAS-dependent RAF-MEK-ERK signaling, while SLS009 inhibits CDK9-mediated phosphorylation of RNA polymerase II and transcriptional elongation. Concurrent blockade of RAS signaling and transcription reduces oncogenic mRNA expression, thereby promoting apoptosis and synthetic lethality in RAS-dependent tumor cells.

SLS009 and RMC-6236 Induce Cell Death

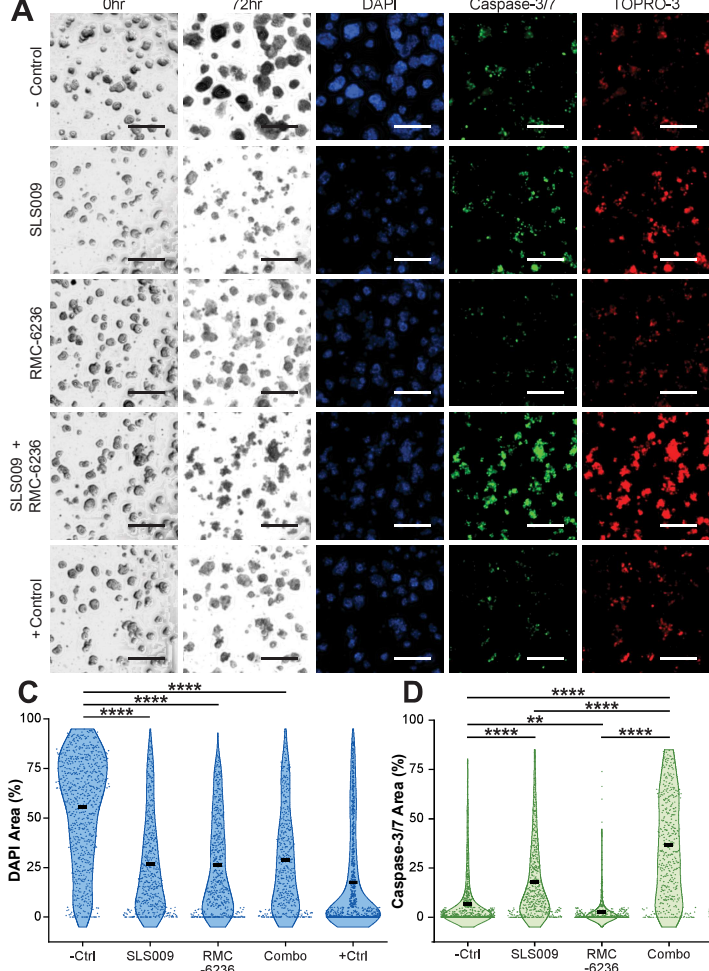


Figure 3. SLS009 and RMC-6236 significantly augment the induction of apoptosis and necrosis. (A) Representative brightfield images at 0hr and 72hr. (B) Growth as assessed for % change in size using brightfield images at 0hr and 72hr. All treatment groups show decreased PCO growth as compared to the negative control ($p < 0.0001$). (C) Viability staining was assessed for % area positive for the SLS009 and RMC-6236 single agents and the combination group decreased relative to the negative control ($p < 0.0001$). (D) Apoptosis staining increased in single agent SLS009 and the combination group relative to the negative control ($p < 0.0001$). The combination group also increased relative to both single agent SLS009 and RMC-6236 ($p < 0.0001$). (E) Necrosis staining increased in single agent SLS009 and the combination group relative to the negative control ($p < 0.0001$). The combination group similarly increased relative to both single agent SLS009 and RMC-6236 ($p < 0.0001$).

SLS009 IC₅₀

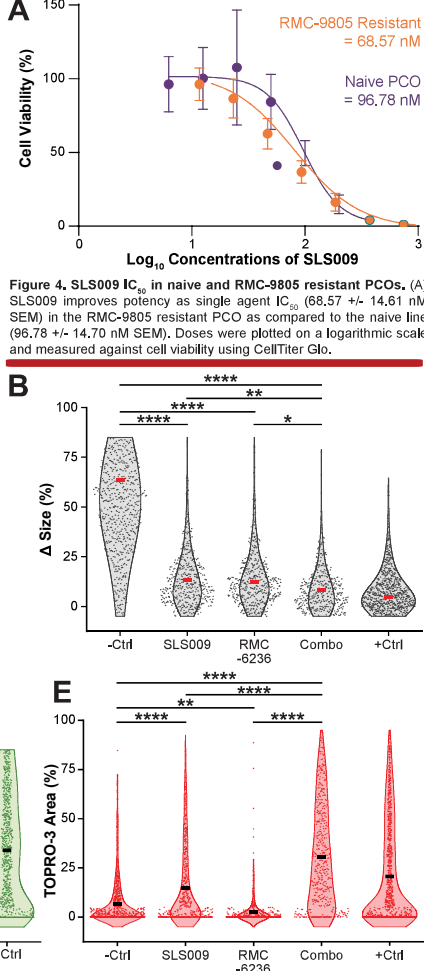


Figure 4. SLS009 IC₅₀ in naive and RMC-9805 resistant PCOs. (A) SLS009 improves potency as single agent IC₅₀ (68.57 $\pm$ 14.61 nM SEM) in the RMC-9805 resistant PCO as compared to the naive line (96.78 $\pm$ 14.70 nM SEM). Doses were plotted on a logarithmic scale and measured against cell viability using CellTiter Glo.

Molecular Response

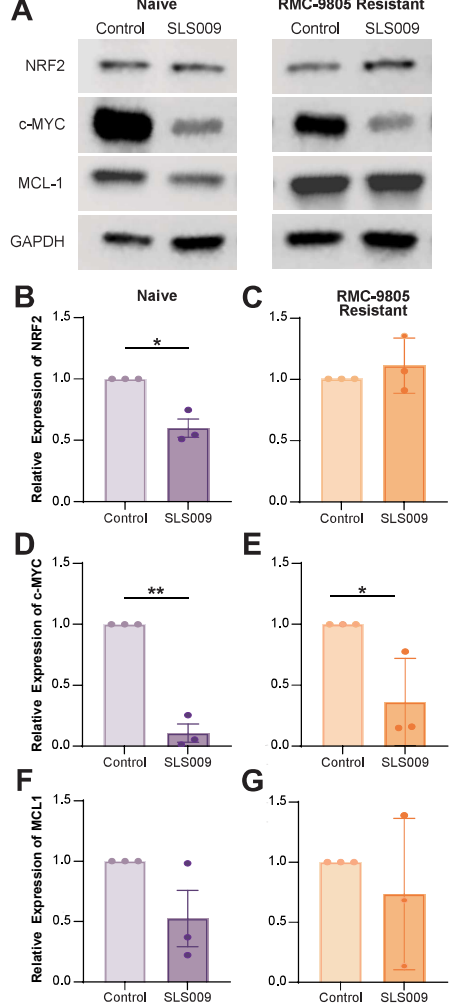


Figure 5. Decrease in oncogenic factors after treatment with SLS009. (A) Western blots of protein collected from naive PCO and RMC-9805 resistant PCO treated with SLS009 after 24hr. Quantified protein expression of NRF2 (B, C), MYC (D, E), and MCL-1 activity (F, G) normalized to GAPDH.

Methods

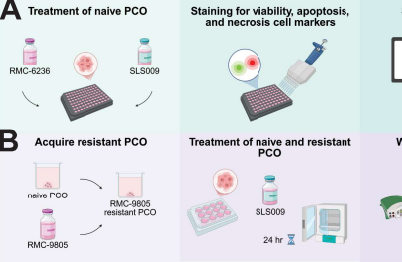


Figure 2. Schematic of the experimental timelines. (A) PCOs were assayed using medium throughput 96 well assay (ibidi, Inc) for high content imaging (Cytation 5). Single and dual agent activity of SLS009 (200nM) and RMC-6236 (100nM) was assessed with an assay endpoint of 72 hours. RMC-6236 was treated continuously, while SLS009 was removed after 24 hours to mimic in vivo pharmacokinetics. Initial response was assessed by normalized change in PCO area after 72 hours. Subsequent staining was performed for cell viability (DAPI), apoptosis (Caspase-3/7), and necrosis (TOPRO3). Statistical analysis was conducted using one-way ANOVA followed by Tukey's post hoc test to compare the mean percentage of area stained between treatment groups. (B) RMC-9805 resistant PCOs were developed at a 200nM dose. Naive and RMC-9805 resistant PCOs were treated with single-agent SLS009 for 24 hours. Western blot analysis was performed for critical resistance mechanisms including NRF2, c-MYC, and MCL-1 using a LICOR M Odyssey system.

Conclusion

The combination of transcriptional targeting with SLS009 in combination with tricomplex RAS (ON) inhibition significantly augments the induction of apoptosis and necrosis in MYC-amplified PDAC PCOs. SLS009 was also found to have improved potency as single agent IC₅₀ in the RMC-9805 resistant PCO as compared to the naive PCO. Notably, SLS009 reduced NRF2, c-MYC, and MCL-1 expression and retained potent single-agent activity in RMC-9805 resistant PCOs, suggesting a potential role for CDK9 inhibition in targeting transcriptional dependencies associated with KRAS inhibitor resistance. Ongoing work includes evaluating biomarkers predictive of this response and activity across heterotopic in vivo models.

References and Acknowledgements

- Dempke, W. C., M., Sippl, C., Fenchel, K., Heinemann, V., van Cutsem, E., & Arnold, D. (2026). The ongoing first-line treatment race for metastatic pancreatic ductal adenocarcinomas: will a tough disease lose its horror? *Future Oncology*, 1-8. <https://doi.org/10.1080/14736694.2026.2725499>
- Fisher, R.P., Geyer, M., Targeting CDKs in the RNAPII transcription cycle. *Nat Rev Drug Discov* (2026). <https://doi.org/10.1038/s41573-026-01517-0>
- O'Reilly, E. M., Wainberg, Z. A., Hendrix, A. E., Borad, M. J., Pietrantonio, F., Pant, S., Hammel, O., Cremolini, C., Manhi, G. A., Oberstein, O. E., et al. (2026). Daraxonrasib or Chemotherapy in Previously Treated Metastatic Pancreatic Cancer. *New England Journal of Medicine*, 395(4), 325-337. <https://doi.org/10.1056/NEJMoa2605555>

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